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

Final Evidence Report

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Prepared for

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About ICER

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In the development if 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:
http://icer-review.org/material/psoriasis-stakeholder-list/

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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

Executive Summary

Background

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

Plaque psoriasis is associated with increased rates of cardiovascular disease and infection, and up to 30% of patients with plaque psoriasis have at least some manifestations of psoriatic arthritis.[4,5,6] Psoriasis is associated with decreased health-related quality of life[7-9] and patients with psoriasis have increased rates of depression, anxiety, and suicidal ideation. [10,11]

There is no cure for plaque psoriasis, but it can be managed with topical therapies, phototherapy, and systemic therapies. Systemic therapies include older agents such as methotrexate and cyclosporine as well as newer "targeted immunomodulators," which include biologic agents and the small molecule drug apremilast. Clinical interest in targeted immunomodulators is high, as many patients with chronic plaque psoriasis do not achieve adequate or durable benefit from older systemic therapies or phototherapy.

The focus of this evidence review was to assess the comparative health and economic outcomes of targeted immunomodulators (biologics plus apremilast) relative to non-targeted therapy among adults with moderate-to-severe plaque psoriasis.

Topic in Context

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).[12,13] Moderate-to-severe plaque psoriasis is generally treated with systemic therapies.

Treatments for psoriasis can be grouped within four broad categories:

- **Topical therapies** include steroids, vitamin D analogs, retinoids, and calcineurin inhibitors. Topical treatments are usually in the forms of creams, ointments, or lotions. Topical

treatment can be impractical for patients with psoriasis that affects a large area or for patients who have significant scalp involvement, and higher potency topical corticosteroids can cause skin atrophy. Topical calcineurin inhibitors may be associated with skin cancer.

- **Older systemic therapies** include acitretin, cyclosporine, and methotrexate. Older systemic therapies have limitations including hepatotoxicity, fatigue, and stomatitis (methotrexate); hypertension, lymphoma, and skin cancer (cyclosporine); or birth defects and elevated triglycerides (acitretin).
- **Phototherapy**, also known as light therapy, exposes the skin to ultraviolet light in order to slow the growth of overactive skin cells.
- **"Targeted immunomodulators"** include biologics and apremilast

Targeted immunomodulators that have been approved, or are nearing approval, for the treatment of moderate-to-severe plaque psoriasis in the United States are listed in Table ES1. Although not technically a biologic, apremilast is a novel, targeted, oral agent also approved for treatment of patients with moderate-to-severe plaque psoriasis.

Table ES1. Targeted Immunomodulator Dosing for Moderate-to-Severe Plaque Psoriasis

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

*Not yet FDA-approved. Although the original PDUFA date was scheduled for November 16, 2016, the FDA's review of brodalumab has been postponed to February 16, 2017 due to requirements for additional time to develop a Risk Evaluation and Mitigation Strategy (REMS).[14]

Concerns regarding the use of targeted immunomodulators include injection or infusion site reactions and development of serious infection or malignancy from long-term immunosuppression, although serious adverse events are relatively rare. Please see the full report for details about short and long-term adverse effects of targeted immunomodulators.

Other Treatment Considerations

Non-standard dosing: to maintain effectiveness when psoriasis is not being controlled at FDA-approved doses, many physicians increase the dose. Physicians may also prescribe *lower*-than-approved doses of effective medications in an attempt to decrease out-of-pocket costs or minimize adverse effects. Two descriptive studies of dose escalation and decreases suggest that dose increases and decreases happen at roughly similar rates.

Early, Aggressive Treatment: It is uncertain whether early aggressive treatment with immunosuppressive medications, phototherapy, or targeted immunomodulators can alter the natural history of psoriasis and/or mitigate the increased cardiovascular risk seen with the disease.

Second-line Targeted Therapy: Although the focus of this report is first-line targeted therapy, the potential role of second-line targeted therapy in patients who do not respond to first-line targeted treatment is relevant. Unfortunately, there is no evidence from RCTs for targeted agents in the second-line setting.

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 might provide enhanced effectiveness. Combination therapy seems likely to be discussed in a forthcoming guideline from the American Academy of Dermatology and the National Psoriasis Foundation.

Emerging Therapies: Biologic "biosimilar" medications are becoming available, including recently-approved biosimilars like Amjevita® (Amgen), Erelzi® (Sandoz, Inc.), and Inflectra® (Pfizer/Celltrion, Inc.). The equivalence of the etanercept biosimilar for moderate-to-severe plaque psoriasis has been reported in a single conference abstract.[15] Briakinumab is an additional anti-IL 12/23 that has been evaluated, but it is unclear if it will come to market. Tofacitinib, a small molecule treatment already approved for the treatment of rheumatoid arthritis, has been shown to be effective for moderate-to-severe plaque psoriasis in randomized controlled trials.[16] Baricitinib, a small molecule being investigated for possible use in psoriasis, has been evaluated in a phase IIIb trial. Finally, a

Biologics License Application (BLA) was submitted to the FDA in November 2016 for guselkumab, an IL-23, and currently has three ongoing Phase III clinical trials.[17]

Insights Gained from Discussions with Patients and Patient Groups

Conversations with advocacy groups and individual patients highlighted the shortcomings associated with clinical trial outcomes, frustrations with the healthcare system, as well as the social, emotional, and financial impact of psoriasis. A full description of insights gained from discussions with patients and patient groups is presented in the full report, but some important highlights include:

- Certain aspects of research into psoriasis are not patient-centered. Many of the tools developed to measure outcomes – including the Psoriasis Area and Severity Index (PASI) – do not capture the patient experience. Patients feel that outcome measures employed in clinical trials have not adequately captured the full range of social, psychological, and emotional effects of psoriasis, including, as noted above, increased rates of depression, anxiety, and suicidal ideation.
- Treatments for plaque psoriasis can be challenging because topical therapies must be frequently applied to large areas. In addition, requirements for multiple injections and time and travel concerns for administration of infused therapy may place additional burdens on patients and their families.
- Patients are often dissatisfied with systemic psoriasis treatments due to unpredictable effectiveness, poor tolerability, and lack of durability of response to previously effective medications.
- Psoriasis affects social functioning because of limitations of activity; clothing choices that seem inappropriate to others (e.g., long sleeves and pants on hot days); and, especially for children and teens, teasing, bullying, and shunning because of the visible nature of the disease.
- Patients are concerned about lack of access, the cost of treatment, and future availability of drugs to treat their disease. About half of patients with psoriasis are either undertreated or not treated,[18] and one of the main reasons is the cost of therapy. Patients are frustrated at coverage decisions and changes in coverage that may seem capricious.

Comparative Clinical Effectiveness

To inform our analysis of the comparative clinical effectiveness of targeted immunomodulators for moderate-to-severe psoriasis, we abstracted evidence from available clinical studies. We included randomized controlled trials as well as high-quality systematic reviews. To evaluate other measures

of potential benefit as well as adverse events, we examined higher-quality comparative cohort studies, other articles from the published medical literature, information from the grey literature, and information from patient groups.

Our literature search identified 1,392 potentially relevant references. A total of 80 references met our inclusion criteria, representing 36 RCTs and 11 observational studies. Eight studies included head-to-head, comparative evaluations of targeted immunomodulators for plaque psoriasis, of which one was available only in the grey literature (IXORA-S). Characteristics of the 29 key trials for each agent are presented in Table ES2. In addition to these 29 studies, there were five placebo-controlled RCTs conducted exclusively in Asia.

Trial populations included patients with moderate-to-severe plaque psoriasis despite generally having used topical treatments, older systemic treatments, phototherapy, or other targeted immunomodulators. Trials required washout and participants to not use non-trial treatments. Use of other treatments was prohibited in the interest of directly evaluating the comparative effectiveness of targeted immunomodulators to placebo or to one another.

The primary outcome for all RCTs of targeted immunomodulator therapy was assessed at the end of the induction period (between 10 and 16 weeks after initiation, depending on agent), after which treatment crossover was typically allowed. Because of this, we could only confidently compare the comparative efficacy of targeted immunomodulators at the end of the induction period. Long-term effectiveness and safety data were variably reported by individual drug.

For the primary outcome, clinical trials of targeted immunomodulators used the **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 can range from 0 to 72, with higher numbers indicating greater surface involvement and severity of lesions. The PASI is generally reported as the percentage reduction in the PASI score from baseline to follow-up. The most consistently reported primary outcome in clinical trials is the "PASI 75," i.e., a 75% reduction in the PASI score. Many trials report other PASI thresholds: PASI 90 is a 90% improvement in the PASI score; PASI 100 indicates full disease clearance, or a follow-up PASI score of zero.

Other outcome measures included in clinical trials were Physician or Investigator Global Assessments about disease severity in which a successful response is usually considered "clear/almost clear;" quality of life as measured by the Dermatology Life Quality Index (DLQI), which includes domains of symptoms, feelings, daily activities, leisure, work, school, social interactions, clothing choice, sexual difficulties, and treatment problems; and measures of symptom control.

Table ES2: Summary of Characteristics of Key Trials

Drug	Trials	Total # of patients	Induction period (weeks)	PASI, (mean)	Age (years)	Psoriasis duration (years)	Previous biologics (%)	PsA (%)
Adalimumab	REVEAL CHAMPION	1,483	16	22	43	19	6	24
Etanercept	Papp, 2005 Leonardi, 2003 Tyring, 2006 Strober, 2011 Gottlieb, 2011 Bagel, 2012 Bachelez, 2015	3,775	12	20	44	17	6	25
Infliximab	EXPRESS I EXPRESS II	1,213	10	21	44	19	10	30
Ustekinumab	ACCEPT PHOENIX 1 PHOENIX 2	2,899	12	30	45	20	33	29
Secukinumab	FEATURE CLEAR JUNCTURE ERASURE FIXTURE	3,079	12	28	45	18	25	20
Ixekizumab	UNCOVER 1 UNCOVER 2 UNCOVER 3 IXORA-S**	3,866	12	24	46	19	27	NR
Brodalumab	AMAGINE 1 AMAGINE 2 AMAGINE 3	4,373	12	23	45	19	33	22
Apremilast	ESTEEM 1 ESTEEM 2 LIBERATE	1,505	16	19	46	19	31	NR

*PASI = Psoriasis Area and Severity Index. PsA = psoriatic arthritis

**Only available in the grey literature.

Because the eight targeted immunomodulators of interest have not all been directly compared, we developed quantitative, indirect comparisons among all eight agents using a Bayesian network meta-analysis (NMA) for PASI outcomes. We used a random-effects approach and, for the base case analysis, adjusted for the placebo response rate in each study which, to some degree, accounts 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. Further details on our NMA methods and findings are available in the full report and Appendix F.

We also examined three key subgroups of patients and studies based on stakeholder feedback: 1) patients with concomitant psoriatic arthritis, who might have more severe skin disease and who might respond better or worse to targeted immunomodulators than patients without psoriatic arthritis; 2) patients who had previously used biologic therapy, who might be less likely to respond to a different targeted immunomodulator; and 3) results from the six studies conducted exclusively in Asia, which might have design (e.g., smaller sample sizes) or patient differences (e.g., younger age, briefer duration of psoriasis, lower BMI) in comparison to the worldwide studies.

Results

Clinical Effectiveness

Psoriasis Area and Severity Index (PASI) Results

All of the targeted immunomodulators showed statistically significantly higher PASI 75 (i.e., 75% or better improvement from baseline PASI) response rates in comparison to placebo at the end of the induction period (10 to 16 weeks depending on agent; Table ES3). In addition, all the targeted immunomodulators for which there were data showed statistically significantly higher PASI 50, 90, and 100 rates in comparison to placebo.

Table ES3. Placebo-Controlled Trials: Ranges of PASI 50/75/90/100 Response Rates

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

In direct comparative trials, ustekinumab, secukinumab, and ixekizumab were superior to etanercept for PASI 90 and 100 (Table ES4). Secukinumab and brodalumab were superior to ustekinumab in PASI 90 and 100. Finally, a head-to-head comparison of ixekizumab and ustekinumab (IXORA-S) showed statistically-significant benefit on all key PASI measures for ixekizumab; this study has not yet been published, however.

Table ES4. Comparative Trials: PASI Responses

Trial	Treatment	PASI 75	PASI 90	PASI 100
ACCEPT	Etanercept	57	23	NR
	Ustekinumab 45 mg	68	36	NR
	Ustekinumab 90 mg	74	45	NR
FIXTURE	Etanercept	44	21	4
	Secukinumab 300 mg	77	54	24
UNCOVER 2&3	Etanercept	42-53	19-26	5-7
	Ixekizumab	87-90	68-70	38-41
CLEAR	Ustekinumab WBD	79	53	26
	Secukinumab 300 mg	91	73	39
AMAGINE 2&3	Ustekinumab WBD	69-70	47-48	19-22
	Brodalumab 210 mg	85-86	69-70	37-44
IXORA-S*	Ixekizumab	91	75	37
	Ustekinumab	69	42	15

*Only available in the grey literature
WBD = weight-based dosing

Another study that is currently only available in the grey literature is the LIBERATE trial, which included apremilast and etanercept treatment arms. However, the study was powered only to detect differences between both active agents and placebo, and also used a dosing schedule for etanercept that is not FDA-approved; for these reasons, it is not considered a true head-to-head trial of targeted immunomodulators.

Network Meta-Analysis: PASI Results

Because there are relatively few direct head-to-head studies among the drugs of interest, we performed a network meta-analysis that allows for rigorous indirect comparisons of different drugs. The results of our analysis showed ixekizumab with the highest relative effectiveness [measured as relative risk (RR)] on initial PASI 75 response during induction, followed by brodalumab, infliximab, secukinumab, ustekinumab, adalimumab, and etanercept. Apremilast had the lowest relative effectiveness (see Table ES5). The network meta-analysis results are consistent with the results of head-to-head trials where those are available.

Other Outcome Measures

Physician Global Assessments (PGA) or Investigators Global Assessments (IGA), general assessments of disease activity, were largely consistent with the PASI 75 results. All immunomodulators showed statistically significantly higher proportions of patients with an assessment of 'clear/almost clear' than placebo at the primary endpoint of each trial. In head-to-head trials, ustekinumab, secukinumab, and ixekizumab were superior to etanercept; secukinumab, ixekizumab, and brodalumab were superior to ustekinumab.

Dermatology Life Quality Index (DLQI) results were also generally consistent with the PASI 75. All targeted immunomodulators statistically significantly improved quality of life relative to placebo. Infliximab produced the overall greatest relative benefit and apremilast produced the smallest as measured at the end of the induction period. In head-to-head trials secukinumab and ixekizumab were superior to etanercept; secukinumab was superior to ustekinumab in one trial.

Measures of symptom control were inconsistently reported across trials and used a variety of instruments. Using one psoriasis symptom index, brodalumab demonstrated a statistically significant benefit over placebo. Two secukinumab trials demonstrated improvement in itching, pain, and scaling relative to placebo. In head-to-head trials, ixekizumab demonstrated superiority over etanercept for skin pain.

Harms

Severe or serious adverse events were rare during the induction phase of treatment. Infections (e.g., nasopharyngitis, upper respiratory tract infections, etc.), injection site or infusion reactions, headache, and nausea were the most common side effects with biologics. Infliximab appears to have higher rates of these events than other drugs.

Because they have been available for longer and are approved for many conditions, long-term safety data on all-cause mortality, major cardiovascular adverse effects, malignancy, and serious infections are available for TNFα agents. For psoriasis, in 1-year follow-up of pivotal trials of

targeted immunomodulators, etanercept, ustekinumab, secukinumab, and brodalumab have comparable safety profiles. For example, they have rates of adverse effects leading to discontinuation of between 1.2 and 3.2 per 100 person years (PY); rates of serious adverse effects of between 4.0 and 13.0 per 100 PY; and rates of serious infections between 0.8 and 1.0 per 100 PY.[19-21] In 5-years of follow up, ustekinumab continues to have comparable rates.[22]

An analysis from a registry of 11,466 psoriasis patients with 22,311 PY of follow-up focused on the rate of severe infectious complications. Infliximab had a higher rate (2.78 per 100 PY) and ustekinumab (0.95 per 100 PY) had a lower rate of serious infections than other available targeted immunomodulators and other systemic psoriasis treatments (1.26 to 1.80 per 100 PY).[23]

Subgroup Analyses

We examined three subgroups: patients with concomitant psoriatic arthritis, patients who had previous used biologic therapy, and results from Asian studies.

For patients with psoriatic arthritis and prior biologic therapy, limitations in the evidence preclude determining whether there are clear, meaningful differences in targeted immunomodulator effectiveness. Although outcomes were statistically significantly in favor for all the agents available for review relative to placebo, data comparing subgroup results between agents were only available in one observational study. Patients with prior biologic therapy use had response rates that were roughly 10% lower than biologic-naive patients. The evidence is insufficient, but there do not appear to be differential effects of the targeted immunomodulators within patients who have previously used a biologic treatment or in patients with psoriatic arthritis.

There were 6 placebo-controlled RCTs that were conducted in Asia, including the Japanese portion of one of the worldwide studies (ERASURE). As with the worldwide studies, the Asian studies demonstrated statistically significant improvement with targeted immunomodulators compared to placebo. None of the Asian studies included head-to-head comparisons.

Table ES5. Network Meta-Analysis Base-Case League Table

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

Controversies and Uncertainties

Across the 28 Phase III RCTs identified for this review, only eight included head-to-head comparisons for the drugs of interest. Our network meta-analysis extended comparisons across all agents, but the results are based primarily on indirect comparisons which generally cannot provide the same level of certainty as head-to-head studies. Our results appear to have strong face validity, however, given that they are consistent with the comparative data where available, and, as described further in the full report, are consistent with the results of other meta-analyses and network meta-analyses.

Although PASI 75 was reported as the primary endpoint in all studies, all other clinical outcomes, including PASI 50, 90, 100 and PGA/IGA, were inconsistently reported across trials, making many cross-drug comparisons difficult. Longer-term data on both drug effectiveness and harms were also variable; many studies reassigned patients to different groups (mostly cross-over to the intervention) and evaluated outcomes at different time periods. Observational data were only available for ustekinumab, secukinumab, and the TNF-α agents, which limited our understanding of real-world effectiveness and durability of benefits for many of these therapies.[24] 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.

Comparative Clinical Effectiveness: Summary and Comment

Using the ICER evidence rating matrix, our evidence ratings for the comparisons of interest are provided in Table ES6; 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 certain between-agent comparisons. However, because of the lack of many head-to-head comparisons, as described previously 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 Table ES6 along with the number of head-to-head studies that informed the rating. There were two head-to-head trials comparing ixekizumab and etanercept, both of which found that ixekizumab was superior in the percentage of patients achieving various PASI thresholds, with a similar magnitude of benefit found when indirect evidence was included. We felt that the

consistency of results across the two trials represented high certainty of a substantial net benefit for ixekizumab ("A") and an inferior net health benefit ("D") for etanercept in this comparison. Similarly, findings from two trials comparing brodalumab to ustekinumab showed consistently superior outcomes for brodalumab, albeit at a more incremental level (ratings of "B" and "D" for brodalumab and ustekinumab respectively).

The remaining head-to-head comparisons were based on the results from single trials, giving us only moderate certainty in our estimates of comparative effectiveness. Both ustekinumab and secukinumab demonstrated better outcomes than etanercept, and these findings were supported by the network meta-analysis, leading us to give a rating of "B+" (incremental or better) to these comparisons. Etanercept was rated "C-" for both comparisons, reflecting our judgment of moderate certainty that net health benefit is either comparable or inferior. Findings from a single trial of secukinumab versus ustekinumab showed improved clinical outcomes at all PASI thresholds for secukinumab, but inclusion of indirect evidence yielded a nonsignificant difference in treatment effect. As such, we rated the evidence "C+" (comparable or better) for secukinumab and "C-" for ustekinumab in this comparison. We judge the evidence to be insufficient (I) to distinguish between etanercept and apremilast, given that the only available head-to-head trial was underpowered to detect differences between active agents and dosing of etanercept does not match the labeling for the product. Finally, the addition of a direct comparison between ixekizumab and ustekinumab is newly available, but only in abstract form, yielding moderate certainty of at least a small net benefit ("B+").

Ratings based on indirect evidence alone are highlighted in blue in the table. In one instance, certainty in the ratings remained high due to a "second-order" effect. Specifically, because we have high certainty from direct evidence that brodalumab provides an incremental net health benefit over ustekinumab, and moderate certainty that ustekinumab provides an incremental or better benefit over etanercept, we have high certainty that brodalumab would also provide an incremental benefit over etanercept or apremilast. For all other ratings, results of the network meta-analyses represented the only guide with which to judge the evidence. Drugs with evidence of net health benefit were judged B+ or C+ based on the observed magnitude of benefit, and their comparators received a 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.

Table ES6: ICER Evidence Ratings for Head-to-Head Comparisons

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

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

Other Benefits and Disadvantages

Beyond effectiveness and safety of targeted immunomodulators, the method of administration, frequency of dosing during maintenance, and rapidity of effect may be important considerations.

All of the targeted immunomodulators are administered subcutaneously except for apremilast (oral) and infliximab (intravenous). Patients may prefer the convenience of oral therapy with apremilast. In contrast, despite its efficacy, patients may wish to avoid the administration time and potential discomfort required for intravenous infusions of infliximab.

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 eight weeks (infliximab), and every 12 weeks (ustekinumab). Patients could favor agents that need to be taken less frequently.

How quickly a drug works to clear psoriasis is likely to be important for patient satisfaction and adherence. For patients who require rapid clearing of moderate-to-severe plaque psoriasis,

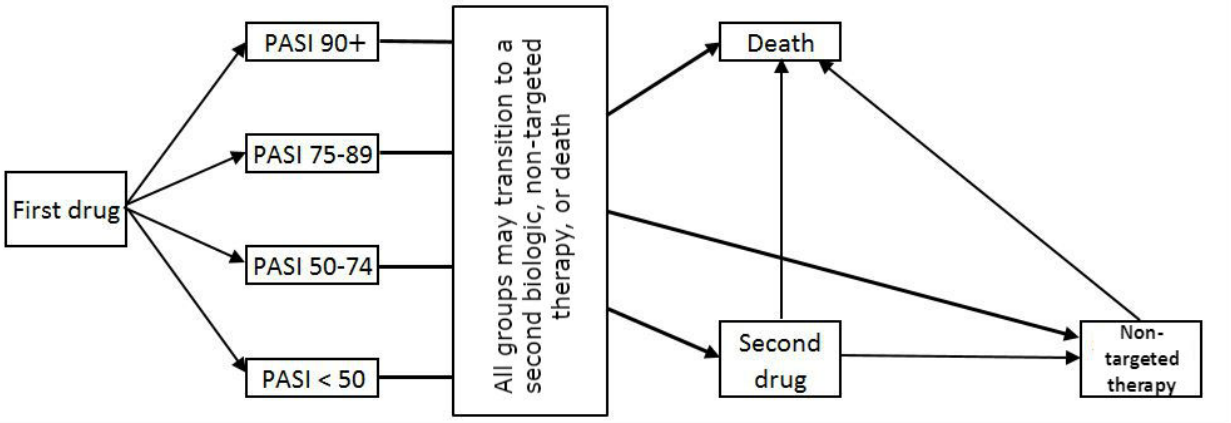
cyclosporine, an older systemic agent, not a focus of this review, and infliximab appear to be superior to other treatments.

Comparative Value

We developed a simulation model to assess the long-term cost-effectiveness of targeted immunomodulators for patients with moderate-to-severe plaque psoriasis for whom topical therapies, older systemic therapies, or phototherapy have been ineffective, contraindicated, or not tolerated. We used as inputs for the model the results from our network meta-analyses and other results from the published literature. The outcomes of the model include total costs, life years, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios. Uncertainty in the data inputs and assumptions were evaluated using sensitivity and scenario analyses.

Consistent with other approaches to modeling sequential therapy in psoriasis, patients with less than 75% improvement after the initiation period (10 weeks for infliximab, 16 weeks for adalimumab and apremilast, 12 weeks for all other drugs) were assumed to discontinue the first-line therapy, and either receive second-line targeted therapy or non-targeted therapy (i.e., a mix of no treatment, topical therapy, other systemic therapy, and phototherapy). Second-line targeted therapy was defined as an average of all available targeted therapies; costs were averaged across available targeted agents as was effectiveness, with a small assumed decrease in effectiveness.

Figure ES1: Markov model of psoriasis treatment and response



The model required a number of assumptions which are represented in Table ES7 below along with the rationale for each assumption.

Table ES7. Key model assumptions

Assumption	Rationale
A patient cannot transition between effectiveness (PASI improvement) levels.	Drug response does not show significant improvement past the trial period; discontinuation rate accounts for decline in effectiveness over time.
Probability of discontinuing first-line therapy is drug specific.	Empirical evidence indicates discontinuation rates beyond the initiation period differ across drugs, and differs in year 1 vs. years 2+
Probability of discontinuing newer drugs (secukinumab, ixekizumab, and brodalumab) is the same as ustekinumab.	There are limited to non-existent data on discontinuation rates for the newer agents. This assumption was evaluated in a sensitivity analyses.
Half of patients discontinuing first-line targeted drug therapy receive second-line targeted drug and remainder receive non-targeted drug.	There are limited data on proportion of patients receiving second-line targeted treatment, particularly in current treatment paradigm with newer agents. This assumption was evaluated in sensitivity analyses.
Second-line targeted therapy was assumed to be an average of all available targeted agents.	There are no RCTs of second-line targeted therapy and limited data on second-line targeted therapy response in general.
Non-targeted therapy was assumed to consist of a mix of no treatment, topical treatment, non-targeted systemic treatment, and phototherapy.	There is little evidence on the mix of treatments, costs, and patient outcomes over time in patients who do not receive targeted therapy, as well as in patients who discontinue targeted therapy.
Risk of death is based on age alone.	Evidence suggesting that treatment of psoriasis improves survival is very weak.
Patients remain on first-line therapy during the trial period.	A full trial period (10 weeks for infliximab, 16 weeks for adalimumab and apremilast, 12 weeks for all others) is needed to determine whether the drug will produce an adequate response.
Subcutaneous drugs are administered in-clinic during the initiation period and by the patient themselves during the maintenance period.	Balance between assuming SQ drugs are always self-administered vs. always administered in clinic.

Key cost, quality of life, and clinical data sources

Feedback on the draft evidence report indicated that WAC is not representative of actual price paid in either public or private settings. To address this concern, we obtained data from SSR Health,[25] which combines data on net US dollar sales with information on unit sales to derive net pricing at the unit level across all payer types.[25] Data on the approved agents of interest are current through the third quarter of 2016. We estimated net prices for these agents by comparing the 4-quarter (i.e., 4Q2015 – 3Q2016) rolling averages of both net prices and WAC prices per unit to arrive at an average discount from WAC. We calculated averages at the drug class level and rounded these to the nearest 5%. Finally, we applied the drug class level average to the most current WAC price for

each medication to arrive at an estimated net price. Drug class level average discounts were as follows:

- TNF-α: 30%
- IL-17A: 40%
- Anti-IL 12/23: 15%
- Apremilast: 20%

For brodalumab, IL-17A agent currently under regulatory review, we estimated the launch price as the average of the WAC prices for the two other agents in this class, and then applied the 40% discount specific to IL-17A drugs. We used wholesale acquisition cost (WAC) in a scenario analysis.[26]

Utilities were obtained from an analysis of EQ-5D data in 3,231 patients enrolled in five RCTs evaluating secukinumab in moderate to severe psoriasis.[27] The EQ-5D is one of the most commonly used generic health status measurement, and has good validity and reliability in various health conditions, including psoriasis. The EQ-5D includes questions across five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D was measured alongside PASI in the secukinumab RCTs, and the relationship between PASI improvement and EQ-5D was evaluated to derive the estimates.

Short and long term drug discontinuation rates were estimated from long-term follow up studies for etanercept, adalimumab, infliximab, and ustekinumab, and were estimated based on class effect assumptions for the other drugs.

Incremental Costs per Outcomes Achieved: Results

Total costs, quality-adjusted life years, and life years for each therapy are shown in Table ES8. Additionally, we show the incremental cost-effectiveness ratio for each of the targeted therapies compared to non-targeted therapy. The base-case results indicate that treatment with targeted drugs, over a 10-year time frame that includes drug discontinuation, leads to QALY improvements ranging from 0.8 (apremilast) to 1.7 (ixekizumab, brodalumab).

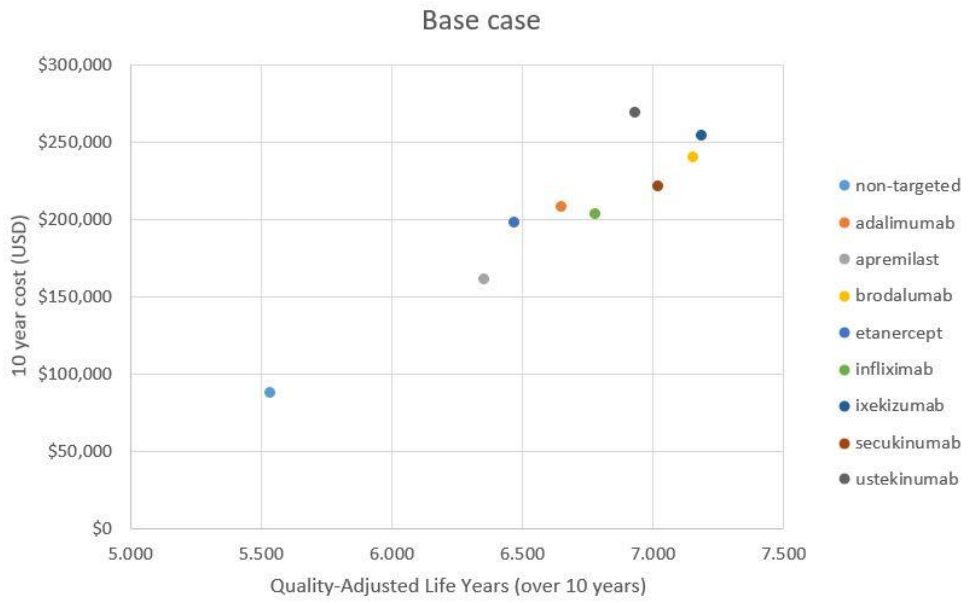
Table ES8. Results for the base case

	Cost	QALYs	LYs	ICER vs. non-target
non-targeted	$88,086	5.531	8.64	
adalimumab	$208,881	6.649	8.64	$108,040
apremilast	$161,741	6.353	8.64	$89,610
brodalumab*	$240,398	7.151	8.64	$94,030
etanercept	$198,519	6.469	8.64	$117,769
infliximab	$203,532	6.776	8.64	$92,715
ixekizumab	$254,287	7.187	8.64	$100,389
secukinumab	$221,704	7.018	8.64	$89,843
ustekinumab	$269,843	6.930	8.64	$129,904

*Results for brodalumab are tentative, as pricing is not currently available

The base-case results shown in Table ES8 are also graphed in Figure ES2. Drugs that are farther to the right provide the greatest clinical benefit, and drugs higher on the y-axis are more expensive. This chart shows a general trend towards better results with more expensive therapies. Secukinumab is the most cost-effective agent versus non-targeted therapy. However, estimated cost-effectiveness ratios for all the drugs fall into a relatively narrow range, with IL-17A targeted drugs generally providing more QALY gains than TNF-α agents, but at higher cost. Ustekinumab appears above the slope of the line formed by more cost-effective competitors, indicating that it is estimated to provide fewer QALYs at higher cost, primarily as a result of including higher dosing (90mg) for heavier patients receiving this drug.

Figure ES2: Cost-effectiveness plane for all comparators (base case)*



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

We also calculated incremental cost-effectiveness ratios for etanercept compared to the IL-17A targeted drugs (Table ES9). We selected these comparisons because etanercept was the only TNF-α agent for which we felt we had adequate evidence to distinguish its overall effectiveness (lower) compared to all IL-17A targeted drugs. In addition, as the least expensive biologic agent, our analysis will help inform policymakers as to whether the incremental cost of IL-17A targeted drugs over etanercept represents good long-term value. The incremental cost-effectiveness ratios versus etanercept ranged from approximately $42,000/QALY for secukinumab up to approximately $78,000 for ixekizumab.

Table ES9. Incremental cost-effectiveness ratios for IL-17A targeted drugs compared to etanercept

Cost/QALY	Versus Etanercept
Brodalumab	$61,396
Ixekizumab	$77,686
Secukinumab	$42,190

Sensitivity and Scenario Analyses

We conducted one-way analyses to determine the impact on the ultimate cost-effectiveness result of varying the range for different inputs (parameters) of the model. We found that cost-effectiveness results were most sensitive to variation in targeted drug costs and utility, the cost and utility of non-targeted therapy, and drug discontinuation rates. In particular, non-targeted therapy considerations are important given the lack of data on the performance of such therapy in a setting

where many patients have already failed prior use. However, comparisons to non-targeted therapy never exceeded $150,000 per QALY gained across the range of estimates for non-targeted therapy cost and utility. More detailed presentations of one-way sensitivity analyses, including tornado diagrams, are available in the full report.

We conducted a scenario analysis in which productivity cost offsets were included in our calculations, which led to cost-effectiveness ratios approximately $20,000 lower than in the base case. Analyses conducted using WAC (i.e., non-discounted) drug prices yielded cost-effectiveness ratios that ranged from $140,000 to $187,000 per QALY gained. Finally, conducting analyses using a lifetime time horizon or using a different set of utilities for PASI 100 had little impact on results compared to the base case.

Potential Budget Impacts: Results

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

Based on anticipated growth in the national economy, ICER has estimated a five-year annualized potential budget impact for each new drug that can serve as a threshold for triggering consideration of heightened policy actions to avoid negative consequences for patient access and overall health system budgets. For 2015-16, this threshold is calculated at $904 million per year for new drugs.

The candidate population for treatment with these agents in our analysis is adults with moderate-to-severe plaque psoriasis who are taking a biologic agent for psoriasis for the first time. To estimate the size of this population, we first determined the estimated incidence of psoriasis in the US. (We used incidence rather than prevalence because we were interested only in patients who were taking a biologic for the first time.) Psoriasis incidence in the United States has been estimated at 78.9 cases per 100,000 persons.[28] This incidence and the proportions of psoriasis patients with plaque psoriasis (79%)[28] and with moderate-to-severe disease (18.2%)[3] were applied to the projected 2016 U.S. population, resulting in an estimate of approximately 36,750 incident cases of moderate-severe plaque psoriasis in the US per year, or approximately 183,750 incident cases over five years. In this analysis, we assumed a 10% uptake pattern for ixekizumab and a 10% uptake for brodalumab in the eligible population.

Over the entire five-year time horizon, we estimate that “unmanaged” uptake would lead to approximately 18,375 persons taking brodalumab and 18,375 taking ixekizumab. Across the full

five-year time horizon, the weighted potential budgetary impact is approximately $65,200 per patient taking brodalumab, and approximately $72,400 per patient taking ixekizumab. Total potential budgetary impact of brodalumab over five years is approximately $1.2 billion, with an average budget impact per year of approximately $239.8 million. For ixekizumab, total potential budgetary impact over five years is approximately $1.3 billion, with an average budget impact per year of approximately $266 million. The annualized potential budget impact of brodalumab is 27% of the budget impact threshold of $904 million for a new drug, while the annualized potential budget impact of ixekizumab is 29% of the threshold.

Table ES10. Estimated Total Potential Budget Impact (BI) of Brodalumab and Ixekizumab for Treatment of Plaque Psoriasis

		Analytic Horizon = 1 Year			Analytic Horizon = 5 Years		
	Eligible Population	Number Treated	Annual BI per Patient*	Total BI (millions)	Number Treated	Weighted BI per **Patient***	Average BI per year (millions)
Brodalumab	183,750	3,675	$32,700	$120.3	18,375	$65,200	$239.8
Ixekizumab	183,750	3,675	$37,400	$137.3	18,375	$72,400	$266.0

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

Value-based Benchmark Prices

Our value-based benchmark prices for each psoriasis treatment are provided in Table ES11. As noted in the ICER methods document, the value-based benchmark price for a drug is defined as the price range that would achieve cost-effectiveness ratios between $100,000 and $150,000 per QALY gained.

As shown in the table, with the exception of adalimumab, apremilast, and infliximab, all drugs would require discounts from current WAC prices to fall within ICER's threshold value range of $100,000 to $150,000/QALY. Importantly, however, our estimates of net prices bring all the drugs of interest either within this threshold value range or generate cost-effectiveness ratios that are already <$100,000 per QALY gained.

Table ES11. Value-based price benchmarks for all psoriasis targeted treatment regimens

	Net price*	WAC*	Cost to achieve $100k/QALY	Cost to achieve $150K/QALY	Discount from WAC to reach WTP threshold

Adalimumab (40mg)	$1,433.98	$2,048.54	$1,311.40	$2,073.74	36% to +1% increase
Apremilast (30mg)	$34.48	$43.10	$42.94	$83.64	0.4% to +94% increase
Brodalumab (210mg)	$2,560.07**	$4,266.79**	$2,696.61	$3,840.28	10% to 37%
Etanercept (50mg)	$717.11	$1,024.44	$566.68	$989.98	3% to 45%
Infliximab (100mg)	$779.24	$1,113.27	$857.54	$1,395.18	23% to +25% increase
Ixekizumab (80mg)	$2,681.40	$4,469	$2,672.66	$3,795.25	15% to 40%
Secukinumab (300mg)	$2,438.74	$4,064.57	$2,680.73	$3,872	5% to 34%
Ustekinumab (45mg)	$7,514.19	$8,840.22	$5,886.50	$8,608.05	3% to 33%

*Net price or WAC per vial/pill

**Assumed net price/WAC

Comparative Value: Summary and Comment

There are three key findings from our analyses. First, all the targeted drugs had reasonably good value for money compared to non-targeted therapy, using our estimated, discounted drug costs. The value of targeted agents is driven primarily by their meaningful impact on patient quality of life, and secondarily by offsetting other costs of care such as clinic visits and use of non-targeted therapies. While there are multiple sources of uncertainty, primarily caused by data limitations, this finding is robust using our base-case drug prices.

Second, despite the somewhat similar cost-effectiveness ratios versus non-targeted therapy, there were important differences in the total amount of patient benefit (measured as QALYs) that could be gained for each drug. Drugs with high first-line efficacy and low discontinuation rates provide the greatest patient benefit, despite the availability of second-line therapy for those who failed first-line treatment. There are several reasons for this. First, not all patients who fail first-line therapy will continue to second-line therapy, and potential patient benefit is lost. Second, initiating second-line therapy incurs the added drug cost of another initiation period. Finally, although there is a paucity of data, it appears that second-line therapy may be slightly less effective than first-line treatment with the same drug.

Third, the newer IL-17A targeted agents provide good economic value in relation to etanercept and adalimumab, and potentially infliximab. The lower initial effectiveness of etanercept and

adalimumab, high long-term discontinuation rates, and the need for more expensive second-line therapy decrease their overall value despite lower initial drug cost.

We have attempted to model psoriasis treatment to both reflect clinical practice and accommodate the limits of available data. The latter necessity has placed some restrictions on how accurately we can model the course of psoriasis treatment. There are four major limitations of our analyses. First, the course and effects of therapy sequencing is not clear due to a lack of trials of targeted drugs in the second-line setting. We assumed that after first-line therapy, half of patients go to a second-line targeted therapy while half move to non-targeted therapy; we explored the effect of our assumptions on the results in sensitivity analyses. Second, we would have preferred direct utility elicitation data from clinical trials, rather than surmising quality of life from improvements in PASI score. Third, we utilized a novel source to estimate the general size of drug rebates at a drug class level, but there is uncertainty in the size of rebates for specific drugs within each class. Fourth, another major limitation of the analyses was uncertainty in the costs and quality of life effects of non-targeted therapy. We encourage decision makers to consider the uncertainty in results related to the cost and quality of life of non-targeted therapy, although findings of one-way sensitivity analyses suggest that cost-effectiveness of targeted versus non-targeted therapy remains below $150,000 per QALY across a range of assumptions.

In summary, our analyses suggest that if health care payers are able to achieve significant drug rebates, the most effective (and most expensive) targeted drugs provide the greatest benefit to psoriasis patients at a reasonable economic value.

New England Comparative Effectiveness Public Advisory Council Votes

The New England Comparative Effectiveness Public Advisory Council deliberated on key questions raised by ICER's report at a public meeting on November 18, 2016. The results of the votes are presented below.

1) Is the evidence adequate to demonstrate that the net health benefit of apremilast is as good as that provided by any of the TNFα inhibitors?

Yes: 0 votes	***No: 14 votes***

2) Is the evidence adequate to distinguish the net health benefit among the IL-17A targeted drugs secukinumab, ixekizumab, and brodalumab?

Yes: 0 votes	***No: 14 votes***

2a) Is the evidence adequate to demonstrate that the net health benefit of IL-17A drugs as a class is better than that provided by adalimumab?

Yes: 5 votes	***No: 9 votes***

2b) Is the evidence adequate to demonstrate that the net health benefit of IL-17A drugs as a class is better than that provided by etanercept?

Yes: 14 votes	No: 0 votes

2c) Is the evidence adequate to demonstrate that the net health benefit of IL-17A drugs as a class is better than that provided by infliximab?

Yes: 1 votes	***No: 13 votes***

3) Is the evidence adequate to demonstrate that the net health benefit of ustekinumab is better than that provided by adalimumab?

Yes: 1 votes	***No: 13 votes***

4) Is the evidence adequate to demonstrate that the net health benefit of ustekinumab is better than that provided by etanercept?

Yes: 14 votes	No: 0 votes

5) Is the evidence adequate to demonstrate that the net health benefit of ustekinumab is better than that provided by infliximab?

Yes: 0 votes	***No: 14 votes***

Care Value Voting Results

6) Given the available evidence on comparative effectiveness and incremental cost-effectiveness using estimated discounted prices for private insurers presented in the report, and taking into

account other benefits, disadvantages, and contextual considerations, what is the long-term value for money of the following drugs compared to continued non-targeted therapy?

Adalimumab:

Low: 0 votes	***Intermediate: 11 votes***	High: 3 votes

Etanercept:

Low: 2 votes	***Intermediate: 11 votes***	High: 1 votes

Infliximab:

Low: 3 votes	***Intermediate: 9 votes***	High: 2 votes

Ustekinumab:

Low: 3 votes	***Intermediate: 9 votes***	High: 2 votes

Secukinumab:

Low: 0 votes	Intermediate: 3 votes	***High: 11 votes***

Ixekizumab:

Low: 0 votes	Intermediate: 6 votes	***High: 8 votes***

Brodalumab:

No comparative value vote was taken on brodalumab, as its anticipated approval by the FDA was delayed beyond the timeline of this review and thus no list price was available for consideration.

Apremilast:

Low: 0 votes	*Intermediate: 7 votes*	*High: 7 votes*

7) Given the available evidence on comparative clinical effectiveness and incremental cost-effectiveness, and taking into account other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with ixekizumab and secukinumab versus etanercept?

Low: 0 votes	Intermediate: 1 votes	***High: 13 votes***

Key Policy Implications

The New England CEPAC engaged in a moderated discussion about how best to apply evidence on targeted immunomodulators for plaque psoriasis in policy and practice. The roundtable included two clinical experts, two patient representatives, and two payer representatives. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. Below are the top-line policy implications; for more information please see the full report.

Specialty Societies and Patient Advocacy Groups

- Update outdated treatment guidelines for patients with moderate-to-severe chronic plaque psoriasis in a form that is easy to understand and easy-to-use by payers, clinicians, and patients.

Purchasers and Insurers

- Consider limiting or abolishing "step therapy" approaches to coverage.
    - Step-therapy can be appropriate for treating certain conditions, but given that all of the targeted immunomodulators have good value relative to non-targeted treatment, payers should strongly consider eliminating most step therapy requirements for patients with moderate-to-severe psoriasis. Any step therapy requiring initial use of TNFα inhibitors before other drugs should be reconsidered to allow rapid and permanent exceptions for patients with co-conditions, co-morbidities, or specific life requirements that make other drugs the best first choice among all available targeted immunomodulators.

- If step therapy will be used:
    - Allow individuals switching insurers to bypass step therapy if they are already on an effective treatment.
    - Remove requirements for patients to have higher out-of-pocket expenses for "later step" treatments.

- As alternative mechanisms to manage costs, consider developing indication-specific formulary designs and outcome-based payment contracts.
- Co-payment and/or co-insurance for therapies should be based on prices net of discounts and rebates instead of list price.

Manufacturers

- Foster transparency in the rationale for price increases.
- Release treatment-specific quality-of-life data.

Researchers and Manufacturers

- Conduct research that directly compares real-world treatment options and sequential treatment effectiveness for both naïve and treatment-experienced patients.
- Generate additional information on the treatment durability of IL-17A agents.

Patient Advocacy Groups, Clinicians, and Researchers

- Patients and patient organizations should take a leadership role in the design of clinical trials and all stakeholders should advocate for rigorous study in diverse populations evaluating real-world comparative treatments.
- Lead research efforts to evaluate heritability of psoriasis and the impact of managing plaque psoriasis on caregivers and families.

1. Background

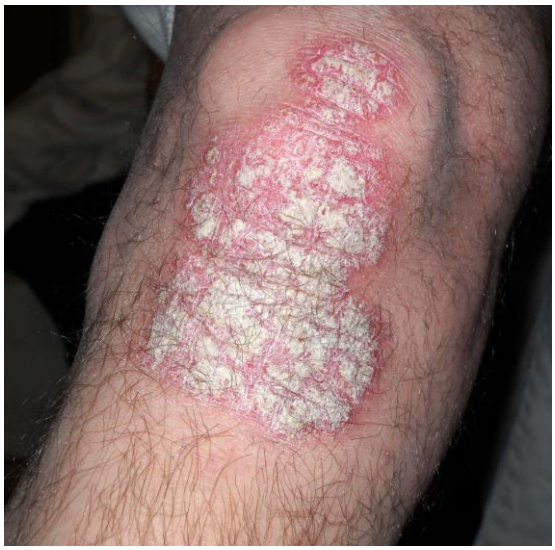
1.1 Introduction

Background

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

Chronic plaque psoriasis accounts for about 80% to 90% of all patients with psoriasis.[28-30] Plaque psoriasis is one of the cutaneous psoriasis types; others include guttate psoriasis, pustular psoriasis, inverse psoriasis, nail psoriasis, and erythrodermic psoriasis. Psoriasis is associated with systemic diseases including other autoimmune diseases (e.g., inflammatory bowel disease), metabolic syndrome, and cardiovascular disease.[31] In addition, up to 30% of patients with plaque psoriasis have at least some manifestations of psoriatic arthritis.[4,5] Symptoms of psoriatic arthritis include inflammation in multiple small or large joints, involvement of the distal joints in the hand, as well as inflammation of tendons, tendon insertions, and fingers.

Figure 1. Typical psoriatic plaque on the knee



Plaque psoriasis significantly decreases health-related quality of life, particularly if lesions are in areas that can affect daily functioning (e.g., the hands or soles of the feet) or social functioning (e.g., the face).[7-9] Psoriasis itself is not a direct cause of increased mortality, but patients with severe psoriasis have increased mortality due to cardiovascular disease and infection.[6]

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

The direct medical costs of psoriasis 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.[32]

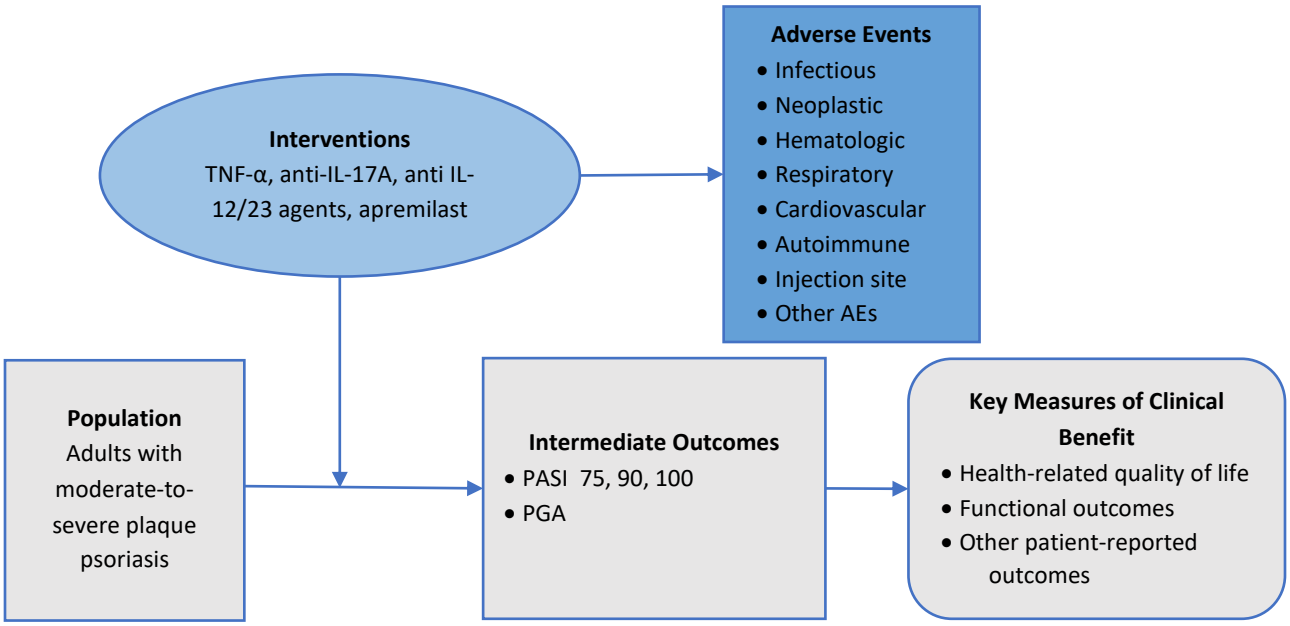
Scope of the Assessment

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

Analytic Framework

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

Figure 2. Analytic Framework:



Population

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

Interventions

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

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

Comparators

Wherever possible, we evaluated head-to-head trials of these interventions. Other comparators included placebo or other active treatments not listed above. Use of other treatments was prohibited in the interest of directly evaluating the comparative effectiveness of targeted immunomodulators to placebo or to one another.

Outcomes

This review examined key clinical outcomes, including outcomes common to plaque psoriasis trials. Discussions with patients, patient groups, clinicians, and industry, as well as publications from academic research groups, indicated that people with psoriasis have symptoms and burdens that are not well-captured by standard trial outcomes.[8,33] Standard trial outcomes are generally not used or feasible to employ in actual clinical practice. We examined available data for evidence about the comparative effectiveness of targeted immunomodulators in affecting outcomes such as itch, scaling, pain, quality-of-life, and work productivity. Outcomes for which we were able to find evidence included:

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

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

Timing

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

Settings

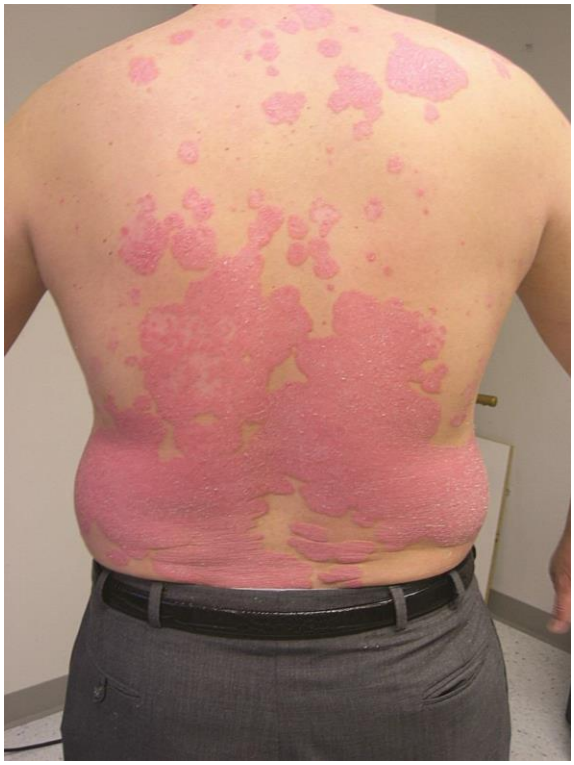
Plaque psoriasis is generally treated in outpatient and/or clinic settings, which was the focus of our review.

2. The Topic in Context

2.1 Overview

Roughly 70% to 80% of patients with plaque psoriasis have mild disease that can be adequately managed with topical therapy. Definitions of "moderate-to-severe" plaque psoriasis vary, but generally consist of psoriasis that affects at least 5% to 10% of a 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).[12,13] Moderate-to-severe plaque psoriasis is generally treated with systemic therapies.

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



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

2.2 Treatments

Treatments for psoriasis can be grouped within 4 broad categories:

1. Topical therapies such as steroids, vitamin D analogs, retinoids, and calcineurin inhibitors;
2. Older systemic therapies, such as acitretin, cyclosporine, and methotrexate;
3. Phototherapy, most commonly ultraviolet B light (UVB); and
4. "Targeted immunomodulators" including biologics and apremilast

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

Older Systemic Therapy includes methotrexate, cyclosporine, and acitretin.

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

Phototherapy includes sun exposure, broadband ultraviolet B (UVB), narrowband UVB, and psoralen with ultraviolet A (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 that have been approved, or are nearing approval, for the treatment of moderate-to-severe plaque psoriasis in the United States consist of medications with activity against the following targets:

Table 1. Targeted immunomodulators for Plaque Psoriasis

Brand name	Generic name	FDA Approval Date for Plaque Psoriasis
TNF-α		
Enbrel®	etanercept	Apr-04
Remicade®	infliximab	Sep-06
Humira®	adalimumab	Jan-08
IL-12/23		
Stelara®	ustekinumab	Sep-09
IL-17A		
Cosentyx ®	secukinumab	Jan-15
Taltz®	ixekizumab	Mar-16
Siliq™	brodalumab*	*Not yet approved*
Phosphodiesterase (PDE)-4		
Otezla®**	apremilast	Sep-14

*Investigational

**Although not technically a biologic, apremilast is a novel, targeted, oral agent also approved for treatment of patients with moderate-to-severe plaque psoriasis.

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

Interventions of Interest

Dosing information for each intervention of interest is provided in Table 2. As the earliest targeted therapies, TNF-α therapy still holds the majority (~60%) of the market share in plaque psoriasis.[34] An exception to this is infliximab, which is rarely used because of its route of administration (infusion) as well as relatively high rates of discontinuation due to certain adverse effects as well as development of neutralizing antibodies (see "Harms" in Section 4.3 for further details). TNF-α share is eroding somewhat, however, based on the introduction of apremilast and the newer classes of biologic immunomodulators.

Table 2. Targeted Immunomodulator Dosing for Moderate-to-Severe Plaque Psoriasis

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

*Not yet FDA-approved. Although the original PDUFA date was scheduled for November 16, 2016, the FDA's review of brodalumab has been postponed to February 16, 2017 due to requirements for additional time to develop a Risk Evaluation and Mitigation Strategy (REMS).[14]

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

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

For the anti IL-17A agents, concerns have included infections and reactivation of latent TB, inflammatory bowel disease, and hypersensitivity reactions for secukinumab; infections, reactivation of TB, hypersensitivity reactions, neutropenia, candidal infection, and inflammatory bowel disease for ixekizumab (approved in March 2016); and candidal infections, neutropenia, and an increased risk of suicide for brodalumab (not yet approved although the FDA Dermatologic and Opthalmic Drugs Advisory Committee recommended its approval in July 2016). As noted in Table 2, the FDA delayed the decision date for brodalumab from November 2016 to February 2017 pending finalization of a Risk Evaluation and Mitigation Strategy (REMS).[14]

Ustekinumab, an IL-12/23 Agent, has been associated with skin cancer, severe infections, and concerns for lymphoma. Although there has also been concern for an increased risk of major cardiovascular events, several observational studies have not confirmed an effect.[22,35] Anti-ustekinumab antibodies occur in a few patients and are of unclear clinical significance.

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

2.3. Other Aspects of Treatment

Non-Standard Dosing: Many psoriatic drugs appear to have waning effectiveness with continued use. To maintain effectiveness physicians often prescribe increasing doses of psoriatic treatments. Occasionally physicians prescribe *lower* doses of effective medications 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%;[36] dose reductions of 49%, 54%, and 37%; and discontinuation rates of 15%, 10%, and 5%, respectively. Within the same 12 months, many patients discontinued, restarted, and switched biologic treatments. In an examination of infliximab use, 26% of treatment series involved use of a greater-than-initially-recommended dose.[37]

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.[38]

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

Emerging Therapies: Biologic "biosimilar" medications are becoming available, including recently-approved biosimilars like Amjevita® (Amgen), Erelzi® (Sandoz, Inc.), and Inflectra® (Pfizer/Celltrion, Inc.). The equivalence of the etanercept biosimilar for moderate-to-severe plaque psoriasis has been reported in a single conference abstract.[15] Briakinumab is an additional anti-IL 12/23 that has been evaluated, but it is unclear if it will come to market. Tofacitinib, a small molecule treatment already approved for the treatment of rheumatoid arthritis, has been shown to be effective for moderate-to-severe plaque psoriasis in randomized controlled trials.[16] Baricitinib, a small molecule being investigated for possible use in psoriasis, has been evaluated in a phase IIIb trial but to date has not been submitted to the FDA. Finally, a Biologics License Application (BLA) was submitted to the FDA in November 2016 for guselkumab, an IL-23, and currently has three ongoing Phase III clinical trials.[17]

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 might provide enhanced effectiveness. Combination therapy seems likely to be discussed in a forthcoming guideline from the American Academy of Dermatology and the National Psoriasis Foundation.

2.4 Insights Gained from Discussions with Patients and Patient Groups

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

Certain aspects of research into psoriasis are not patient-centered. Many of the tools developed to measure outcomes were not developed with patients in mind, and psoriasis-specific patient-centered outcome measures are limited (although the Psoriasis Symptom Inventory (PSI) and the

Psoriasis Disability Index (PDI) are being used; see below). For example, PASI is cumbersome and is not generally used in clinical practice and the DLQI is not psoriasis-specific. Patients at a recent FDA meeting rated flaking/scaling and itching as a having a more significant impact on their quality of life than the rash itself. Simple body surface area (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, may have on an individual's quality of life. Patients also pointed out that average treatment responses described in clinical trials may not capture individual patient variability.

Up to half of patients are dissatisfied with their psoriasis treatment.[8,18] 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.[8] 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, more frequent non-treatment, and are less likely to be included in clinical trials.

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

Plaque psoriasis has both psychological and emotional effects. The psychological impact of severe psoriasis is comparable to that of diabetes or depression.[39] Psoriasis is associated with a higher likelihood of having depression, anxiety, and suicidal ideation.[10,11] 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,[18] and one of the main reasons is the cost of therapy. Patients are frustrated that they are being forced to start treatment with less efficacious medications due to insurance requirements for "step therapy" that mandates use of "preferred medications" first. In addition, switching insurance 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, non-psoriasis conditions, like rheumatoid arthritis, which is a listed indication for many of the drugs of interest for this review.

2.5 Definitions

Psoriasis Area and Severity Index (PASI)

The PASI is a measure of the percent body surface area with psoriatic lesions in each of 4 regions (head, trunk, arms, and legs) as well as the degree of erythema, induration, and scale of the lesions in each area. PASI scores 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)

The *Static Physician Global Assessment (sPGA)* is scored by the treating or evaluating physician and only considers the time of evaluation. Scores range from 0 to 7 with higher scores indicating worse severity. A good response in clinical trials in treatment generally requires sPGA scores of 0 ("clear") or 1 ("almost clear"). The Dynamic Physician Global Assessment (dPGA), also scored from 0 to 7, 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.

Investigator's Global Assessment (IGA)

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

Dermatology Life Quality Index (DLQI)

The DLQI is ten questions relating to symptoms, feelings, daily activities, leisure, work, school, social interactions, clothing choice, sexual difficulties, and treatment problems. DLQI scores range from 0 to 30 with lower scores 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).

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

EuroQol Five Dimensions (EQ-5D)

The EQ-5D is a standardized, self-reported questionnaire for evaluating a patient's health status across disease states, and is based on five dimensions: self-care, pain/discomfort, anxiety/depression, mobility, and usual care activities. It is often used to compute a quality-adjusted life year.

Short Form-36 (SF-36)

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

Psoriasis Disability Index (PDI)

The Psoriasis Disability Index assesses is a 15-question instrument that assesses five domains of health-related quality of life: daily activities; work or school performance; personal relationships; leisure; and treatment.[40] 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, and can also be used to assess the skin pain associated with scaly plaques in psoriatic patients, which can have a serious impact on quality of life. This modified version of the VAS is based on a score of 0 (no skin pain) to 100 (severe skin pain).

Visual Analog Scale (VAS)-itch

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

Psoriasis Symptom Inventory (PSI)

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

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.

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 6 questions about current employment and, in the past 7 days, hours missed due to health problems, hours missed for other reasons, hours worked, productivity impairment at work ("presenteeism"), and productivity impairment in 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.[41]

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.

3. Summary of Coverage Policies and Clinical Guidelines

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

All public and private carriers in New England manage utilization of the seven approved medications under review through tiering, step therapy and excluding drugs from coverage (see Table 3). In nearly every plan, systemic therapies (such as phototherapy or methotrexate) are on the lowest tier or are considered the first-line of therapy before treatment with biologics or apremilast. Etanercept and adalimumab are most often the preferred second-line treatment and are commonly placed on lower tiers than other therapies in this review. Carriers often have discounting arrangements for etanercept and adalimumab that are driven by other conditions, most commonly rheumatoid arthritis.

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

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

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

Clinical Guidelines

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

The most recent clinical guidelines from the American Academy of Dermatology (AAD) were published in 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.

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

In 2012, the National Psoriasis Foundation reviewed the Canadian Guidelines for the Management of Plaque Psoriasis.[42] In their review, they recognized adalimumab, etanercept and ustekinumab as first-line systemic treatments for plaque psoriasis. They recognize infliximab as a second or third line treatment for plaque psoriasis. They did not prioritize among the then available targeted immunomodulators. No other drugs were reviewed at the time of the report.

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

The UK National Institute for Health and Care Excellence (NICE) reviewed therapies and offered guidance for treatment. The most recent review was in 2014. 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 etanercept or adalimumab for patients with a PASI >10. NICE also recommends secukinumab if a discount is available and ustekinumab at the higher dose only if provided at the same cost as for the lower dose. Infliximab is recommended after failure of first-line treatment for those patients with a PASI >20 ("very severe psoriasis"). In October 2016, NICE released a new determination recommending apremilast for severe disease if apremilast is provided at a discount. NICE recommends switching therapies after treatment failure of infliximab after 10 weeks; etanercept and secukinumab after 12 weeks; and adalimumab, ustekinumab, and apremilast after 16 weeks.

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

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

An expert panel nominated by the European Dermatology Forum, the European Association for Dermatology and Venereology (EADV) and the International Psoriasis Council (IPC) stated that all treatments should be preceded by objective assessment of disease and health-related quality of life (HRQL). They stated that older treatments have many unwanted side effects and toxicity, but should be first-line systemic therapy. If phototherapy and older systemic agents are ineffective, contraindicated, or not tolerated, they recommended treatment with TNF-α inhibitors. Ustekinumab was recommended as "second-line therapy," but there was "no strong consensus" as to where in the ordering of therapy, relative to TNF-α inhibitors, ustekinumab should fall. Secukinumab, apremilast, and brodalumab were not included in the review.

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

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

Table 3. Representative Private Payer Policies for Plaque Psoriasis in New England

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

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

4. Comparative Clinical Effectiveness

4.1 Overview

To inform our analysis of the comparative clinical effectiveness of targeted immunomodulators for moderate-to-severe chronic plaque psoriasis, we abstracted evidence from available clinical studies, whether in published, unpublished, or abstract form. The drugs and regimens of interest are included in Table 2.

As described in the Background section, we included evidence from placebo-controlled trials, but focused on evidence about the comparative clinical effectiveness of these treatments compared to each other. 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)

4.2 Methods

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

comparisons, but these comparisons are not discussed in detail. Finally, we did not include studies that evaluated targeted immunomodulators as part of combination treatment.

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

We also looked for studies evaluating biosimilar forms of the TNF-α agents. No peer-reviewed data were available, but a brief description of etanercept, infliximab, and adalimumab biosimilars is included in the Emerging Therapies section of this report.

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

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.[43] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[44] The PRISMA guidelines include a checklist of 27 items, further details of which is available in Appendix Table A1.

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

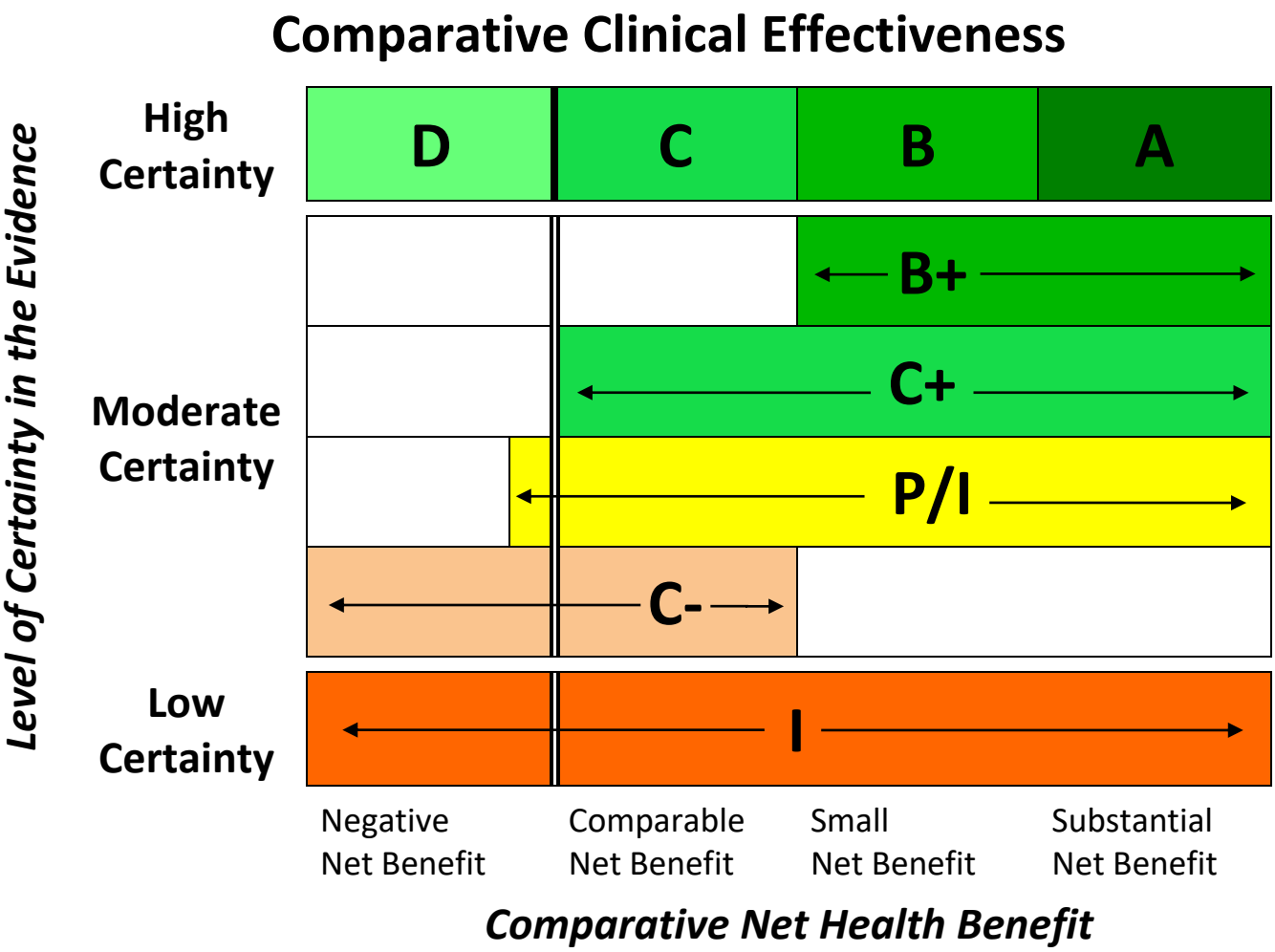
data very recently presented during the European Academy of Dermatology and Venereology (EADV) conference in Vienna, Austria from September 28-October 2, 2016. Further details on the search algorithms, methods for study selection, data extraction, quality assessment, assessment for publication bias, and our approach to meta-analyses of the data are available in Appendix A. We included several articles published after our initial search date if the data appeared to inform this report.

Assessment of Level of Certainty in Evidence

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

The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
The level of **certainty** in the best point estimate of net health benefit.[45]

Figure 4. ICER Evidence Rating Matrix



A = "Superior" *- High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" *- High certainty of a small net health benefit*
C = "Comparable"*- High certainty of a comparable net health benefit*
D = "Negative"*- High certainty of an inferior net health benefit*
B+ = "Incremental or Better" *- Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Better" *- Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit*
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*

4.3 Results

Study Selection

Our literature search identified 1,392 potentially relevant references. Key comparative studies of the TNF-α agents were gathered and cross-checked from six recent high-quality systematic reviews.[27,46-50] A total of 80 references met our inclusion criteria; these citations related to 42 publications and 27 abstracts/conference presentations relating to 36 individual RCTs, as well as 11 observational studies. Primary reasons for study exclusion included use of regimens not approved by the FDA, study population 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 4.

Quality of Individual Studies

We rated all 36 trials, of which 34 were Phase III, to be of good or fair quality using criteria from U.S. Preventive Services Task Force (USPSTF).[51] Trials of good quality had study arms that were comparable at baseline, the authors used valid instruments to evaluate outcomes, and no differential attrition was observed. Fair quality studies typically used modified intention-to-treat (mITT) as the primary method of analysis. Of the 11 observational studies, five were judged to be good, three fair, and three poor quality. We did not assign a quality rating to references that were obtained from the grey literature.

Key Studies

Of the 36 individual RCTs, we identified 29 key clinical studies evaluating at least one of the eight therapies of interest for this review. Two of the remaining studies were Phase II, and five were conducted exclusively in Asia which are discussed separately in the subgroups section of this report. Eight studies included head-to-head trials of the drugs of interest for this review (etanercept vs. ustekinumab [ACCEPT], secukinumab [FIXTURE], and ixekizumab [UNCOVER 2 and 3]; and ustekinumab vs. brodalumab [AMAGINE 2 and 3], secukinumab [CLEAR], and ixekizumab [IXORA-S]). Three of these studies (ACCEPT, CLEAR, and IXORA-S) did not include a placebo arm. We also included a Phase IIIb trial, LIBERATE, which compared apremilast to placebo and a maintenance dose of etanercept to placebo that has not yet been published but was available in the grey literature (results from this trial are presented for the apremilast and placebo comparisons only). We also included five studies which evaluated one of the drugs of interest to another active comparator (1 of methotrexate vs. adalimumab, 2 of briakinumab vs. etanercept, and 1 of

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

All the key studies were multicenter, double-blind, Phase III RCTs, though some removed blinding following the induction period for each drug. Many trials 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. 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, ≥6 months of plaque psoriasis diagnosis, and candidates for phototherapy or systemic therapy despite prior treatment with topicals, older systemic treatments, phototherapy, or other targeted immunomodulators) and were comparable with respect to age (range of means: 41-46 years, median: 45) and duration of psoriasis (range of means: 14-21 years, median: 19). Baseline PASI scores varied substantially across trials (range of means: 16-33, median: 23). Given potential other between-trial heterogeneity, we conducted a sensitivity analysis in our network meta-analysis adjusting for baseline variations; the details and results of this analysis are discussed in Appendix F.

Subgroups

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

Asian Studies: As previously mentioned, we separately considered five trials that were conducted exclusively in Asia (i.e., Japan, Korea, China, and Taiwan), plus a subgroup analysis of the ERASURE study. These trials were generally smaller (with the exception of LOTUS, n=322)[52] with patients who were slightly younger (range of means: 40-50 years) had a briefer duration of psoriasis (range of means: 13-16 years), and lower BMI than the other trials. 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. Fewer patients were biologic-experienced in the studies of the older TNF-α drugs relative to the newer therapies. Across all studies, an average of 20% (range of means: 0% to 51%) of patients received prior biologic therapy. Patients who previously used biologic therapy might be less likely to respond to a subsequent targeted immunomodulator.

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

15% to 34%) had 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 4. Key Studies

Drug	Trials	Total # of patients	Induction period (weeks)	PASI, (mean)	Age (years)	Psoriasis duration (years)	Previous biologics (%)	PsA (%)
Adalimumab	REVEAL CHAMPION	1,483	16	22	43	19	6	24
Etanercept	Papp, 2005 Leonardi, 2003 Tyring, 2006 Strober, 2011 Gottlieb, 2011 Bagel, 2012 Bachelez, 2015	3,775	12	20	44	17	6	25
Infliximab	EXPRESS I EXPRESS II	1,213	10	21	44	19	10	30
Ustekinumab	ACCEPT PHOENIX 1 PHOENIX 2	2,899	12	20	45	20	33	29
Secukinumab	FEATURE CLEAR† JUNCTURE ERASURE FIXTURE	3,079	12	28	45	18	25	20
Ixekizumab	UNCOVER 1 UNCOVER 2 UNCOVER 3 IXORA-S*	3,866	12	24	46	19	27	NR
Brodalumab	AMAGINE 1 AMAGINE 2 AMAGINE 3	4,373	12	23	45	19	33	22
Apremilast	ESTEEM 1 ESTEEM 2 LIBERATE*	1,505	16	19	46	19	31	NR

*Only available in the grey literature. †The primary outcome for the CLEAR study was week 16, but to be consistent with the other secukinumab trials we considered the primary outcome to be 12 weeks.

Clinical Benefits

The primary outcome of all trials was the proportion of patients achieving PASI 75 at the end of the induction period. The duration of the induction period varied by agent: week 10 for infliximab; week 12 for ixekizumab, secukinumab, ustekinumab, and etanercept; and week 16 for adalimumab and apremilast. Other clinical outcomes included the proportion of patients meeting additional PASI thresholds (e.g., 50, 90, 100), or achieving a score of 0 or 1 ("cleared or minimal") on the Physician Global Assessment (PGA) or Investigator's Global Assessment (IGA), although these were less consistently reported. Patient-reported outcomes, including quality of life, were primarily based on mean change or proportion of patients achieving a score of 0 or 1 on the DLQI (indicating very little to no disease effect on quality of life); other quality of life instruments, such as the SF-36, were less commonly used. Measures of symptom control, such as VAS scales for itch or skin pain, as well as a recently validated tool for assessing symptom control in psoriasis patients (Psoriasis Symptom Inventory [PSI]), were infrequently employed.

All data are reported based on the FDA-approved or proposed dosing at the end of the induction period for each drug with the two exceptions. First, for secukinumab, while the drug label indicates that 150mg may be appropriate for some patients, we only describe outcomes for the 300mg dose. 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. The labeling was instead based on a pooled analysis of PHOENIX 1 and 2 which found that patients weighing more than 100kg achieved a better response with the 90mg, while those weighing less than 100kg had similar efficacy with either the 45mg and 90mg doses.[53]

In addition, although the LIBERATE trial included the approved dose of apremilast, patients in the etanercept arm received a maintenance dose (i.e., 50 mg once weekly); the study was also not statistically powered to detect differences between the agents. As such, the PASI outcomes from the etanercept arm were not included in the NMA, and only comparison of apremilast to placebo are described in the sections that follow.

Psoriasis Area Severity Index (PASI)

PASI 75

All targeted immunomodulators showed statistically-significantly higher PASI 75 response rates in comparison to placebo at the end of induction (10 to 16 weeks, depending on agent). In direct comparative trials, ustekinumab, secukinumab, and ixekizumab were superior to etanercept; secukinumab, ixekizumab, and brodalumab were superior to ustekinumab.

All immunomodulators showed a statistically significantly higher absolute percentage of PASI 75 responders compared to placebo. The range of PASI 75 responses in the intervention and placebo groups across trials is shown in Table 5. In individual placebo-controlled RCTs, the incremental proportion of patients achieving PASI 75 above placebo within trials was 62% to 64% for adalimumab (2 trials);[54,55] 33% to 54% for etanercept (7 trials);[56-62] 74% to 77% for infliximab (2 trials);[63,64] 80-88% for ixekizumab (3 trials);[65-67] 63%-64% for ustekinumab 45 mg (2 trials);[68,69] 63% to 72% for ustekinumab 90 mg (2 trials);[68,69] 72% to 84% for secukinumab at 12 weeks (4 trials);[21,70,71] 78% to 80% for brodalumab (3 trials);[19,72] and 13% to 18% for apremilast (2 trials).[73,74]) Additionally, a newly approved biosimilar to etanercept, Erelzi, had a PASI 75 response very similar to etanercept (73.4% with Erelzi vs. 75% with etanercept).[15] Because this study is currently only available in the grey literature, it is unclear why response rates were higher than in other clinical trials of etanercept.

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

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

We identified nine head-to-head RCTs, all, but one of which showed statistically-significant differences between treatments in PASI 75 response (Table 6). In four trials, three agents were superior to etanercept: ustekinumab (57% vs. 68% and 74% for ustekinumab 45 mg and 90 mg, respectively);[75] secukinumab 300 mg (44% vs. 77%);[21] and ixekizumab (42% vs. 90% in UNCOVER 2[76] and 53% vs. 87% in UNCOVER 3).[67] In four trials, two agents were superior to ustekinumab:

secukinumab (79% vs. 91% for secukinumab 300 mg at 12 weeks; 83% vs. 93% at 16 weeks),[77] ixekizumab (69% vs. 91% in IXORA-S),[78] and brodalumab (70% vs. 86% in AMAGINE 2 and 69% vs. 85% in AMAGINE 3).[19] Note that the IXORA-S study is currently only available in abstract form, and so was not included in our network meta-analysis or economic model (see below).

In a recently published report of 52-week data from the CLEAR study the rate of achieving PASI 75 for secukinumab and ustekinumab was 93% vs. 80%, respectively.[20,79]

Table 6. Comparative Trials: PASI Responses

Trial	Treatment	PASI 75	PASI 90	PASI 100
ACCEPT	Etanercept	57	23	NR
	Ustekinumab 45 mg	68	36	NR
	Ustekinumab 90 mg	74	45	NR
FIXTURE	Etanercept	44	21	4
	Secukinumab 300 mg	77	54	24
UNCOVER 2&3	Etanercept	42-53	19-26	5-7
	Ixekizumab	87-90	68-70	38-41
CLEAR	Ustekinumab WBD	79	53	26
	Secukinumab 300 mg	91	73	39
AMAGINE 2&3	Ustekinumab WBD	69-70	47-48	19-22
	Brodalumab 210 mg	85-86	69-70	37-44
IXORA-S*	Ixekizumab	91	75	37
	Ustekinumab	69	42	15

*Only available in the grey literature as of October 10, 2016. Not included in the NMA or economic model (see evidence summary).

WBD = weight-based dosing

An additional three observational studies directly comparing TNFα agents either reported non-significant findings [80] or did not conduct statistical tests on PASI 75 between groups.[81,82]

Network Meta-Analysis of PASI 75 Results

Given the paucity of head-to-head data comparing treatments, we performed indirect comparisons of PASI response using Bayesian network meta-analyses (NMAs). NMA was felt to be appropriate, as the populations of the individual trials were sufficiently similar. Detailed descriptions of methods and results can be found in Appendix F. Briefly, we used a random-effects approach. For the primary analysis, we also adjusted for the placebo response rate in each study which, to some degree, accounts 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 network meta-analysis showed that all immunomodulators had a statistically significantly higher efficacy on PASI 75 than placebo. In head-to-head comparisons, ixekizumab had the highest relative effectiveness [measured as relative risk (RR)] of achieving initial PASI 75 response during induction, followed by brodalumab, infliximab, secukinumab 300 mg, and ustekinumab 45/90 mg, and other TNFα agents (in the order of adalimumab, etanercept, and Erelzi). Apremilast had the lowest RR. (see Table 7 and Appendix F5)

Table 7. Base case NMA: league table of PASI 75 response

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

Other PASI Thresholds

Results for other PASI thresholds were generally consistent with results for the PASI 75. All target immunomodulators showed statistically significantly higher PASI 50, 90, and 100 rates than placebo (except that no published PASI 50 results were found for ixekizumab). In direct comparative trials, ustekinumab, secukinumab, and ixekizumab were superior to etanercept for PASI 90 and 100. Secukinumab and brodalumab were superior to ustekinumab in PASI 90 and 100.

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

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

In addition, the recently reported 52-week results of a comparison of secukinumab and ustekinumab reported results for PASI 90 (76% vs. 61%; $p < .0001$) and PASI 100 (46% vs. 36%, respectively; $p = .01$).[83]

The direct comparative trials did not report PASI 50. However, we did identify two observational studies that compared PASI 50 response between treatments. One of them was a prospective, multi-center study in 162 patients (mean age 47, 68% male, mean duration of psoriasis 18 years, mean PASI 17.5) who received either infliximab or ustekinumab that found no statistically significant between-group difference in PASI 50 at seven months (96% vs. 82%).[80] The other was a retrospective analysis in 89 elderly patients (mean age 70, 55% male, mean duration of psoriasis 28 years, mean PASI 11) treated with etanercept or adalimumab, finding that adalimumab had higher response rates at 12 weeks (86% vs. 82%) but lower at 24 weeks (82% vs. 90%), one year (79% vs. 90%), two years (82% vs. 92%), and three years (82% vs. 92%). However, the statistical significance of these differences was not tested.[82]

Our network meta-analysis showed that all targeted immunomodulators were statistically significantly better than placebo on PASI 50. The effect sizes were similar among treatments, with RR ranging from 3.4 to 6.9. Pair-wise comparisons showed no difference between treatments (see Appendix F). Similarly, all immunomodulators had a statistically significantly higher efficacy on PASI 90 and 100. In head-to-head comparisons for initial PASI 90 and PASI 100, infliximab had the highest initial RR, followed by anti-interleukin agents (in the order of brodalumab, ixekizumab, secukinumab 300 mg, ustekinumab 45/90 mg combined), and other TNFα agents (in the order of adalimumab, etanercept, and Erelzi). Apremilast had the lowest RR (Appendix F).

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 75 results. All immunomodulators showed statistically significantly higher proportions of patients with Physician Global Assessment (PGA) or Investigator's Global Assessment (IGA) of 'clear/almost clear' than placebo at the primary end point of each trial. In head-to-head trials, 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 trials, the ranges of PGA/IGA response rates were 1% to 18% for placebo, 60% to 73% for adalimumab,[54,55] 40% to 66% for etanercept,[56,57,59-62] 76% to 83% for infliximab,[63,64] 60% to 74% for ustekinumab,[68,69] 65% to 74% for secukinumab,[21,70,71] 76-85% for brodalumab,[19,72] and 20% to 22% for apremilast.[73,74]

Eight of nine head-to-head RCTs reported PGA response. All found statistically significant differences between treatments. The pattern response rates and differences between treatments were similar to those of PASI 75 response. In four trials, three agents had a higher proportion of patients achieve PGA scores of 0/1 than etanercept: ustekinumab (49% vs. 65% and 71% for ustekinumab 45 mg and 90 mg, respectively);[75] secukinumab (27% vs. 63%);[21] and ixekizumab (36% vs. 83% in UNCOVER 2[76] and 42% vs. 81% in UNCOVER 3;[67] both $p<0.0001$). In four trials, three agents had a significantly higher proportion of patients with PGA scores of 0/1 than ustekinumab: secukinumab (65% vs. 81% at 12 weeks; 68% vs. 83% at 16 weeks),[77] ixekizumab (18% vs. 43% for sPGA score of 0),[78] and brodalumab (61% vs. 79% in AMAGINE 2 and 69% vs. 85% in AMAGINE3[19]).

Recently reported 52-week results of the CLEAR trial showed that secukinumab had a higher proportion of subjects with IGA scores of 0/1 than ustekinumab (80% vs. 65%; $p < .0001$).[20]

Two observational studies, adjusted for clinical and sociodemographic factors, compared PGA among drugs. One cross-sectional study in the U.S. with a sample size of 713 (mean age 49, 51% male, mean duration of psoriasis 19 years) showed that adalimumab had better adjusted PGA

response compared to etanercept and ustekinumab (48% vs. 34% and 36%, p<0.001[84]). The PSOLAR registry (N=2076, mean age 47, 57% male, mean duration of psoriasis 17 years) found ustekinumab had better PGA response than infliximab (60% vs. 42%) at 12 months, but found no difference compared with etanercept or adalimumab.[85]

Dermatology Life Quality Index (DLQI)

DLQI results were generally consistent with PASI 75 results. All targeted immunomodulators statistically significantly improved quality of life relative to placebo, with infliximab producing the overall greatest benefit and apremilast producing the smallest. In head-to-head trials, 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. Overall, 18 of the 29 key studies evaluated mean DLQI change, while nine evaluated the proportion of patients achieving a DLQI score of 0 or 1 (indicating very little to no effect on quality of life); six included both measures.

The 13 placebo-controlled trials reporting the mean DLQI change also showed a statistically significantly greater improvement for all therapies. Mean absolute difference between the intervention and placebo group improvement compared to placebo across the available studies for to each drug were as follows: adalimumab (-5.7),[86] etanercept (-5.5 to -5.6),[57,58] infliximab (-9.0),[64] ustekinumab (-7.4 to -8.8 and -8.1 to -9.5 for 45 or 90mg, respectively),[68,69] ixekizumab (-8.4),[67] secukinumab (-8.8),[21] and apremilast (-3.9 to -4.5)[74,87,88](all outcomes, p<0.01).

Brodalumab was the only agent for which no study measured mean DLQI change, though an abstract based on the AMAGINE 1 trial did report the proportion of patients achieving a DLQI score of 0/1, which was statistically significant in favor of brodalumab (absolute difference: 50.9%, p<0.001).[89] Among those three placebo-controlled trials that also reported the proportion of patients with a score of 0/1, secukinumab (absolute difference: 48.3%, p<0.001)[21] and ustekinumab (absolute difference: 45.3-49.3%/49.2-53.2% for 45/90mg, p<0.0001)[68,69] were statistically significantly greater than placebo.

Among the eight head-to-head trials, four studies evaluated improvements on the DLQI: CLEAR, FIXTURE, UNCOVER 2 and 3, and IXORA-S. Both secukinumab and ixekizumab achieved a statistically significantly greater improvement on the DLQI than etanercept and ustekinumab. Table 8 presents the data from these trials.

Table 8. DLQI Outcomes Across Direct Comparative Trials

Trial	Drug	Mean change	p-value	DLQI 0/1 (%)	p-value
CLEAR	ustekinumab	NR	NR	56.5	p=0.0109
	secukinumab	NR		66.2	
FIXTURE	etanercept	-7.9	p<0.001	34.5	p<0.001
	secukinumab	-10.4		56.7	
UNCOVER 2	etanercept	-7.7	p<0.0001	33.8	p<0.0001
	ixekizumab	-10.4		64.1	
UNCOVER 3	etanercept	-8.0	p<0.0001	43.7	p<0.0001
	ixekizumab	-10.2		64.7	
IXORA-S*	ixekizumab	NR	NR	63	p<0.001
	ustekinumab	NR		45	

*Only available in the grey literature

Data on minimum clinically-important differences (MCID) DLQI changes (defined as at least a 5-point reduction) were statistically significantly in favor of apremilast, ustekinumab (both 45/90mg doses), and brodalumab compared to placebo (absolute differences: 27.9%, 54.6/59.4%, and 66.0%, respectively; all outcomes, p<0.001).[74,89,90]

Other Quality of Life and Mental Health Measures

Few studies used other instruments to measure quality of life. One Phase II publication each for brodalumab and apremilast reported SF-36 scores. Brodalumab was associated with statistically significant improvement compared to placebo in the SF-36 PCS (+4.0 vs. +1.5) and MCS (+5.0 vs. +1.7).[91] Apremilast failed to demonstrate any significant improvement relative to placebo, although improvement from baseline on the MCS was statistically significant (+2.9, p=0.0045) and numerically higher than the placebo group, which worsened (-0.8).[92] Both brodalumab (+0.25 vs. -0.01, for placebo, p<0.001)[93] and adalimumab (+0.20 vs. +0.10 for placebo, p<0.01)[86] demonstrated statistically significant improvements compared to placebo on the EQ-5D, though only the former was available in the peer-reviewed literature.

For associated mental health outcomes, one trial of brodalumab and one trial of ustekinumab measured improvements in anxiety and depression on the HADS scale relative to placebo. In the publication of the AMAGINE 1 study, brodalumab improved both anxiety (-2.3) and depression (-2.0) relative to placebo (-0.7 and -0.4, respectively, treatment difference: -1.5 and -2.1, p<0.001 for both outcomes).[72] In a secondary analysis of PHOENIX 2, Langley and colleagues also reported a statistically significant improvement of both doses (45/90mg) of ustekinumab for anxiety (-1.6/-1/7 vs. -0.11) and depression (-1.7/-2.1 vs. -0.21) over placebo (both outcomes, p<0.001).[94]

Symptom Control

Measures of symptom control were inconsistently reported across trials and used a variety of instruments. Brodalumab was the only agent to measure PSI outcomes, and demonstrated a statistically significant benefit over placebo. Three secukinumab trials measured improvements on the PSD, and improved itching, pain, and scaling better than placebo or ustekinumab. Apremilast was also statistically significantly better than placebo on VAS-itch, while ixekizumab demonstrated superiority over etanercept for VAS-skin pain.

Across the two ESTEEM RCTs and the LIBERATE trial, apremilast demonstrated a statistically significant absolute improvement over placebo for pruritus VAS of 21.0mm-35.6mm ($p<0.01$).[74,87,88] On the PSI, significantly more patients in the brodalumab group were PSI responders (defined as a total score ≤8, with each item rated as 0 [not at all] or 1 [mild]) compared to placebo in the AMAGINE 1 study (absolute difference: 57%, $p<0.001$).[72] The proportion of responders (defined as a minimum of 2.2 reduction for all symptoms) receiving secukinumab was statistically significantly greater than placebo on the PSD for itching (83.0% vs. 16.9%), pain (72.8% vs. 15.6%), and scaling (83.0% vs. 13.8%) in the ERASURE and FIXTURE studies ($p<0.05$).[95] Compared to ustekinumab, statistically significantly more secukinumab patients achieved complete relief of itching (25% vs. 44%), pain (35% vs. 59%), and scaling (21% vs. 42%) (all outcomes, $p<0.05$), and remained statistically significantly better at week 52.[96,97]

In direct comparison trials, an abstract reported that ixekizumab was statistically significantly better than etanercept for VAS-skin pain (least-squares mean change from baseline: -42.2 vs. -29.0, $p<0.001$).[98] A single publication reporting results from the AMAGINE 2 and 3 trials found that numerically more patients were PSI responders (defined as PSI score ≤8, with no item having a score >1) in the brodalumab group compared to ustekinumab group (68% vs. 55% [AMAGINE 2] and 61% vs. 52% [AMAGINE 3], respectively); groups were not compared statistically for this particular outcome in either trial, however.[19]

Worker Productivity

Positive effects on productivity were seen in analyses of several RCTs. Four targeted immunomodulators (adalimumab, infliximab, ustekinumab, and apremilast) showed significant improvements compared to placebo. In direct comparisons, there was a greater relative benefit of ixekizumab over etanercept and secukinumab over ustekinumab. However, tools used to measure productivity outcomes (i.e., WPAI, WLQ, VAS productivity) were variably employed across studies, which hinders our ability to make inferences about the potential benefit of one drug over another based on the reported data.

We identified three publications that were secondary analyses of Phase III placebo-controlled RCTs, including REVEAL, EXPRESS, PHOENIX 2, as well as an abstract pooling data from the ESTEEM trials. See the Definitions section of the report for details about the productivity instruments mentioned below.

The secondary analysis of the REVEAL trial[99] demonstrated a statistically significant improvement for adalimumab relative to placebo on the WPAI for total work productivity impairment (15.1%, p<0.001); the data for the placebo group were not reported, however. In the EXPRESS trial, infliximab was statistically significantly better than placebo on VAS productivity scores, with a mean 22.5% increase in the intervention group compared to a 1.1% decrease change in the placebo group; a similar trend was observed on the SF-36 physical component score (+12.1 vs. -5.2, p<0.001).[100]

The secondary analysis of PHOENIX 2 also demonstrated statistically significant improvements of ustekinumab 45/90mg over placebo based on WLQ domains for output demands (6.8/7.0 vs. -1.1), mental-interpersonal (7.8/7.5 vs. -1.1), and time management (6.6/9.1 vs. -0.7) compared to placebo (all outcomes, p<0.001).[101] An abstract that pooled data from the ESTEEM trials also used the WLQ tool but found apremilast to be statistically significantly improved based on two of the four domains relative to placebo: time management (-2.1 vs. +2.8, p=0.002) and output demands (-1.5 vs. +1.0, p=0.046).[73] Finally, median percent improvements from baseline in productivity were better for ustekinumab 45/90mg (72.6%/71.4%) compared to no change for placebo, but groups were not compared statistically.[101]

Among head-to-head trials, a secondary analysis of the UNCOVER trials compared of ixekizumab and etanercept.[102] Outcomes were evaluated based on the WPAI and demonstrated a statistically significant improvement over placebo in UNCOVER 1 (-19.8 vs. -0.8), and over etanercept and placebo in UNCOVER 2 (-19.5 vs. -13.7 and -2.0) and UNCOVER 3 (-19.3 vs. -17.4 and +0.6) for work productivity loss (least mean squares, p<0.001 for all outcomes).

The 52-week results from the CLEAR study also demonstrated that secukinumab was statistically significantly better (p<0.01) than ustekinumab in reducing presenteeism (-24% vs. -18 %), work productivity loss (-23% vs. -17%), and activity impairment (-32% vs. -28%) on the WPAI in one abstract.[103]

Sexual Function

Very few studies reported sexual function as an outcome. Two abstracts of head to head studies included data showing superiority of ixekizumab over etanercept and secukinumab over ustekinumab.

A publication which pooled patients from PHOENIX 1 and 2 reported that the proportion of patients with impaired sexual function was statistically significantly lower with ustekinumab 45/90mg (2.6/2.8%) than placebo which remained unchanged from baseline (23.0%, p<0.001).[104]

In direct comparison trials, an abstract reported that secukinumab was superior to ustekinumab with statistically significantly fewer patients reporting no sexual difficulties at week 52 in the CLEAR study (89% vs. 74%, p<0.01).[105] In addition, in a secondary analysis of the UNCOVER trials, one abstract reported that statistically significantly more patients reported improvements in sexual function with the ixekizumab compared to etanercept in both UNCOVER 2 (80% vs. 51%, p<0.001) and UNCOVER 3 (81% vs. 69%, respectively, p<0.05).[106]

Treatment Satisfaction

Only two placebo-controlled trials, one of brodalumab and one of etanercept, reported treatment satisfaction, which was better for both interventions compared to placebo.

Only two studies reported treatment satisfaction. The proportion of patients who were "satisfied" or "very satisfied" with treatment was statistically significantly higher in the etanercept group versus placebo (76% vs. 18%, p<0.0001).[59] While one abstract reported that treatment satisfaction was statistically significantly higher in the brodalumab group relative to placebo (p<0.001), no additional data were reported.[89]

Harms

Severe or serious adverse events were rare during treatment. During the induction phase of treatment, infections (e.g., nasopharyngitis, upper respiratory tract infections, etc.), injection site or infusion reactions, headache, and nausea were the most common side effects with biologics. Infliximab appears to have higher rates of these events than other drugs. Long-term safety data on all-cause mortality, MACE, malignancy, and serious infections are available for TNF-α agents and ustekinumab but not for the other drugs of interest for this review. Findings suggest an increased rate of serious infections for infliximab and other biologic agents relative to nonbiologic therapy, although not for ustekinumab. There were no material differences on other safety concerns among the biologic agents or in comparison with nonbiologic therapy.

Adverse Events During Induction

Adverse events (AEs) that occurred in ≥5% of patients in any treatment group as well as specific AEs of interest are shown as trial-weighted averages in Table 9. Most adverse events were mild or moderate. Severe or serious adverse events, death, and AEs leading to discontinuation were rare and comparable between the treatment and placebo groups.

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

Table 9. Adverse events during the placebo-controlled period

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

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

Long-term Adverse Events

Long term results of adverse events reported from pivotal trials of targeted immunomodulators are summarized in Table 10. In follow-up of trials of one to five years, etanercept, ustekinumab, secukinumab, and brodalumab had comparable safety profiles.

Table 10. Long-Term Adverse Events from Trials of Targeted Immunomodulators

Trial	Agent	Length of Follow-up	Any AE	Leading to D/C	Serious AE	Any Infection	Serious Infection	Cardiac or MACE	Neoplasms
		Years	Per 100 person-years						
AMAGINE 2	Brodalumab Ustekinumab	1	409 413	2.6 1.2	8.3 13.0	NR NR	1.0 0.8	0.4 0.8	0.1 0.8
AMAGINE 3	Brodalumab Ustekinumab	1	388 376	3.2 2.8	7.9 4.0	NR NR	1.3 1.2	0.7 0.0	0.5 0.8
FIXTURE	Secukinumab* Etanercept	1	252 243	NR† NR	6.8 7.0	105 91	NR NR	0.5 1.0	0.2 0
PHOENIX 1	Ustekinumab	5	215	2.1	5.3	83	1.0	0.3	0.9
PHOENIX 2	Ustekinumab	5	202	2.4	7.3	80	1.0	0.5	1.0
CLEAR	Secukinumab Ustekinumab	1	281 250	NR‡ NR	NR NR	98 96	NR NR	NR NR	NR NR

D/C = discontinuation; MACE = major adverse cardiac events; NR = not reported. *Among subjects who received secukinumab 300 mg. †In the FIXTURE trial the rate of adverse events leading to discontinuation was not calculated, but the number of patients who discontinued secukinumab and etanercept due to adverse events were 14 and 12, respectively.

A corrected proof of one-year efficacy and safety data from the CLEAR trial which compared secukinumab to ustekinumab was published online on September 20, 2016.[20] The rates of any adverse effect per 100 PY for secukinumab and ustekinumab were 281 and 250, respectively. The rates of any infection per 100 PY for secukinumab and ustekinumab were 98 and 96, respectively. The number of patients who, over one year, discontinued the study medication due to an adverse effect was 10 of 335 subjects for secukinumab and 9 of 336 subjects for ustekinumab.

Long-term safety data are also available from PSOLAR (Psoriasis Longitudinal Assessment and Registry). PSOLAR is a multicenter, longitudinal, psoriasis-based registry study evaluating the risk of infection in biologics and other systemic therapies. The overall population was 55% male, with a mean age of 49 and a mean duration of disease of 18 years. We identified two publications describing PSOLAR results.[22,23]

Table 11: Incidence of adverse events from the PSOLAR Registry[22]

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.

In one analysis including 12,095 patients and 31,818 PY of follow-up, participants were hierarchically attributed to having been exposed to ustekinumab, infliximab, other biologics, or nonbiologic medications. Nonbiologics were associated with a significantly higher rate of AE rates than biologics for all-cause mortality, MACE, and malignancy (Table 11).[22]

Another analysis of the PSOLAR Registry with 11,466 patients and 22,311 PY of follow-up, focused on serious infections. Infliximab had a higher rate and ustekinumab had a lower rate of serious infections than other available biologics, methotrexate, and nonmethotrexate nonbiologic treatment (systemic retinoids, psoralen plus UV-A, and UV-B).[23] In descending order, the rate of serious infections per 100 patient years was 2.5 for infliximab, 2.0 for adalimumab, 1.5 for etanercept, 1.3 for methotrexate nonbiologics, 1.1 for nonmethotrexate nonbiologics, and 0.8 for ustekinumab.

For newer targeted immunomodulators – ixekizumab, brodalumab, and apremilast – no long-term safety data beyond the duration of clinical trials have been published.

Subgroup Analyses

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

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

Patients with Psoriatic Arthritis

We identified five secondary analyses evaluating outcomes for patients with psoriatic arthritis, four of which were from the grey literature.[90,107-110] No data were available for the TNF-α agents or apremilast. One post hoc analysis of a Phase IIb study in brodalumab reported outcomes for those with and without psoriatic arthritis, but between group comparisons were not statistically evaluated.

Three placebo-controlled RCTs included secukinumab, ixekizumab, and ustekinumab, and brodalumab and reported results among patients with psoriatic arthritis. All agents were statistically significantly better relative to placebo on the PASI 75 among patients with psoriatic arthritis (Table 12).

One abstract reported results of the FIXTURE trial among patients with psoriatic arthritis. Patients with plaque psoriasis and psoriatic arthritis receiving secukinumab had a statistically significantly higher rate of achieving PASI 75 (72% vs. 39% and 2%) and PASI 90 (44% and 39% vs. 18% and 2%) compared to etanercept and placebo, respectively ($p<0.01$). These differences were similar to those observed for the overall trial population.[110]

Table 12. Proportion of patients with and without psoriatic arthritis reaching PASI 75

Drug (Trial)	# of PsA patients	PsA Achieving PASI 75 (%)		Overall Population	
		Intervention	Placebo	Intervention	Placebo
Secukinumab (FIXTURE)	175	72	2	82	5
Etanercept (FIXTURE)	Same trial	39	4	44	Same trial
Secukinumab (ERASURE)	171	70	4	82	5
Ustekinumab 45/90mg (PHOENIX 1 and 2)	563	63/62	4	67/66	3
Ixekizumab (all UNCOVER trials)	749	90	3	87-90	4
Brodalumab (Phase IIb)	198	92	0	82	0

The secondary analysis of a Phase IIb trial of brodalumab was the only one that reported outcomes for patients with and without psoriatic arthritis. Patients with psoriatic arthritis (n=46) had numerically similar proportions of achieving PASI 75 compared to patients without psoriatic arthritis (n=152; 92% and 79% vs. no change for placebo), PASI 90 (83% and 71% vs. no change for placebo), a DLQI response (defined as a ≥5-point improvement; 100% vs. 79% vs. 0% and 42% for placebo), and a PSI response (defined as a score ≤8, with no item having a score >1; 94% and 79% vs. 14% and 13% for placebo) The authors stated that adverse events were similar between subgroups, no data were reported.[109]

One abstract evaluated SF-36 outcomes based on pooled data from the UNCOVER trials for ixekizumab and found that patients with psoriatic arthritis who received ixekizumab, relative to patients who received placebo, achieved statistically significantly greater improvements on the MCS (5.2 vs. 0.8) and PCS (5.4 vs. -1.1) subscales (both outcomes, p<0.001).[108]

Patients with Previous Biologic Therapy Exposure

We identified seven studies that evaluated outcomes in patients who were and were not previously exposed to biologic therapy.[23,74,111-115] Subgroup analyses from four RCTs were primarily reported in the grey literature, though we found two peer-reviewed publications: one a key clinical trial of apremilast (ESTEEM 2) and one Phase II study on brodalumab. No head-to-head data were available. Across placebo-controlled studies, a statistically significantly greater proportion of patients achieved a PASI 75 response with the intervention for patients with and without prior biologic therapy. Rates between groups were numerically similar, but not compared statistically, and other outcomes (PASI 50, 90, and sPGA score of 0/1) followed the same trend where reported.

Table 13. 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[74]	=0.0069	<0.001
Brodalumab	88	79
Placebo	0	0
p-value[111]	<0.001	<0.001
Ixekizumab	89.5	88.4
Placebo	2.7	5.2
p-value[112]	<0.001	<0.001
Secukinumab	75.7	84.0
Placebo	4.1	4.6
p-value[113]	<0.0001	<0.0001

In addition to the above-described analyses from RCTs, we identified three observational studies. One small database study (DERMBIO) evaluated efficacy outcomes associated with subgroups of Danish patients (n=179, 51.4% male, age 43.4 years, mean PASI 10.9) taking ustekinumab who were and were not previously exposed to TNF-α agents, or who failed previous TNF-α therapy.[114] There were no statistical differences in PASI 75 response for patients taking one, two, or three prior TNF-α. Although patients who had previously been exposed to TNF-αs achieved PASI 75 response 20 days sooner than those patients who were TNF-α naïve, the difference was also not statistically significant. Data for each subgroup were not reported in the publication, though 80% of all patients overall achieved PASI 75 at the end of the study period.[114] Another study from the same database evaluated the three anti- TNF-αs and ustekinumab and found that patients (n=1,867, mean age 45.1, 64.5% male, mean PASI 12.8) taking adalimumab (OR: 1.8, 95% CI 1.4-2.3), etanercept (OR: 2.6, 95% CI 0-3.3), or infliximab (OR: 1.990, 95% CI 1.5-2.6) were statistically significantly more likely to terminate treatment than those on ustekinumab after adjusting for sex and previous biologic treatment at baseline (all outcomes, p<0.0001).[115] The authors note, however, all patients who were previously exposed to biologic therapy had a higher probability of treatment discontinuation (primarily due to loss of efficacy) across all agents (OR: 1.24, 95% CI 1.05-1.46, p=0.011).[115]

The final observational study was a large database study (PSOLAR) comparing rates of serious infections among patients (n=11,466, 55.4% male, age 48.4 years, mean psoriasis diagnosis 17.6 years) taking TNF-αs or ustekinumab.[23] The investigators evaluated the rate of serious infections across patients taking adalimumab, etanercept, infliximab, and ustekinumab and found that infliximab and adalimumab has the highest rates of infections (2.49 per 100 PYPY and 1.97 per 100 PYPY) while etanercept and ustekinumab had the lowest (1.47 per 100 PYPY and 0.83 per 100 PYPY). When divided into subgroups of patients who were biologic-exposed and biologic-naïve across agents, incidence rates were 1.35 per 100 PYPY and 1.12 per 100 PYPY, respectively; the trend was similar to the overall rates when evaluated according to drug but were not compared statistically[23]

Asian Studies

We identified five placebo-controlled RCTs that were conducted in Asia, plus a subanalysis of the Japanese portion of the ERASURE study. No head-to-head Asian studies were available.[52,116-120] Three distinct trials of ustekinumab included patients in Japan,[117] China (LOTUS),[52] and Taiwan and Korea (PEARL) patients,[119] while the subgroup analysis for the secukinumab trial[118] included Japanese patients, and the trial for infliximab[120] included Chinese patients.[104] We did not identify any trials conducted in Asia for ixekizumab, apremilast, or brodalumab.

As in multinational studies, all studies demonstrated statistically significant differences on all PASI measures (where reported) for each therapy compared to placebo; these results are presented in the table below. The proportion of patients achieving a PASI 75 response across RCTs of

adalimumab (71-80%), infliximab (76-80%), secukinumab (76-91%), and ustekinumab 45mg (67-68%) and 90mg (66-76%) did not demonstrate any identifiable differences. Other commonly reported outcomes included improvements on the DLQI and the proportion of patients achieving a PGA or IGA score of 0/1, which were consistent with PASI score improvement. One of the studies evaluating ustekinumab also measured SF-36, and was the only trial that met our inclusion criteria to include PDI outcomes; these results are available in the summary evidence tables in Appendix B.[117]

Table 14. Proportion of patients Achieving PASI Scores across Asian Studies

Study	Study group	PASI 50	p-value	PASI 75	p-value	PASI 90	p-value	PASI 100	p-value
Asahina, 2010	Adalimumab	81	<0.001	63	<0.001	40	<0.001	NR	NR
	Placebo	20		4		0		NR	
Igarashi, 2012	Ustekinumab 45mg	83	<0.001	59	<0.001	33	<0.001	NR	NR
	Ustekinumab 90mg	84		68		44		NR	
	Placebo	13		7		3		NR	
Tsai, 2011	Ustekinumab 45mg	84	<0.001	67	<0.001	49	<0.001	8	=0.024
	Placebo	13		5		2		0	
Zhu, 2013	Ustekinumab 45mg	91	<0.001	83	<0.001	67	<0.001	24	<0.001
	Placebo	20		11		3		1	
Yang, 2012	Infliximab	94	<0.001	81	<0.001	57	<0.001	NR	NR
	Placebo	13		2		0		NR	
Ohtsuki, 2014	Secukinumab	NR	NR	83	<0.0001	62	<0.0001	28	<0.01
	Placebo	NR		7		0		0	

*NA=not available; NR=not reported

Across the ustekinumab trials, the mean absolute difference in improvement on the DLQI ranged from -7.4 to -10.7, with all studies reporting outcomes that were statistically significantly better than placebo (p<0.001).[52,117,119] Adalimumab also demonstrated a statistically significant improvement (-6.1, p<0.001),[116] as did infliximab (-6.6, p<0.001).[120] Rather than mean DLQI change, Ohtsuki and colleagues only reported the proportion of patients with a DLQI score of 0 or 1 which was statistically significant in favor of secukinumab in the ERASURE study (71.4% vs. 24.1% for placebo, p<0.001).[118]

The absolute mean proportion of patients achieving a score of 0 or 1 on the PGA across the placebo-controlled studies that reported PGSA was 48% to 64% higher with ustekinumab, 51.8%

higher with apremilast, 81.4% higher with infliximab (all p<0.001). The subgroup analysis of the ERASURE trial was the only study to report outcomes based on the modified IGA measure and found that statistically significantly more patients were responders (a score of 0/1) in the secukinumab group compared to those receiving placebo (55.2% vs. 3.4%, p<0.0001).[118]

Two studies conducted in Japan, one of ustekinumab[117] and one of adalimumab,[116] reported SF-36 outcomes. For ustekinumab, both doses were statistically significantly better than placebo on the PCS of the SF-36 (7.8/5.1 vs. -0.95, p=0.0033 and p=0.0164 for 45mg and 90mg of ustekinumab, respectively). There were no significant differences for the MCS. For adalimumab compared to placebo, there were significant improvements in the PCS (4.6 vs. -0.4; p < 0.01) and MCS (2.4 vs. -2.6; p < 0.05).

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

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

Controversies and Uncertainties

Across the 29 Phase III RCTs identified for this review, only eight included head-to-head comparisons for the drugs of interest. The network meta-analysis extended comparisons to those between all agents, but is based on indirect comparisons. Our results are largely consistent with the comparative data, other meta-analyses, and other network meta-analyses. Although PASI 75 was reported as the primary endpoint in nearly all studies (the one exception being IXORA-S, in which the primary outcome was PASI 90), all other clinical outcomes, including PASI 50, 90, 100 and PGA/IGA, 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 had 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 next-best treatment would not be placebo or permit evaluation of combination therapy (e.g., topical use during targeted immunomodulator treatment).

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

There are also concerns with the reporting of patient-centered outcomes. DLQI was evaluated in 18 of the 29 clinical trials, not all trials used the same standard of measurement, and other scales were not uniformly employed. Additionally, many of the tools developed to measure outcomes were not developed with patients in mind, and psoriasis-specific instruments are limited.

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

Summary

Using the ICER evidence rating matrix, our evidence ratings for the comparisons of interest are provided in Table 15; 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 some between-agent comparisons. However, because of the lack of many head-to-head comparisons, we relied on a network meta-analysis to estimate the comparative clinical effectiveness between many targeted immunomodulators (see Appendix 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. There were two head-to-head trials comparing ixekizumab and etanercept, both of which showed substantial improvement in the percentage of patients achieving various PASI thresholds, and a similar magnitude of benefit when indirect evidence was included. We felt that the consistency of results across the two trials represented high certainty of a substantial net benefit for ixekizumab ("A") and an inferior net health benefit ("D") for etanercept in this comparison. Similarly, findings from two trials comparing

brodalumab to ustekinumab showed consistent benefit for brodalumab, albeit at an incremental level (ratings of "B" and "D" for brodalumab and ustekinumab, respectively).

The remaining head-to-head comparisons were based on the results from single trials, giving us only moderate certainty in our estimates of comparative effectiveness. Both ustekinumab and secukinumab demonstrated better outcomes than etanercept, and these findings were supported by the network meta-analysis, leading us to give a rating of "B+" (incremental or better) to these comparisons. Etanercept was rated "C-" for both comparisons, reflecting our judgment of moderate certainty that net health benefit is either comparable or inferior. Findings from a single trial of secukinumab vs. ustekinumab showed improved clinical outcomes at all PASI thresholds for secukinumab, but inclusion of indirect evidence yielded a nonsignificant difference in treatment effect. As such, we rated the evidence "C+" (comparable or better) for secukinumab and "C-" for ustekinumab in this comparison. We judge the evidence to be insufficient (I) to distinguish between etanercept and apremilast, given that the only available head-to-head trial was underpowered to detect differences between active agents and dosing of etanercept does not match the labeling for the product. Finally, the addition of a direct comparison between ixekizumab and ustekinumab is newly available, but only in abstract form, yielding moderate certainty of at least a small net benefit ("B+").

Table 15. ICER evidence ratings for available head-to-head comparisons

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

Note: The table should be read row-to-column. For example, there is moderate certainty that adalimumab has a comparable to substantial net benefit compared to apremilast (C+). 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

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

5. Other Benefits or Disadvantages

Beyond effectiveness and safety of targeted immunomodulators, the method of administration, frequency of dosing during maintenance, and rapidity of effect may be important considerations.

Regarding method of administration, all of the targeted immunomodulators are administered subcutaneously except for apremilast (oral) and infliximab (intravenous). Patients could favor the convenience of an oral drug like apremilast. Although infliximab is comparatively effective, patients might be disinclined to use an intravenous medication that is associated with administration time and discomfort.

The frequency of administration during maintenance is greatest for apremilast (twice a day). Other targeted immunomodulators are taken weekly (adalimumab, etanercept), every 2 weeks (brodalumab), every 4 weeks (secukinumab and ixekizumab), every 8 weeks (infliximab), and every 12 weeks (ustekinumab). Patients could favor agents that need to be taken less frequently.

How quickly a drug works to clear psoriasis is likely to be important for patient satisfaction and adherence. For patients who require rapid clearing of moderate-to-severe plaque psoriasis, cyclosporine, an older systemic agent, not a focus of this review, and infliximab appear to be superior to other treatments.

6. Comparative Value

6.1 Overview

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

6.2 Prior Published Evidence on Costs and Cost-Effectiveness of Psoriasis Treatments

A review of the literature for prior economic models yielded several published cost-effectiveness models comparing psoriasis treatment regimens within and across classes.

Among studies conducted in the U.S., one study[121] comparing ustekinumab versus etanercept, based on the ACCEPT clinical trial,[122] showed that ustekinumab 90mg had an incremental cost-effectiveness of $384,401/QALY versus etanercept 50mg, and ustekinumab 45mg dominated (more effective and less expensive) etanercept 50mg. The key differences between this study and our analysis are: 1) a three-year time horizon versus 10 years in our model; 2) societal perspective versus a health system perspective in our model; 3) cost of etanercept was significantly lower than that in our model; and 4) the model assumed partial responders (PASI 50-74) continued treatment, while we assumed first-line treatment continued only when PASI >75 was achieved. One other manufacturer-funded study[123] evaluating various biologic therapies (TNFα antagonists: adalimumab, etanercept, and infliximab; T-cell inhibitors: alefacept and efalizumab) found adalimumab had a favorable incremental cost-effectiveness ratio compared to etanercept, at $544/QALY. Infliximab accrued the highest QALYs gained, while etanercept was least costly. This study: 1) did not account for decrease in treatment efficacy for subsequent lines of treatment after first-line, 2) assumed that treatment response would be maintained indefinitely through the course of therapy, and 3) did not clearly state the model time horizon. Owing to the lack of transparency in the methods, a critical comparison with our model was not feasible.

Studies conducted in settings outside of the U.S. included a manufacturer-funded Canadian model[124] comparing ustekinumab (45mg) with etanercept. This analysis found that ustekinumab had an incremental cost-effectiveness of CAN$590,870/QALY (US$442,203/QALY) compared to etanercept. The model used inputs for the initial phase (initial trial period) from the ACCEPT trial[122] and extrapolated the same trial data for the maintenance phase. Additionally, resource utilization was obtained from expert opinion, although validated by a burden of illness study. The model assumed second-line treatment to be supportive care and did not include the possibility of a second biologic treatment for those who experienced treatment failure (defined as PASI ≤75).

Other studies of interest from outside the U.S. were the manufacturer submissions to the U.K. National Institute for Health and Care Excellence (NICE).[125-128] All of the models submitted to NICE were based on the York model,[129] with a 10-year time horizon, and were from an NHS perspective. Overall summary and differences included that: 1) most of these analyses accounted for the possibility of second-line targeted therapy use (except ustekinumab and secukinumab); 2) drug costs used were vastly different than those in the U.S.; and 3) most assumed very large cost offsets related to avoided hospitalizations, an assumption which was viewed by the NICE Evidence Review Group (ERG) as being unrealistic and unsupported by data. Details on the NICE submissions can be found in Appendix C.

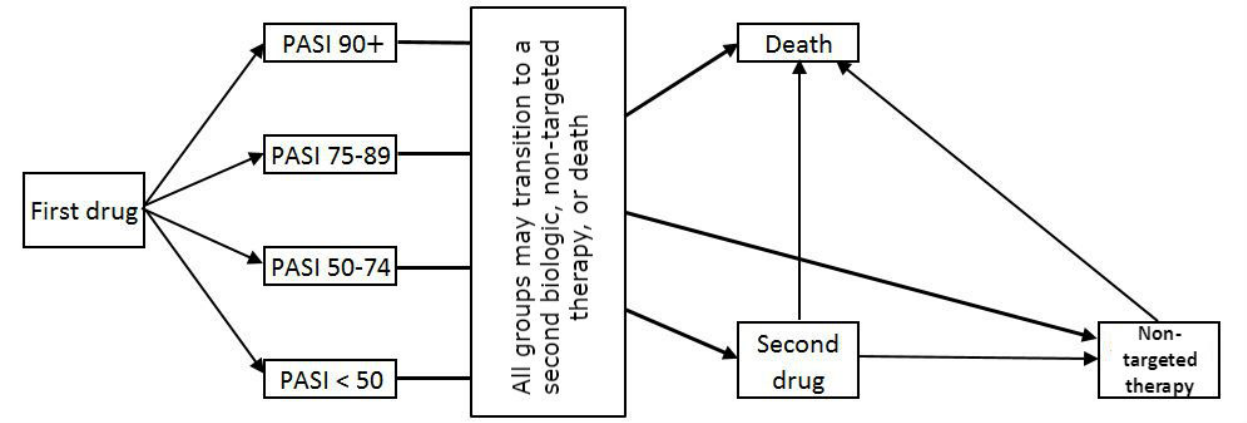
6.3 Cost-Effectiveness Model: Methods

Model Structure

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

Patients with response below 75% improvement after the initiation period (16 weeks for adalimumab and apremilast, 10 weeks for infliximab, and 12 weeks for all other drugs) were assumed to discontinue the first-line therapy. A proportion of these patients then begin second-line targeted therapy and the remainder receive non-targeted therapy (i.e., topical therapy, other systemic therapy, and phototherapy). Second-line therapy was defined as an average of all available targeted therapies given the complete lack of RCT data in the second-line setting. Costs and effects for second-line were averaged across therapies as described below.

Figure 5: Markov model of psoriasis treatment and response



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

Non-targeted therapy was assumed to consist of a mix of no treatment, topical treatment, non-targeted systemic treatment, and phototherapy. Given the lack of specificity in the definition of non-targeted therapy, as well as a lack of clarity in the performance of such therapy in a population that has failed prior attempts at treatment, there obviously is uncertainty associated with the costs and outcomes (quality of life) in this health state; these uncertainties were incorporated in our analyses as described below.

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

The time horizon for the base case analysis was 10 years, rather than the more standard lifetime analysis, for several reasons. First, previous economic evaluations have used a 10-year timeframe, and doing so in this study will facilitate comparison with previous analyses. Second, because we have included second-line therapy, and eventually many patients will end up on second-line treatment in a lifetime analysis, second-line treatment would likely dominate the results, taking away from our focus on first-line therapy. Thus, a 10-year time horizon provides greater focus on the effects of first-line vs. second-line treatment. We evaluated a lifetime time horizon in a scenario analysis.

Target Population

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

Treatment Strategies

The interventions included for review are those assessed in the evidence review and NMA; their administration schedules are listed in Appendix G. Each of these therapies includes an initiation period. Regimens are based on labeled dosing recommendations for all currently marketed drugs;[1,130-135] dosing for brodalumab is based on the approach used in the key clinical trials.[136]

Key model choices and assumptions

The model used a health system perspective. All future psoriasis-related healthcare costs, QALYs and LYs were discounted at 3% per year. The model was informed by several assumptions, which are represented in Table 16 along with the rationale for each assumption.

Table 16. Key model assumptions

Assumption	Rationale
A patient cannot transition between effectiveness (PASI improvement) levels.	Drug response does not show significant improvement past the trial period; discontinuation rate accounts for decline in effectiveness over time.
Probability of discontinuing first-line therapy is drug specific.	Empirical evidence indicates discontinuation rates beyond the initiation period differ across drugs, and differs in year 1 vs. years 2+.
Probability of discontinuing newer drugs (secukinumab, ixekizumab, and brodalumab) is the same as ustekinumab.	There are limited to non-existent data on discontinuation rates for the newer agents. This assumption was evaluated in a sensitivity analysis.
Half of patients discontinuing first-line targeted drug therapy receive second-line targeted drug and remainder receive non-targeted drug.	There are limited data on proportion of patients receiving second-line targeted treatment, particularly in current treatment paradigm with newer agents. This assumption was evaluated in sensitivity analyses.
Second-line targeted therapy was assumed to be an average of all available targeted agents.	There are no RCTs of second-line targeted therapy and limited data on second-line targeted therapy response in general, yet second-line treatment reflects current clinical practice.
Non-targeted therapy was assumed to consist of a mix of no treatment, topical treatment, non-targeted systemic treatment, and phototherapy.	There is little evidence on the mix of treatments, costs, and patient outcomes over time in patients who do not receive targeted therapy, as well as in patients who discontinue targeted therapy.
Risk of death is based on age alone.	Evidence suggesting that treatment of psoriasis improves survival is weak.
Patients remain on first-line therapy during the initiation period.	A full initiation period (16 weeks for adalimumab and apremilast, 10 weeks for infliximab, 12 weeks for all others) is needed to determine whether the drug will produce an adequate response.
Subcutaneous drugs are administered in-clinic at the first visit and by the patient themselves thereafter.	Reflects usual current clinical practice

Economic Inputs

Costs

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

Drug acquisition costs

For each cycle of the model, surviving patients are assumed to receive one of the included drug therapies. Therefore, if patients discontinued first-line targeted therapy and were still alive, they would incur costs for either a second-line targeted therapy or for non-targeted therapy.

Feedback on the draft evidence report indicated that WAC is not representative of actual price paid in either public or private settings. To address this concern, we obtained data from SSR Health,[25] which combines data on net US dollar sales with information on unit sales to derive net pricing at the unit level across all payer types. Data on the approved agents of interest are current through the third quarter of 2016. We estimated net prices for these agents by comparing the four-quarter (i.e., 4Q2015 – 3Q2016) rolling averages of both net prices and WAC prices per unit to arrive at an average discount from WAC. We calculated averages at the drug class level and rounded these to the nearest five percent. Finally, we applied the drug class level average to the most current WAC price for each medication to arrive at an estimated net price. Drug class level average discounts were as follows:

- TNF-α: 30%
- IL-17A: 40%
- Anti-IL 12/23: 15%
- Apremilast: 20%

For brodalumab, the IL-17A agent currently under regulatory review, we estimated the launch price as the average of the WAC prices for the two other agents in this class, and then applied the 40% discount specific to IL-17A drugs. We used wholesale acquisition cost (WAC) in a scenario analysis.[26]

Table 17: Drug acquisition costs

Treatment	Unit cost	Cost of initiation period	Monthly cost of maintenance	Cost of 1st year of therapy	Source
adalimumab (per 40mg)	$1,434	$14,361 (4 mo.)	$2,868	$37,305	Net price calculation*
apremilast (per 30mg)	$34	$7,549 (4 mo.)	$1,931	$22,997	Net price calculation
brodalumab (per 210mg)	[$2,560]	[$17,969] (3 mo.)	[$2,560]	[$41,009]	Assumed average of ixekizumab and secukinumab, with IL-17A discount
etanercept (per 50mg)	$717	$17,283 (3 mo.)	$2,868	$43,095	Net price calculation
infliximab (per 100mg)	$779	$16,874 (10 wks.)	$1,948	$35,380	Net price calculation
ixekizumab (per 80mg)	$2,681	$21,523 (3 mo.)	$2,681	$45,652	Net price calculation
secukinumab (per 300mg)	$2,439	$14,656 (3 mo.)	$2,439	$36,607	Net price calculation
ustekinumab (70% 45mg/30% 90mg)	$7,514	$26,072 (3 mo.)	$3,256	$55,376	Net price calculation
2nd line targeted drug (per cycle)	$2,569	$8,272** (1 mo.)	$2,569	$36,531	Average monthly cost of above drugs
non-targeted therapy (per cycle)	$820	n/a	$820	n/a	Yu, Curr Med Res Opin 2009 (inflated to 2016 dollars using medical cost inflation rate)[137]

*Calculated using WAC and SSR

**Switching cost

Infliximab and ustekinumab are dosed based on body weight. We assumed that each infliximab administration used five 100 mg vials to account for incomplete vial usage (drug wastage). Based on weight distribution data from the ustekinumab trials, we assumed that 30% of patients were greater than 100kg and therefore would receive a 90 mg rather than the standard 45 mg dose. While one recent study has indicated up to approximately 50% of patients receive the 90mg dose after dose escalations, we used the more conservative 30% estimate in our base case because dose adjustments were not included in our base case analysis, as discussed below.[138]

The cost of second-line targeted therapy was calculated as the average of all first-line targeted therapies. As described above in our modeling approach, this assumption was necessary to reflect real-world practice of treatment switching yet accommodate the complete lack of data on the safety and effectiveness of specific second-line treatment scenarios. A switching cost was assigned to the first month of second-line therapy to reflect the additional cost of initiation above and beyond maintenance therapy, based on the average incremental cost across first-line therapies.

The cost for non-targeted therapy was derived from a study by Yu et al.[137] Yu and colleagues analyzed medical care costs for patients with psoriasis using 2003 claims data, and found that incremental adjusted total cost for patients with moderate to severe psoriasis vs. mild psoriasis was $9,841 per year in 2016 US dollars. This cost is likely representative of the difference in health care cost between a patient with active moderate to severe disease and a patient who has achieved response with treatment (not including cost of targeted treatment). The costs include utilization of non-topical systemic therapies and phototherapy, outpatient visits, and hospitalization costs. While some previous economic evaluations have assumed significant hospitalization cost offsets as a result of successful treatment, the adjusted difference in hospital costs between moderate to severe patients and mild patients in the Yu study was only $119 (2007 USD).

In a separate study by Feldman and colleagues comparing health care costs for patients with moderate to severe psoriasis versus those without psoriasis, inpatient costs were approximately $1000 higher and outpatient costs $2100 higher in psoriasis patients, although the differences are difficult to interpret because the majority of patients (65%) received targeted treatments.[139] Foster and colleagues found no difference in hospitalization cost changes before and after initiation of a targeted therapy in treatment responders vs. non-responders.[140] These studies strongly suggest that significant cost savings from avoiding hospitalizations with successful treatment are unlikely. We found no data on the health care costs for patients who had undergone targeted treatment and failed. We assumed these patients were similar to those who underwent non-targeted treatment. We did not account for extensive use of newer or more intensive non-targeted treatments; doing so would require that we assume some degree of treatment benefit (utility improvement) to the non-targeted health state, which would offset the added cost. Given the uncertainty in the cost for patients in the non-targeted therapy health state, however, the cost of non-targeted therapy was varied by +/- 50% in sensitivity analyses.

Although in clinical practice patients can experience dose changes in response to changes in effectiveness or adverse effects, we did not include dose decreases or increases, because a recent study indicated that dose increases were as common as dose decreases, and the majority of dose increases were followed by dose decreases or drug discontinuation.[139] For example, 41.0% of etanercept patients had a dose increase in the 12 months following drug initiation, yet 48.7% had a dose decrease; analogous results for adalimumab are 36.6% and 53.%, and for ustekinumab 35.9%

and 37.4%. Furthermore, while patients may experience dose increases as treatment effectiveness wanes, treatment failures are explicitly captured in the model by transitions to second-line targeted therapy, which is reflective of the current treatment era with multiple options.

Administration costs

All targeted therapies in this comparison other than apremilast were injectable or infused drugs. For subcutaneous drug therapies, we assumed that the injection was administered at the first clinic visit and was self-administered by the patient thereafter. Cost per subcutaneous injection administration at a clinic, obtained from the Redbook (CPT code 96372), was $25.44.[26]

Infliximab, the only drug in the analysis that requires intravenous administration, is delivered over a two-hour infusion. Each administration was assumed to cost $164.54: $136.15 for the first hour (CPT code 96413) and $28.39 for the second hour (CPT code 96415). We also included the cost of one day lost from work ($193) to account for patient time cost related to IV administration.[4] There were no administration costs for the only oral medication in the analysis, apremilast.

The monthly cost for administration of second-line therapy was estimated by averaging the monthly administration costs for all first-line drugs during their maintenance phases.

Laboratory and clinic visit costs

Due to the interaction of the targeted therapies with the immune system, many psoriasis patients require monitoring for potential infection. Some also require testing of physiologic systems, such as hepatic function. The costs for each of the laboratory tests required by one or more targeted psoriasis therapies and the schedule of laboratory tests indicated for each drug are provided in Appendix G. 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.[4] In addition to these laboratory tests, each patient was assumed to receive four physician visits per year related to the disease.

Adverse event costs

No previous economic analyses have indicated that adverse events significantly impact the cost effectiveness of targeted therapies in psoriasis. However, the impact of the cost of one serious adverse event, pneumonia, was included to assess the potential importance of adverse events in relation to health care costs. Pneumonia incidence was taken from the prescribing information of each drug that has already entered the market, and a meta-analysis of phase III trials for brodalumab.[141] Due to non-standard terminology, the figure for each drug reflected the incidence of 'pneumonia', 'serious infection', or 'serious respiratory infection.' In the case of apremilast, no mention of serious infection was found in the prescribing information, and so we assumed that it

did not increase risk of pneumonia. Absolute rates, rather than placebo-adjusted rates, were used. A cost of $5,873 per hospitalized case of pneumonia was used, based on Medicare reimbursement rates.[142]

Productivity costs

Productivity cost offsets were included in a scenario analysis rather than the base-case analysis (as in the draft report), to reflect the dominant healthcare payer perspective used in US settings. Productivity costs were derived from work productivity impact measures in RCTs of adalimumab and ixekizumab.[99,102] 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.[143] We liberally 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 $4,900. We estimated a $4,400 productivity cost offset for second-line treatment based on an assumed 10% lower clinical effect of targeted drugs in second-line.

Clinical Inputs

Utilities

Utilities for the base case scenario were obtained from an analysis of EQ-5D data in 3,231 patients enrolled in five RCTs evaluating secukinumab in moderate to severe psoriasis.[27] The EQ-5D is one of the most commonly used generic health status measurement, and has good validity and reliability in various health conditions, including psoriasis. The EQ-5D includes questions across five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. It was measured alongside PASI in the secukinumab RCTs, and the relationship between PASI improvement and EQ-5D was evaluated to derive the estimates shown in Table 18. These scores unfortunately were averaged across both arms of the trials (i.e., targeted therapy and placebo), prohibiting separate evaluation of utility scores in each arm of the trial.

These utilities were selected because they were derived from relatively recent clinical trials, were used in a recent NICE technology appraisal of secukinumab, and are representative of utility scores derived from multiple clinical trials including thousands of patients and a variety of targeted treatments.[27] We assumed the utility for the non-targeted therapy health state was 0.642, equal to the baseline utility for patients enrolled in the secukinumab trials. While the utility score for patients with PASI <50 (0.751) could have been used, patients who were receiving targeted treatment were included in this group, and their treatment, albeit moderate, likely had an upward influence on the utility score.

Table 18. Utility by health state

State	Utility	Source[144]
PASI 90-100	0.906	NICE secukinumab submission
PASI 75-89	0.868	NICE secukinumab submission
PASI 50-74	0.835	NICE secukinumab submission
PASI <50	0.751	NICE secukinumab submission
Second-line therapy	0.846	Estimated
Non-targeted therapy	0.642	NICE secukinumab submission

The utility of second-line therapy was calculated based on estimated second-line response across all available targeted therapies. We assumed second-line treatment had a 10% absolute lower probability of achieving PASI 75;[113,145,146] this was applied as a 5% decrease in PASI 90 and PASI 75-89, and a 5% increase in PASI <50 and PASI 50-74. We then calculated the utility for each drug and averaged across drugs.

Due to similar adverse event profiles between drugs and the absence of their utility evaluation in other cost-effectiveness analyses in psoriasis, we did not include any adverse event-associated disutilities. It is very unlikely that inclusion of these disutilities would have any meaningful effect on results given the low rate of serious adverse events for the drugs evaluated in this study.

Clinical probabilities

Patient response to first-line targeted therapy was derived from the network meta-analysis (NMA) (see Appendix F). In the NMA, clinical trials of ustekinumab using 45mg and 90mg dosing were combined given the similar response rates; our analysis thus reflects this assumption. A re-evaluation of PHOENIX 1 and 2 trials by Lebwohl and colleagues found the 28-week PASI 75 response was 74.2% in patients weighing >100kg on the 90mg dose, and 76.9% in patients weighing 100kg or less on the 45mg dose.[53] PASI 75 from the NMA at 12 weeks is 69.4% for both doses combined. In the PHOENIX 1 and 2 trials, PASI 75 increased by ~4% from the end-of-RCT 12-week measurement to the uncontrolled 28-week measurement; thus, the 69.4% PASI 75 12-week response used in the model is likely to be reasonably reflective of the effectiveness expected for weight-based dosing outcomes at 12 weeks.

Several recent studies provide drug-specific discontinuation rates. Discontinuation rates during the first year after the initiation period were derived from a study by Feldman et al., who conducted a retrospective analysis using claims data for 4,309 psoriasis patients from 2007 through 2012.[141] The majority of patients received etanercept or adalimumab, and a small number (N=195) received ustekinumab. Over the follow-up period, 35%, 27%, and 16% of etanercept, adalimumab, and

ustekinumab patients discontinued therapy. We assumed the discontinuation rate for apremilast was the same as for etanercept, the rate for infliximab was between that of etanercept and adalimumab (30%), and that secukinumab, ixekizumab, and brodalumab had the same rate as ustekinumab (16%).

Discontinuation rates after year one were estimated from a long term Danish cohort study (DERMBIO). [147] The study evaluates an 1867 treatment series (adalimumab n = 774, etanercept n = 449, infliximab n = 253, ustekinumab n = 391) administered in 1277 patients for up to 10 years. Based on a multivariate Cox model of treatment-naïve patients, we estimated approximately 15% of adalimumab, etanercept, and infliximab patients discontinued treatment each year, while 5% of ustekinumab patients did. We assumed secukinumab, ixekizumab, and brodalumab had the same discontinuation rates as ustekinumab. Another large long-term cohort study, the Psoriasis Longitudinal Assessment and Registry (PSOLAR), followed 4,000 patients with new starts for targeted agents. The findings were generally similar to the DERMBIO cohort study, although adjusted discontinuation curves were not provided.[148] While long-term data are not available for ixekizumab and brodalumab because they are newer to market, a recent study presented in fall 2016 suggests secukinumab patients who initially respond maintain that response up to four years.[24] Based on the DERMBIO study analysis of patients who had previously received a targeted treatment, we estimated the discontinuation rate from second-line therapy was 15% per year.

An important question is what proportion of patients who discontinue therapy because of non-response then switch to another targeted agent rather than discontinue targeted therapy altogether. A study by Doshi et al. in the Medicare population from 2009 to 2012 (N=2,707) found that approximately 37% of patient who discontinued a targeted therapy restarted or switched.[149] Foster et al., in a study of 2,146 commercially insured patients from 2010 through 2011, found that approximately 50% of patients who failed treatment did not continue with a targeted therapy.[140] While the more recent availability of additional targeted agents with higher response rates may increase the rate of second-line targeted treatment, we assumed in our base case that 50% of patients who discontinued targeted treatment because of non-response would go on to second-line therapy; this estimate was varied from 25% to 75% in sensitivity analyses.

Model validation

We used several approaches to validate the model. First, we provided information on the preliminary model approach, inputs, and results to the manufacturers of the targeted drugs. Feedback from these companies resulted in the identification of an error in drug cost, and revisions to the model including addition of drug-specific discontinuation rates, modification of average patient weight, and inclusion of a switching cost for second-line targeted drug treatment. We also adjusted our base-case drug costs from WAC to discounts off WAC to reflect real-world pricing,

based on net price data from SSR.[25] We also added scenario analyses to assess the patient-centered impacts of achieving PASI 100 and improvement in work productivity.

Second, we developed a simple 'back-of-the-envelope' model to assess one-year clinical and economic outcomes based on first-line targeted therapy only. The results of the two models were similar. Third, we compared our results with an independently developed (unpublished) model based on the York model framework.[129] The results from these two models were generally similar. Lastly, we conducted various sensitivity and scenario analyses, as described below, to assess model behavior.

Sensitivity analyses

We conducted one-way sensitivity analyses to assess the impact of model input uncertainty on the results. Given the numerous potential comparisons, we selected four to highlight the importance of parameter (evidence) uncertainty: 1) infliximab vs. non-targeted therapy, 2) ixekizumab vs. non-targeted therapy, 3) ixekizumab vs. infliximab, and 4) ixekizumab vs. etanercept. These comparisons were selected because infliximab had a favorable cost-effectiveness ratio compared to non-targeted therapy, etanercept was a common comparator in head-to-head trials, and ixekizumab is representative of drugs with higher efficacy and cost and a relatively low discontinuation rate. Laboratory testing costs were not varied in the one-way sensitivity analyses, because their effects were extremely small in all models. Although productivity costs were not included in the base case analysis, we included a range of productivity cost offsets in the one-way sensitivity analyses.

Scenario analyses

We also conducted four specific scenario analyses:

1. Using WAC drug prices rather than discounted net prices
2. Including productivity costs
3. Estimating the impact of accounting for PASI 100 attainment
4. Using a lifetime horizon

6.4 Cost-Effectiveness Model: Results

Base Case Results

Total costs, QALYs, and LYs for each therapy accrued over the 10-year time horizon of the model are shown in Table 19 below. Additionally, we show the incremental cost-effectiveness ratio (ICER) for each of the targeted therapies compared to non-targeted therapy.

Table 19. Results for the base case

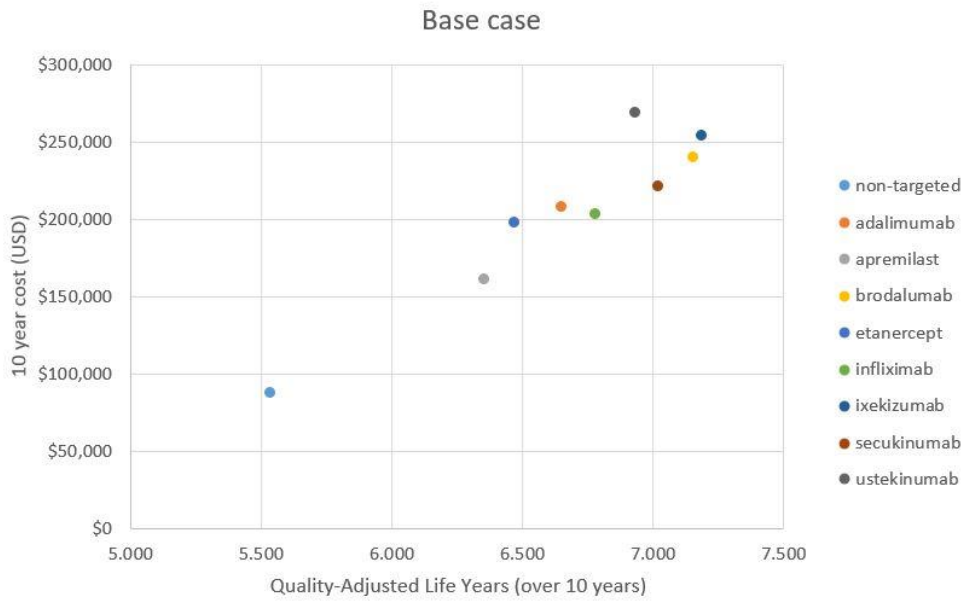
	Cost	QALYs	LYs	ICER vs. non-target
non-targeted	$88,086	5.531	8.64	
adalimumab	$208,881	6.649	8.64	$108,040
apremilast	$161,741	6.353	8.64	$89,610
brodalumab*	$240,398	7.151	8.64	$94,030
etanercept	$198,519	6.469	8.64	$117,769
infliximab	$203,532	6.776	8.64	$92,715
ixekizumab	$254,287	7.187	8.64	$100,389
secukinumab	$221,704	7.018	8.64	$89,843
ustekinumab	$269,843	6.930	8.64	$129,904

*Results for brodalumab are tentative, as pricing is not currently available

The base-case results indicate that treatment with targeted drugs, over a 10-year time frame that includes drug discontinuation, leads to QALY improvements ranging from 0.8 (apremilast) to nearly 1.7 (ixekizumab, brodalumab).

The base-case results shown in Table 19 are also graphed in Figure 6. Drugs that are farther to the right provide the greatest clinical benefit, and drugs higher on the y-axis are more expensive. This chart shows a general trend towards better results with more expensive therapies. Secukinumab is the most cost-effective agent versus non-targeted therapy. However, estimated cost-effectiveness ratios for all the drugs fall into a relatively narrow range, with IL-17A targeted drugs generally providing more QALY gains than TNF-α agents, but at higher cost. Ustekinumab appears above the slope of the line formed by more cost-effective competitors, indicating that it is estimated to provide fewer QALYs at higher cost, primarily as a result of including higher dosing (90mg) for heavier patients receiving this drug.

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



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

We also calculated incremental cost-effectiveness ratios for etanercept compared to the IL-17A targeted drugs (Table 20). We selected these comparisons because etanercept was the only TNF-α for which we felt we had adequate evidence to distinguish its overall effectiveness (lower) compared to all IL-17A targeted drugs. In addition, as the least expensive biologic agent, our analysis will help inform policymakers as to whether the incremental cost of IL-17A targeted drugs over etanercept represents good long-term value. The incremental cost-effectiveness ratios versus etanercept ranged from approximately $42,000/QALY for secukinumab up to approximately $78,000 for ixekizumab.

Table 20. Incremental cost-effectiveness ratios for IL-17A targeted drugs compared to etanercept

Cost/QALY	Versus Etanercept
Brodalumab	$61,396
Ixekizumab	$77,686
Secukinumab	$42,190

Sensitivity Analysis Results

The impacts of varying each of the parameters in the model over ranges reflecting their uncertainty are shown in Figure 7 for infliximab compared to non-targeted therapy. The cost and utility of non-targeted therapy, drug costs, and the utility of targeted treatment were associated with the greatest uncertainty in the model. In particular, non-targeted therapy considerations are important

given the lack of data on the performance of such therapy in a setting where many patients have already failed prior use. However, the incremental results for infliximab versus non-targeted therapy never exceeded the commonly-cited threshold of $150,000 per QALY gained, ranging from approximately $73,000 to $127,000/QALY gained across the range of non-targeted therapy cost and utility.

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

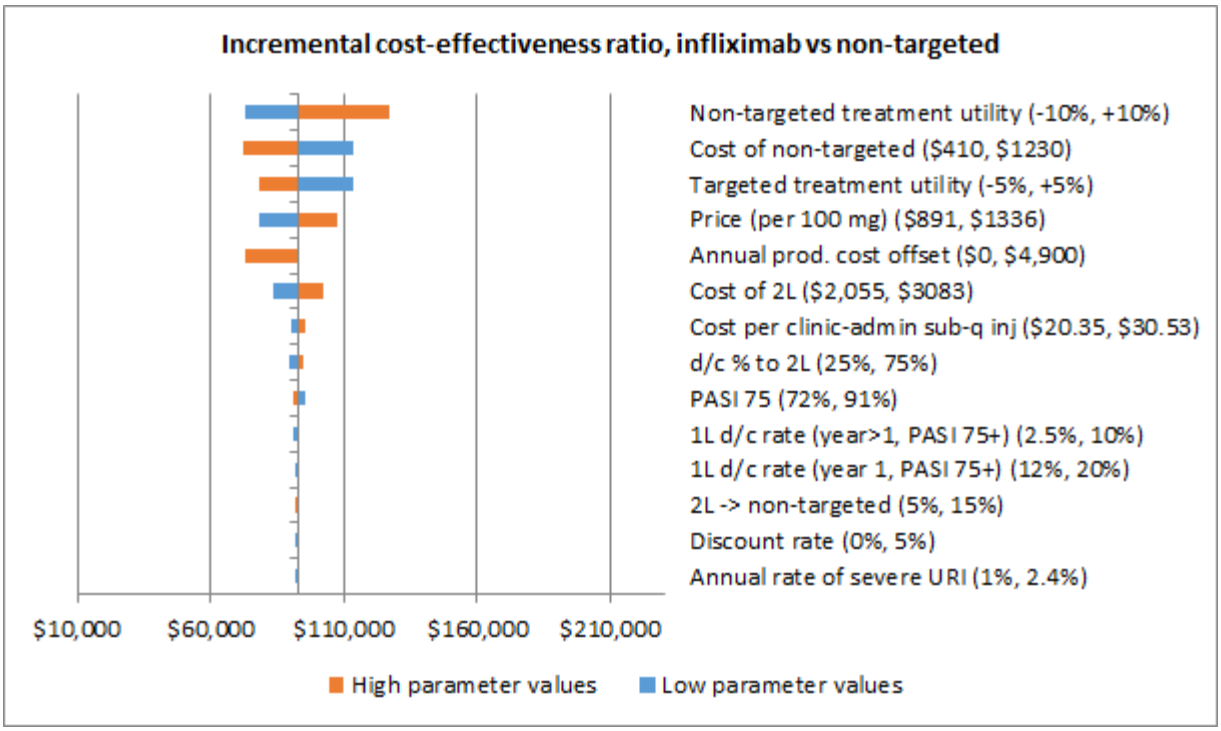
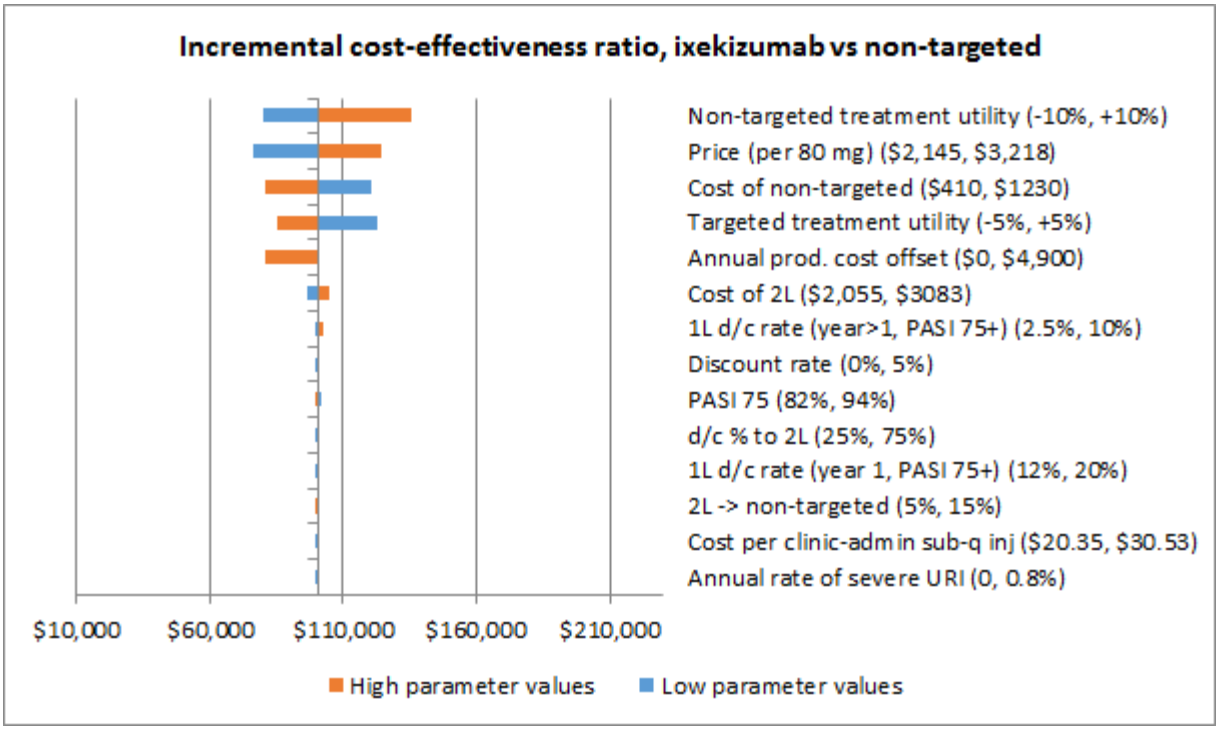


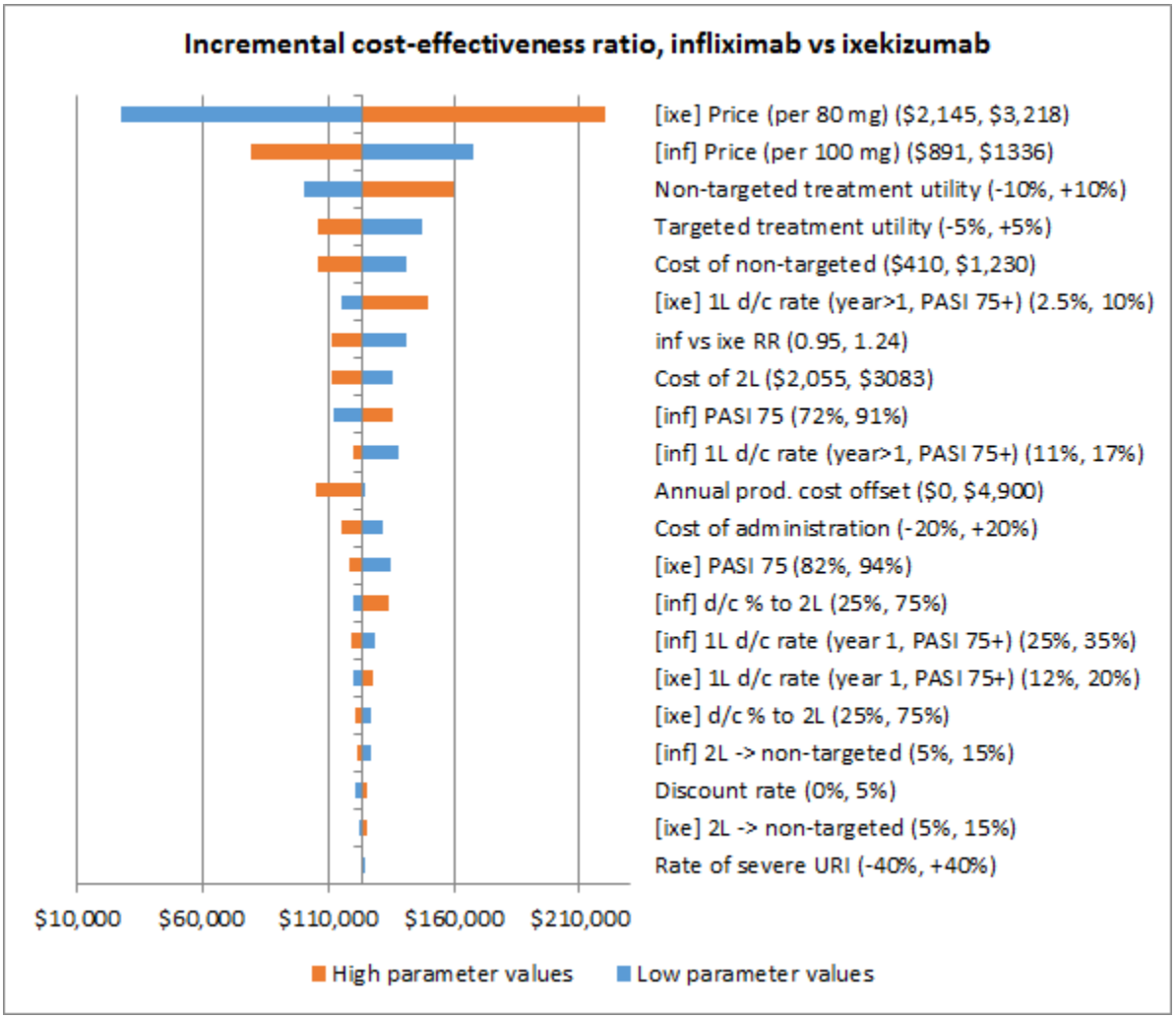
Figure 8 demonstrates the impact of varying these same parameters on the cost effectiveness of ixekizumab versus non-targeted therapy. Similar to the infliximab evaluation above, the greatest uncertainty arises from the cost and utility for non-targeted therapy, drug cost, and targeted treatment utility. The incremental cost-effectiveness ratio ranged from approximately $77,000 to $136,000/QALY gained across the range of assumed drug prices.

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



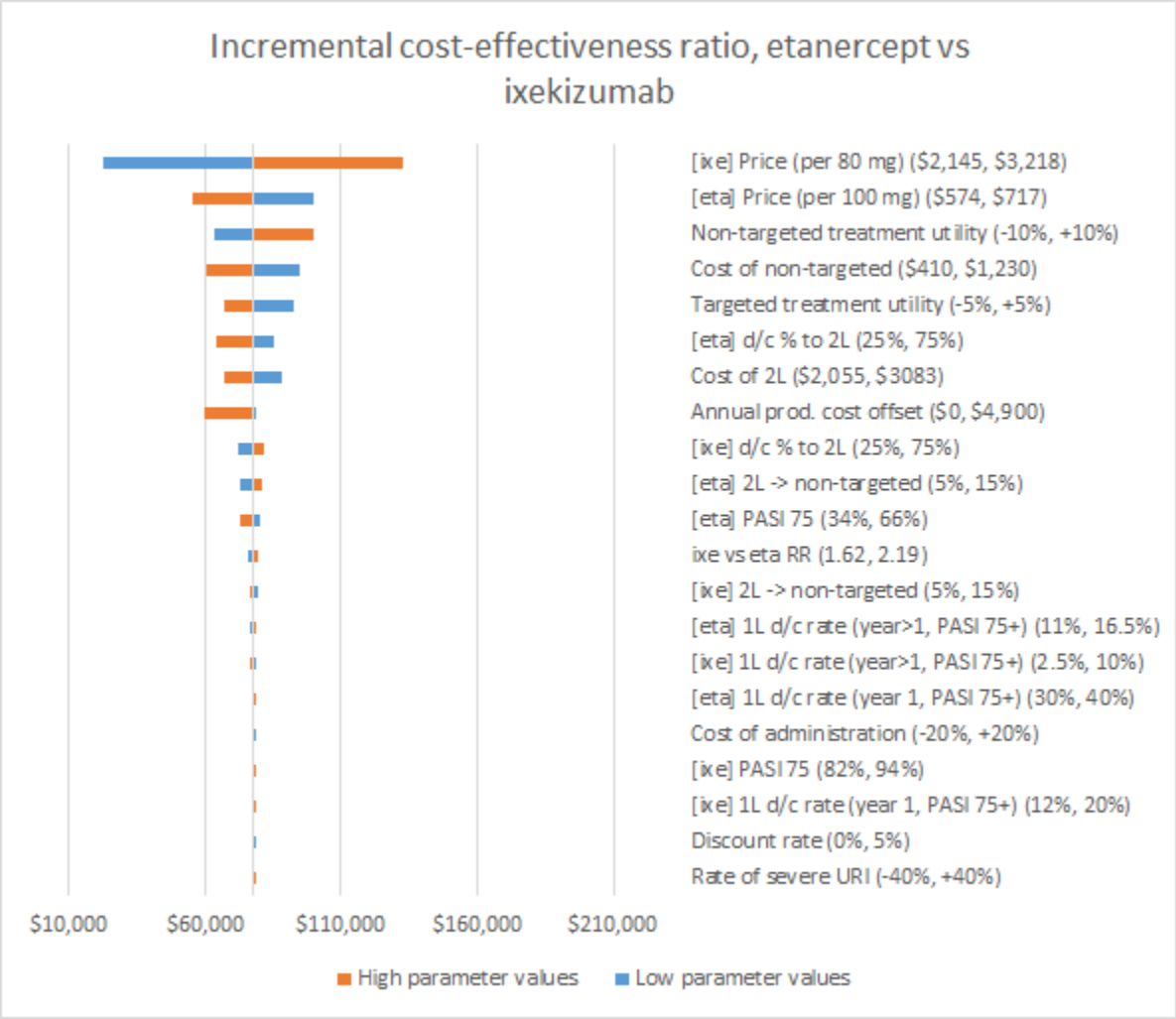
We also conducted one-way sensitivity analyses of ixekizumab versus infliximab. The results of varying both drug-specific and non-drug-specific parameters can be seen in Figure 9. Given that the outcomes (QALYs) of the two drugs are closer than between non-targeted and targeted therapies, the incremental cost-effectiveness ratio is more sensitive to parameter uncertainty. We see that a variety of parameters are influential, including the cost of each drug, the cost and utility of non-targeted therapy, each drug's discontinuation rate, and the relative effectiveness. The incremental cost-effectiveness, which ranges from approximately $27,000 to $220,000 across the assumed range of ixekizumab prices.

Figure 9. One-way sensitivity analysis: Infliximab versus ixekizumab



Lastly, we evaluated ixekizumab vs. etanercept. The results were generally similar to the ixekizumab vs. infliximab comparison, but overall there was less uncertainty (Fig. 10).

Figure 10. One-way sensitivity analysis: etanercept versus ixekizumab



In summary, the sensitivity analyses show that, as expected, drug costs have the greatest impact on the uncertainty in the value of targeted agents because of their relative importance and uncertainty. Another important source of uncertainty is the cost and quality of life associated with non-targeted therapy. Lastly, depending on the comparison, drug discontinuation rates are important contributors to uncertainty.

Scenario Analyses

Results when productivity costs are taken into account

Table 21 shows the results of the scenario in which productivity cost offsets, as described in the Methods above, are included. The ICERs in this scenario analysis – each roughly $20,000 lower than

the base case – demonstrate the potentially significant role that productivity gains might play in the value of targeted agents for psoriasis.

Table 21: Results comparing each drug to non-targeted therapy with productivity offset included

	Cost	QALYs	LYs	ICER vs. non-target
Non-targeted	$88,086	5.531	8.64	-
Adalimumab	$185,883	6.649	8.64	$87,470
Apremilast	$144,026	6.353	8.64	$68,057
Brodalumab	$208,489	7.151	8.64	$74,331
Etanercept	$178,838	6.469	8.64	$96,781
Infliximab	$178,536	6.776	8.64	$72,641
Ixekizumab	$221,812	7.187	8.64	$80,774
Secukinumab	$191,971	7.018	8.64	$69,851
Ustekinumab	$241,611	6.930	8.64	$109,726

Results when PASI 100 is taken into account

We also assessed the impact of attaining PASI 100, by stratifying the PASI 90+ group into PASI 90-99 and PASI 100, which necessitated the use of utility estimates derived using a novel instrument based on the EQ-5D designed specifically for psoriasis (the EQ-PSO).[150,120]When we switched to using these utilities, the ratio for ixekizumab relative to non-targeted therapy, for example, increased to $170,163 per QALY gained, because the gains relative to baseline are smaller for this utility set. When we then used drug-specific utilities that accounted for the proportion of patients achieving PASI 100 (estimated for drugs without PASI 100 data), the incremental cost-effectiveness ratio for ixekizumab was $151 per QALY. We conclude from this scenario analysis that the impact of achieving PASI 100 relative to PASI 90-99 is unlikely to meaningfully impact the overall economic value of psoriasis treatments.

Results when non-discounted WAC drug costs are used

Our base case uses class-specific discounts from WAC rounded to the nearest 5%. Appendix G shows the results of the model when WAC is used to price each drug. As suggested by the one-way sensitivity analyses, these results and their much higher ICERs reinforce that drug prices are the largest determinant of cost-effectiveness.

Lifetime time horizon results

Our base case and all scenarios listed above use a 10-year time horizon. Appendix Table G8 shows the results of using a lifetime time horizon. As more time is spent on second-line and non-targeted therapy in this scenario, the ICERs are more similar to each other and the contributions of the first-line agents become harder to discern compared to the 10-year base case analysis.

Threshold Analyses

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 22, along with the wholesale acquisition cost per tablet or vial. In many 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.

Table 22. Threshold analysis for price per drug for psoriasis treatments

	$50k / QALY	$100k / QALY	$150k / QALY	WAC price per vial*
Adalimumab (per 40mg)	$549.08	$1,311.40	$2,073.74	$2,048.54
Apremilast (per 30mg)* **	$2.24	$42.94	$83.64	$43.10
Brodalumab (per 210mg)	[$1,552.95]	[$2,696.61]	[$3,840.28]	[$4,266.79]**
Etanercept (per 50mg)	$143.37	$566.68	$989.98	$1,024.22
Infliximab (per 100mg)	$318.99	$857.54	$1,395.18	$1,113.27
Ixekizumab (per 80mg)	$1,550.08	$2,672.66	$3,795.25	$4,469.00
Secukinumab (per 300mg)	$1,489.47	$2,680.73	$3,872.00	$4,064.57
Ustekinumab (per 45mg)	$3,164.93	$5,886.50	$8,608.05	$8,840.22

*Wholesale acquisition cost as of October 28, 2016

**Brodalumab pricing is assumed, as not yet available

***Pill

6.5 Potential Budget Impact

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

Potential Budget Impact Model: Methods

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

The potential budget impact analysis included the entire candidate population for treatment, which 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 brodalumab or ixekizumab, we first determined the estimated incidence of psoriasis in the US. We used incidence rather than prevalence because we were interested only in patients who were taking a biologic for the first time. Psoriasis incidence in the United States has been estimated at 78.9 cases per 100,000 persons.[28] The proportion of psoriasis patients with plaque psoriasis has been estimated to be 79%.[28] Helmick found that 18.2% of psoriasis patients have moderate-to-severe disease, defined as involving greater than 3% of body surface area.[3] Applying these proportions to the projected 2016 U.S. population results in an estimate of approximately 36,750 incident cases of moderate-severe plaque psoriasis in the US per year, or approximately 183,750 incident cases over five years, assuming equal incidence rates for each of the five years in our analysis. This was assumed to be the candidate population for treatment with these novel agents.

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

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

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

Based on our assessment of these criteria, we assign a new drug or device to one of four categories of unmanaged drug uptake patterns: 1) very high (75% uptake by year 5); 2) high (50% uptake by year 5); 3) intermediate (25% uptake by year 5); and 4) low (10% uptake by year 5). In this analysis, we assumed a 10% uptake pattern for ixekizumab and a 10% uptake for brodalumab in the eligible population. We assumed that uptake would be low for ixekizumab and brodalumab because they would be the second and third 1L-17 inhibitor therapies for psoriasis patients to enter what is considered "an increasingly saturated market."[152]

Using this approach to estimate potential budget impact, we then compared our estimates to a budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation, this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA each year, and the contribution of spending on retail and facility-based drugs to total health care spending. Calculations are performed as shown in Table 23.

Table 23. Calculation of Potential Budget Impact Threshold

Item	Parameter	Estimate	Source
1	Growth in US GDP, 2015-2016 (est.) +1%	3.75%	World Bank, 2015
2	Total health care spending ($)	$3.08 trillion	CMS NHE, 2014
3	Contribution of drug spending to total health care spending (%)	13.3%	CMS National Health Expenditures (NHE), Altarum Institute, 2014
4	Contribution of drug spending to total health care spending ($) (Row 2 x Row 3)	$410 billion	Calculation
5	Annual threshold for net health care cost growth for ALL new drugs (Row 1 x Row 4)	$15.4 billion	Calculation
6	Average annual number of new molecular entity approvals, 2013-2014	34	FDA, 2014
7	Annual threshold for average cost growth per individual new molecular entity (Row 5 ÷ Row 6)	$452 million	Calculation
8	Annual threshold for estimated potential budget impact for each individual new molecular entity (doubling of Row 7)	$904 million	Calculation

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

Potential Budget Impact Model: Results

Table 24 presents the potential budget impact of one year and five years of brodalumab and ixekizumab in the candidate population, assuming the uptake patterns previously described. Results are presented for both one-year and five-year time horizons.

Results from the potential budget impact model showed that, with the uptake pattern assumptions mentioned above, an estimated 3,675 individuals would receive brodalumab in the first year, and an estimated 3,675 would receive ixekizumab in the first year. After one year of treatment with brodalumab, with net annual costs of approximately $32,700 per patient, one-year budget impact is estimated to be approximately $120.3 million. After one year of treatment with ixekizumab, net annual costs were estimated as approximately $37,400 per patient, and one-year budget impact as approximately $137.3 million.

Over the entire five-year time horizon, we estimate that "unmanaged" uptake would lead to approximately 18,375 persons taking brodalumab and 18,375 taking ixekizumab. Across the full five-year time horizon, the weighted potential budgetary impact (i.e., adjusted for differing periods of drug utilization and associated cost-offsets) is approximately $65,200 per patient taking brodalumab, and approximately $72,400 per patient taking ixekizumab. Total potential budgetary impact of brodalumab over five years is approximately $1.2 billion, with an average budget impact per year of approximately $240 million. For ixekizumab, total potential budgetary impact over five years is approximately $1.3 billion, with an average budget impact per year of approximately $266 million. The annualized potential budget impact of brodalumab is 27% of the budget impact threshold of $904 million for a new drug, while the annualized potential budget impact of ixekizumab is 29% of the threshold.

Table 24. Estimated Total Potential Budget Impact (BI) of Brodalumab and Ixekizumab for Treatment of Plaque Psoriasis

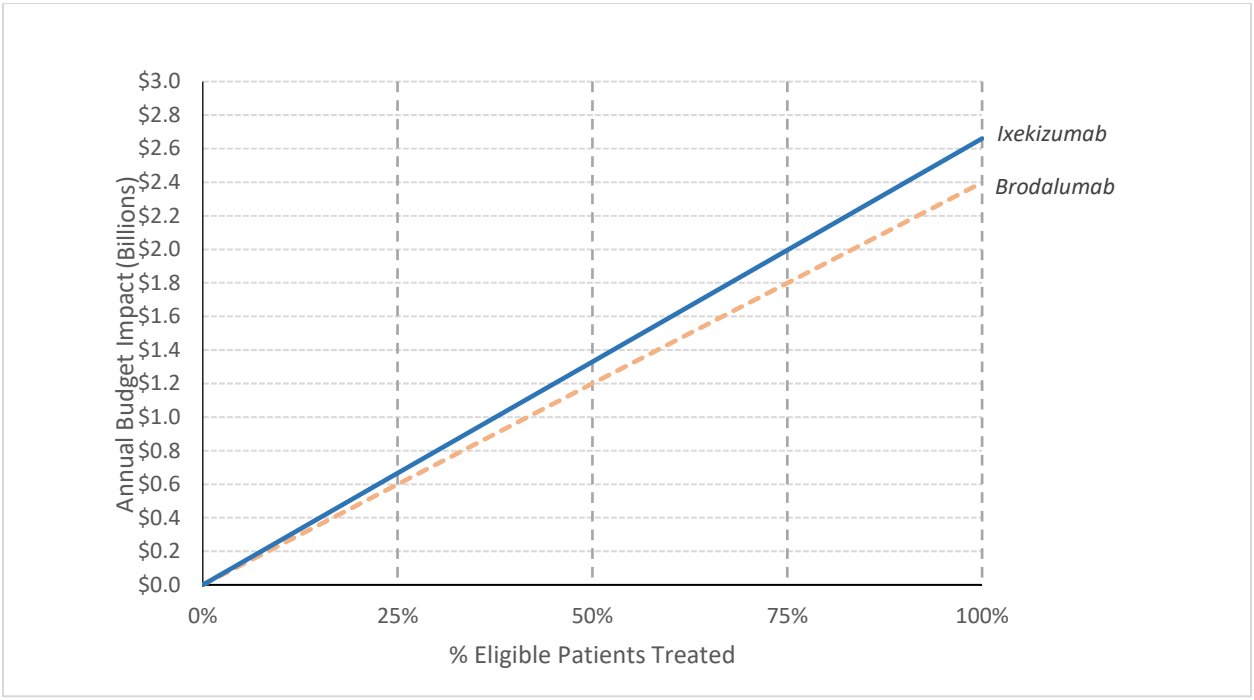
		Analytic Horizon = 1 Year			Analytic Horizon = 5 Years		
	Eligible Population	Number Treated	Annual BI per Patient*	Total BI (millions)	Number Treated	Weighted BI per Patient*	Average BI per year (millions)
Brodalumab	183,750	3,675	$32,700	$120.3	18,375	$65,200	$239.8
Ixekizumab	183,750	3,675	$37,400	$137.3	18,375	$72,400	$266.0

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

Figure 12 shows the relationship between varying possible uptake patterns and potential budget impact for each drug. The vertical axis shows the annualized potential budget impact, and the horizontal axis represents the percentage of eligible patients treated over a five-year period. The colored lines demonstrate how quickly the annual potential budget impact increases with increasing percentages of patients treated at the net prices used in this analysis.

As can be seen in Figure 12, potential budget impact of brodalumab is estimated to be below an annual threshold of $904 million until approximately 38% of eligible patients are treated. Approximately 34% of eligible patients could be treated with ixekizumab before potential budget impact reaches $904 million

Figure 12. Potential Budget Impact of brodalumab and ixekizumab treatment for psoriasis patients over different assumed product uptake patterns



Note: Colored lines represent the annualized budget impact of different uptake patterns (eligible patients treated) at the net price of each

6.6 Value-based Benchmark Prices

Our value-based benchmark prices for each psoriasis treatment are provided in Table 25. As noted in the ICER methods document, the value-based benchmark price for a drug is defined as the price range that would achieve cost-effectiveness ratios between $100,000 and $150,000 per QALY gained.

As shown in the table, with the exception of adalimumab, apremilast, and infliximab, all drugs would require discounts from current WAC prices to fall within ICER's threshold value range of $100,000 to $150,000/QALY. Importantly, however, our estimates of net prices bring all of the drugs of interest either within this threshold value range or generate cost-effectiveness ratios that are already <$100,000 per QALY gained.

Table 25. Value-based price benchmarks for all psoriasis targeted treatment regimens

	Net price*	WAC*	Cost to achieve $100k/QALY	Cost to achieve $150K/QALY	Discount from WAC to reach WTP threshold
Adalimumab (40mg)	$1,433.98	$2,048.54	$1,311.40	$2,073.74	36% to +1% increase
Apremilast (30mg)	$34.48	$43.10	$42.94	$83.64	0.4% to +94% increase
Brodalumab (210mg)	$2,560.07**	$4,266.79**	$2,696.61	$3,840.28	10% to 37%
Etanercept (50mg)	$717.11	$1,024.44	$566.68	$989.98	3% to 45%
Infliximab (100mg)	$779.24	$1,113.27	$857.54	$1,395.18	23% to +25% increase
Ixekizumab (80mg)	$2,681.40	$4,469	$2,672.66	$3,795.25	15% to 40%
Secukinumab (300mg)	$2,438.74	$4,064.57	$2,680.73	$3,872	5% to 34%
Ustekinumab (45mg)	$7,514.19	$8,840.22	$5,886.50	$8,608.05	3% to 33%

*Net price or WAC per vial/pill

**Assumed net price/WAC

6.7 Summary and Comments

Limitations and Discussion

We have attempted to model psoriasis treatment to both reflect clinical practice and accommodate the limits of available data. The latter necessity has placed some restrictions on how accurately we can model the course of psoriasis treatment. There are four major limitations of our analyses.

First, the course and effects of therapy sequencing is not clear – we did not identify a single RCT of a targeted drug in the second-line setting. We have assumed that after first-line therapy, half of patients take up a second-line targeted therapy while half de-escalate therapy and move to non-targeted therapy. While we weighted all first-line agents equally for purposes of estimating the costs and utility of second-line therapy, there is no doubt that some agents are preferred over others as second-line treatment. Because there are limited data to understand second-line therapy choice, we explored the effect of our assumptions on the results in sensitivity analyses. Given the importance of second-line effectiveness, controlled trials of targeted agents in the second-line setting should be a high research priority for private and public research organizations.

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

Second, we would have preferred direct utility elicitation data from clinical trials. Instead, we have had to surmise quality of life from improvements in PASI score. We believe that this is not an invalid method, but the uncertainty that it introduces into the model is greater than would be seen in a model that included direct patient reports of utility. In addition, more severe disease suffered by racial and ethnic minority patients may not be captured in model utilities.

Third, targeted agents in the psoriasis clinical area have seen significant drug price increases recently. At the same time, rebates for these drugs are large and variable. Because drug rebates are not publicly available, yet we desired to provide analyses that were reflective of real-world decisions that healthcare payers are facing, we utilized a novel source to estimate the general size of drug rebates within drug class. There is uncertainty in the size of these rebates, and we encourage policy makers to consider the threshold prices provided in Table 25.

Fourth, another major limitation of the analyses was uncertainty in the costs and quality of life effects of non-targeted therapy, which was assumed to consist of a mix of no treatment and various non-targeted treatments. We assumed patients in the non-targeted therapy health state had the same quality of life as at baseline in the clinical trials; this assumption could bias results in favor of targeted therapies by underestimating the quality of life in the non-targeted health state. We also estimated that patients in the non-targeted health state had approximately $10,000 in annual healthcare costs attributable to moderate/severe psoriasis; we believe this is a reasonable estimate given our definition of non-targeted therapy. Including specific interventions in the non-targeted arm would likely increase costs (biasing in favor of targeted agents) but also likely improve quality of life (biasing against targeted agents). We believe we have made reasonable compromises in our estimates, and findings of one-way sensitivity analyses suggest that cost-effectiveness of targeted vs. non-targeted therapy remains below $150,000 per QALY across a range of assumptions. We nevertheless encourage decision makers to consider the uncertainty in results related to the cost and quality of life of non-targeted therapy.

There are a variety of other limitations that should be noted. We did not explicitly model patients with psoriatic arthritis. However, since 20%-30% of patients enrolled in the clinical trials were diagnosed with psoriatic arthritis, our results are relevant for plaque psoriasis populations with

similar proportions of patients with comorbid psoriatic arthritis. Given that quality of life improvements are very likely to be greater in patients with psoriatic arthritis compared to the mixed population we modeled, the value of targeted agents in patients with psoriatic arthritis is expected to be greater on average.

We included only one serious adverse event (upper respiratory tract infection/pneumonia) to explore the potential impact of adverse events on value. Similar to previous economic analyses, we found that serious adverse events play only a small role in the overall value of targeted agents, because they are relatively rare and generally similar across agents.

It is worth noting that infliximab is the only IV administered drug considered here. Although we included patient time costs associated with infusions, other patient-focused considerations such as convenience and out of pocket expenses should be considered in decision making.

Biosimilars have been FDA-approved for adalimumab, etanercept, and infliximab, although none are currently available on the market. We did not attempt to include the future impact of these agents on the value of targeted agents in psoriasis because clinical data is limited and, more importantly, drug pricing is not available. However, the threshold prices presented above provide a reference point for value-based pricing of biosimilars.

Lastly, there were multiple public comments about the appropriateness of using QALYs to assess the value of drug therapies. It is worth noting that QALYs are a patient-centered outcome. In this study, our QALY estimates were derived from a measure (the EQ-5D) that captures the following five domains of patient quality of life: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Arguably, all of these domains are highly relevant for patients with psoriasis. And importantly, if quality of life benefits were not accounted for in psoriasis treatment, targeted agents would have little to no value based on current evidence.

Conclusion

There are three key findings from our analyses. First, all of the targeted drugs had reasonably good value for money compared to non-targeted therapy, using our estimated, discounted drug costs. The value of targeted agents is driven primarily by their meaningful impact on patient quality of life, and secondarily by offsetting other costs of care such as clinic visits and use of non-targeted therapies. While there are multiple sources of uncertainty, primarily caused by data limitations, this finding is robust using our base-case drug prices.

Second, despite the somewhat similar cost-effectiveness ratios vs. non-targeted therapy, there were important differences in the total amount of patient benefit (measured as QALYs) that could be gained for each drug. Drugs with high first-line efficacy and low discontinuation rates provide the greatest patient benefit, despite the availability of second-line therapy for those who failed

first-line treatment. There are several reasons for this. First, not all patients who fail first-line therapy will continue to second-line therapy, and potential patient benefit is lost. Second, initiating second-line therapy incurs the added drug cost of another initiation period. Finally, although there is a paucity of data, it appears that second-line therapy may be slightly less effective than first-line treatment with the same drug.

Third, the newer IL-17A targeted agents provide good economic value in relation to etanercept. The lower initial effectiveness of etanercept, high long-term discontinuation rates, and the need for more expensive second-line therapy decrease its overall value despite lower initial drug cost.

In summary, our analyses suggest that if health care payers are able to achieve significant drug rebates, the most effective (and most expensive) targeted drugs provide the greatest benefit to psoriasis patients at a reasonable economic value.

7. Summary of the Votes and Considerations for Policy

7.1 About the New England CEPAC Process

During New England CEPAC public meetings, the New England CEPAC Panel deliberates and votes on key questions related to the systematic review of the clinical evidence, an economic analysis of the applications of treatments under examination, and the supplementary information presented. Panel members are not pre-selected based on the topic being addressed and are intentionally selected to represent a range of expertise and diverse perspectives.

Acknowledging that any judgment of evidence is strengthened by real-life clinical and patient perspectives, subject matter experts are recruited for each meeting topic and provide input to New England CEPAC Panel members before the meeting to help clarify their understanding of the different interventions being analyzed in the evidence review. The same clinical experts serve as a resource to the New England CEPAC Panel during their deliberation, and help to shape recommendations on ways the evidence can apply to policy and practice.

At each meeting, after the New England CEPAC Panel votes, a policy roundtable discussion is held with the New England CEPAC Panel, clinical experts, and representatives from payers and patient groups. The goal of this discussion is to bring stakeholders together to apply the evidence to guide patient education, clinical practice, and coverage and public policies. Participants on policy roundtables are selected for their expertise on the specific meeting topic, are different for each meeting, and do not vote on any questions.

At the November 18, 2016 meeting, the New England CEPAC Panel discussed issues regarding the application of 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 (public comments from the meeting can be accessed here, starting at 1:27:14), the New England CEPAC Panel voted on key questions concerning the comparative clinical effectiveness and comparative value of treatment options for moderate-to-severe chronic plaque psoriasis. These questions are developed by the ICER research team for each assessment to ensure that the questions are framed to address the issues that are most important in applying the evidence to support clinical practice, medical policy decisions, and patient decision-making. The voting results are presented below, along with comments reflecting considerations mentioned by New England CEPAC Panel members during the voting process.

In its deliberations and votes related to value, the New England CEPAC Panel made use of a value assessment framework with four different components of “long term value for money,” a concept

that represents the long-term perspective, at the individual patient level, on patient benefits with a given intervention and the incremental costs to achieve those benefits. The four components of long term value for money are comparative clinical effectiveness, estimated incremental cost-effectiveness, other benefits or disadvantages, and contextual considerations regarding the illness or therapy.

There are four elements to consider when deliberating on long term value for money:

1. Comparative clinical effectiveness is a judgment of the overall difference in clinical outcomes between two interventions (or between an intervention and placebo), tempered by the level of certainty possible given the strengths and weaknesses of the body of evidence. The New England CEPAC uses the ICER Evidence Rating Matrix as its conceptual framework for considering comparative clinical effectiveness.

2. Estimated incremental cost-effectiveness is the average per-patient incremental cost of one intervention compared to another to achieve a desired "health gain," such as an additional stroke prevented, case of cancer diagnosed, or gain of a year of life. Alternative interventions are compared in terms of cost per unit of effectiveness, and the resulting comparison is presented as a cost-effectiveness ratio. Relative certainty in the cost and outcome estimates continues to be a consideration. As a measure of cost-effectiveness, ICER follows common academic and World Health Organization (WHO) standards by using cost per quality-adjusted life years (QALYs) and adopting thresholds at $100,000 per QALY and $150,000 per QALY as guides to reasonable ratios for cost-effectiveness.

3. Other benefits or disadvantages refers to any significant benefits or disadvantages offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. Examples of other benefits include better access to treatment centers, mechanisms of treatment delivery that require fewer visits to the clinician's office, treatments that reduce disparities across various patient groups, and new potential mechanisms of action for treating clinical conditions that have demonstrated low rates of response to currently available therapies. Other disadvantages could include increased burden of treatment on patients or their caregivers. For each intervention evaluated, it will be open to discussion whether other benefits or disadvantages such as these are important enough to factor into the overall judgment of care value. There is no quantitative measure for other benefits or disadvantages.

4. Contextual considerations include ethical, legal, or other issues (but not cost) that influence the relative priority of illnesses and interventions. Examples of contextual considerations

include whether there are currently any existing treatments for the condition, whether the condition severely affects quality of life or not, and whether the condition affects priority populations. There is no quantitative measure for contextual considerations.

7.2 Clinical Effectiveness Voting Results

1) Is the evidence adequate to demonstrate that the net health benefit of apremilast is as good as that provided by any of the TNFα inhibitors?

Yes: 0 votes	***No: 14 votes***

Comments: Members of the New England CEPAC unanimously voted that the evidence was not adequate to demonstrate that the net health benefit of apremilast is as good as provided by any of the TNFα inhibitors because there were no direct comparisons and the results of the network meta-analysis suggested at least comparable if not better effectiveness for the TNFα inhibitors versus apremilast.

2) Is the evidence adequate to distinguish the net health benefit among the IL-17A targeted drugs secukinumab, ixekizumab, and brodalumab?

Yes: 0 votes	***No: 14 votes***

Comments: Members of the New England CEPAC unanimously voted that the evidence was not adequate to distinguish the net health benefit among the IL-17A drugs given the absence of direct comparative evidence and their similar performance in the network meta-analysis.

2a) Is the evidence adequate to demonstrate that the net health benefit of IL-17A drugs as a class is better than that provided by adalimumab?

Yes: 5 votes	***No: 9 votes***

Comments: In discussing the evidence, clinical experts emphasized that concomitant clinical conditions such as psoriatic arthritis (e.g., with axial disease or uveitis) might influence the

choice by a clinician for adalimumab versus an anti-IL-17A agent. It was agreed that the results of this vote should be viewed as excluding important considerations of co-morbidities and co-conditions that might strongly affect the net health benefit for IL-17A drugs versus TNFα inhibitors. Members of the New England CEPAC were split in their vote. One member of the New England CEPAC who voted "no" felt the indirect comparisons left too much uncertainty of the magnitude of relative benefit of IL-17As. One member of the New England CEPAC who voted "yes" agreed that the evidence had limitations, but based on the consistency of PASI 90 and PASI 100 differences with the PASI 75 findings, the IL-17A inhibitors appeared to be more effective. Another member who voted "yes" was impressed by the lower projected discontinuation rate for the IL-17A inhibitors, a potential reason for their success.

2b) Is the evidence adequate to demonstrate that the net health benefit of IL-17A drugs as a class is better than that provided by etanercept?

Yes: 14 votes	No: 0 votes

Comments: The unanimous vote was ascribed to the consistent results of head-to-head studies, mirrored in the findings of the network meta-analysis.

2c) Is the evidence adequate to demonstrate that the net health benefit of IL-17A drugs as a class is better than that provided by infliximab?

Yes: 1 votes	***No: 13 votes***

Comments: The preponderance of "no" votes were ascribed to the results of the network meta-analysis in which the credible interval of this comparison overlapped with 1.0—in other words, the available data could not rule out the possibility of no difference between treatments. One New England CEPAC member voted "yes" because of concerns about access to infliximab, an intravenous medication, and because net health benefits appeared to trend better with the IL-17A inhibitors.

3) Is the evidence adequate to demonstrate that the net health benefit of ustekinumab is better than that provided by adalimumab?

Yes: 1 votes	***No: 13 votes***

Comments: Members of the New England CEPAC largely followed the "insufficient" finding from the network meta-analysis in this vote. The member of the New England CEPAC who voted "yes" argued that having a quarterly therapy instead of a monthly or bi-monthly therapy might be important for patient quality of life and adherence.

4) Is the evidence adequate to demonstrate that the net health benefit of ustekinumab is better than that provided by etanercept?

Yes: 14 votes	No: 0 votes

Comments: The panel unanimously agreed that the evidence was adequate to demonstrate the net health benefit of ustekinumab over etanercept, based on direct comparative evidence between these agents and the similar findings from the network meta-analysis.

5) Is the evidence adequate to demonstrate that the net health benefit of ustekinumab is better than that provided by infliximab?

Yes: 0 votes	***No: 14 votes***

Comments: While the panel voted unanimously, there was a discussion about patient heterogeneity. A practicing clinical expert acknowledged that individual patients' responses are hard to predict. While there are some genetic differences between patients that are meaningful on a population basis, there are no indicators for individual patients and patients do occasionally see different responses between different TNFα inhibitors. In addition, panel members acknowledged that their votes were based on indirect evidence only.

7.3 Care Value Voting Results

6) Given the available evidence on comparative effectiveness and incremental cost-effectiveness using estimated discounted prices for private insurers presented in the report, and taking into account other benefits, disadvantages, and contextual considerations, what is the long-term value for money of the following drugs compared to continued non-targeted therapy?

Adalimumab:

Low: 0 votes	***Intermediate: 11 votes***	High: 3 votes

Etanercept:

Low: 2 votes	***Intermediate: 11 votes***	High: 1 votes

Comment: One of the members of the New England CEPAC who voted "low" value felt that etanercept was too expensive given the benefits seen.

Infliximab:

Low: 3 votes	***Intermediate: 9 votes***	High: 2 votes

Comment: One member of the New England CEPAC who voted "low" was concerned that the time commitment and frequency of dosing for an IV therapy made it lower value.

Ustekinumab:

Low: 3 votes	***Intermediate: 9 votes***	High: 2 votes

Comment: One member of the New England CEPAC who voted "high" value considered the convenience of quarterly dosing for patients who have an aversion to injections. Other panel members who voted "intermediate" and "low" value were concerned with weight-based dosing costs for overweight patients.

Secukinumab:

Low: 0 votes	Intermediate: 3 votes	***High: 11 votes***

Comment: In general, members of the New England CEPAC who voted "high" felt that IL-17A inhibitors showed demonstrable improvements in clinical outcomes at marginal costs that were at or sometimes below $100,000 per QALY, thus representing in their opinion a "high" value.

Ixekizumab:

Low: 0 votes	Intermediate: 6 votes	***High: 8 votes***

Comment: Members of the New England CEPAC who voted "high" for both secukinumab and ixekizumab stated that this class of agents had the highest QALY gains and are the best options for patients with a challenging-to-treat disease. Two members of the New England CEPAC changed their vote for secukinumab and ixekizumab from "high" to "intermediate" because the incremental cost effectiveness ratios crossed the $100,000/QALY threshold.

Brodalumab:

No comparative value vote was taken on brodalumab, as its anticipated approval by the FDA was delayed beyond this review and thus no list price was available for consideration.

Apremilast:

Low: 0 votes	*Intermediate: 7 votes*	*High: 7 votes*

Comments: Members of the New England CEPAC were split evenly between an intermediate and a high value vote for apremilast. The discussion centered on balancing the facts that apremilast had perhaps the lowest efficacy among drugs reviewed, offers the benefit of a unique route of administration—apremilast is the only oral drug—and has a low incremental cost effectiveness ratio. Panel members acknowledged the subset of patients who are pleased to have an oral option without drug monitoring so that they can drink alcohol and use birth control. Still, other members who leaned toward intermediate recognized apremilast's lower efficacy and high discontinuation rate due to side effects (e.g. gastrointestinal distress) and non-response.

7) Given the available evidence on comparative clinical effectiveness and incremental cost-effectiveness, and taking into account other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with ixekizumab and secukinumab versus etanercept?

Low: 0 votes	Intermediate: 1 votes	***High: 13 votes***

Comments: The panel member who voted intermediate noted that while comorbidities were not reflected in the voting questions, IL-17A agents are contraindicated for patients with certain conditions (e.g., inflammatory bowel disease), which should factor into value considerations.

7.4 Roundtable Discussion and Key Policy Implications

Following its deliberation on the evidence, the New England CEPAC Panel engaged in a moderated discussion about use of targeted immunomodulators for the treatment of chronic plaque psoriasis with a Policy Roundtable that included 2 clinical experts, 2 patient representatives, and 2 payer representatives. The policy roundtable discussion with the New England CEPAC Panel reflected multiple perspectives and opinions, and therefore, none of the recommendations below should be taken as a consensus view held by all participants. The names of the Policy Roundtable participants are shown below.

Table 26. Policy Roundtable Participants

Joseph F. Merola, MD, MMSC Department of Dermatology |Harvard Medical School Director of the Clinical Unit for Research Innovation & Trials; Director of the Center for Skin & Related Musculoskeletal Diseases |Brigham and Women's Hospital	**Paul Jeffrey, PharmD** Director of Pharmacy; Office of Clinical Affairs University of Massachusetts Medical School; MassHealth (Massachusetts Medicaid)
Leah McCormick Howard, JD Vice President of Government Relations and Advocacy National Psoriasis Foundation	**Chris Pettit** Patient Advocate Portland, Oregon
Abby S. Van Voorhees, MD Chair, Department of Dermatology Eastern Virginia Medical School Chair, National Psoriasis Foundation	**Thomas Kowalski, RPh** Clinical Pharmacy Director, Health and Medical Management Blue Cross Blue Shield of Massachusetts

The roundtable discussion was facilitated by Dr. Steven Pearson, MD, MSc, President of ICER. The main themes and recommendations from the discussion are organized by audience and summarized below.

Specialty Societies and Patient Advocacy Groups

Update treatment guidelines for patients with moderate-to-severe chronic plaque psoriasis in a form that is easy to understand and easy-to-use by payers, clinicians, and patients

Payers base their coverage decisions and integration of utilization tools to a great extent on clinical guidelines. Payers on the policy roundtable expressed frustration with difficult-to-interpret, out-of-date clinical guidelines that precede the introduction of IL-17A agents. For example, there was discussion over whether methotrexate should represent a uniform first

step in treatment or whether this was an artifact of older guidelines that included a smaller number of biologic agents than are available today. The National Psoriasis Foundation anticipates that revised treatment guidelines will be released in the spring of 2018, but payers are currently structuring coverage decisions based on the latest treatment guideline update from the American Academy of Dermatology and the American College of Rheumatology that was published in 2011, in which methotrexate and PUVA (a form of phototherapy now considered outdated) both play prominent roles.[153]

Payers expressed the need for updated guidelines from clinical societies with detailed guidance and understanding of clinical nuance that would allow for creation of meaningful step therapy approaches with "edits" that would represent reasonable clinical exceptions—for example, use of an agent that can address both psoriasis and psoriatic arthritis, or avoidance of an agent with suboptimal performance in patients with a certain comorbidity profile.

Relatedly, the National Psoriasis Foundation has just released a "treat-to-target" consensus statement, based on input from 25 experts in plaque psoriasis.[154,155] The statement is based on body surface area (BSA), which the authors felt was a commonly-used, practical, understandable measure for clinicians, patients, and payers. The statement established an initial treatment target BSA of ≤ 1% at 3 months and a continuing target of ≤ 1% BSA every 6 months. The consensus statement considers an initial BSA of ≤ 3% or a 75% improvement from baseline "acceptable". Future guidelines and clinical studies should incorporate such treat-to-target goals in a way that is specific, interpretable, and implementable for payers to guide coverage decisions.

Purchasers and Insurers

Consider limiting or abolishing "step therapy" approaches to coverage.

Based on the comparative value evaluation, for patients with moderate-to-severe plaque psoriasis all targeted immunomodulators represent reasonable long-term value for money compared to non-targeted treatment. Nonetheless, in part because of outdated clinical guidelines, and in part because many patients with psoriasis will respond to topical and other non-targeted treatments, the norm for both public and private insurers in the US has been to use step therapy protocols for access to targeted drugs and for selection among the targeted immunomodulators. Payers on the policy roundtable described step therapy as a practical, logical, cost-effective tool that seeks to mirror the idea of "treatment algorithms" common to clinicians. Payers also stated that step therapy protocols requiring treatment with TNFα inhibitors are also reasonable given their longer-term safety record. That being said, payers expressed willingness to consider modifying or eliminating step therapy

protocols based on systematic evidence reviews, value assessments, and updated evidence-based guidelines.

The importance of reconsidering step therapy policies was highlighted during the discussion of the policy roundtable. Patients and clinicians stated that step therapy protocols can seriously delay improvements to patients' quality of life. Patients are often required to continue with less effective drugs for months or years prior to being allowed access to more effective, well-tolerated treatments. Patient representatives also said that step therapy can discourage patients from being treated at all, especially when clinicians do not have the resources to vigorously advocate on behalf of patients with payers.

Expert clinicians agreed that step therapy and access to medications is the number one challenge in managing patients with severe plaque psoriasis. Clinicians expressed frustration with unyielding requirements to use topical therapies (which are challenging to apply to large proportions of the body surface, particularly the back); methotrexate (which can cause "methotrexate fog" and must be discontinued eventually due to the risk of liver toxicity); phototherapy (which requires frequent office visits, making adherence challenging for many patients, especially young students and working individuals); and combinations of methotrexate, phototherapy, and acitretin, which are complicated and lead to poor outcomes for many patients. Clinicians were concerned about patients dropping out of treatment because of frustrations with non-response and the administrative burdens of step therapy, burdens that are frequently repeated with every change of insurer. Clinicians argued that excellent clinical care required access to all targeted immunomodulators because of the unique benefits or disadvantages of some targeted immunomodulators for certain clinical scenarios (e.g., treatment of a patient with concomitant uveitis or axial arthritis); and availability of multiple routes of administration and dosing schedules that allow tailored regimens for patients who must travel, live far from home, or have other relevant considerations.

Given that the targeted immunomodulators have good value relative to non-targeted treatment, payers should strongly consider eliminating most step therapy requirements for patients with moderate-to-severe psoriasis, especially for those patients who demonstrate the need for intensive, ongoing regimens. Given that the incremental clinical benefits of IL-17A inhibitors cannot categorically be demonstrated to be superior to adalimumab, there may still be a reasonable justification for requiring a trial of adalimumab (or another TNFα inhibitor) prior to use of more expensive drugs, but, as discussed further below, any step therapy between TNFα inhibitors and other drugs should be carefully constructed to allow rapid and permanent exceptions for patients with co-conditions, co-morbidities, or specific

life requirements that make other drugs the best first choice among all available targeted immunomodulators.

If step therapy will be used:

Allow individuals switching insurers to bypass step therapy if they are already on an effective treatment.

Psoriasis is a chronic disease that patients manage for decades. It is important that patients maintain continuity of care, despite switching employers or insurers. Individuals switching insurer for any reason should be able to bypass step therapy protocols if current treatment is working, especially if they have used prior steps in the past. Some insurers, such as Blue Cross Blue Shield of Massachusetts, allow new members, with eligibility less than 90 days, to bypass step therapy to avoid interruption of therapy and treatment.

Remove requirements for patients to have higher out-of-pocket expenses for "later step" treatments.

For patients who follow a step therapy protocol and end up on a higher tier or "later step" medication, efforts should be taken to design the formulary so that patients are not required to pay a substantially higher co-payment or switch from co-payment to co-insurance. One patient advocate commented that when out-of-pocket costs go over $100 per month, adherence tends to drop.[156] The general principle in formulary design should be that patients who are "good soldiers" and have tried but failed the first drug in a step therapy protocol should not be required to pay substantially more out of pocket for a subsequent treatment.

As alternative mechanisms to manage costs, consider developing indication-specific formulary designs and outcome-based payment contracts.

Payers should explore the use of mechanisms other than step therapy to help manage the outcomes and costs of care. Chief among the options to be considered are indication-specific formulary designs and outcome-based payment contracts. Indication-specific formulary design would allow payers to benefit from competition within each clinical indication for targeted immunomodulators. The general pattern has been for certain drugs with broad indications to gain formulary preference since most payers have not developed practical ways to link the use of these drugs to specific diagnoses. Payers should consider following the lead of Express Scripts, which has developed an indication-specific formulary design for the auto-immune conditions, allowing "niche" drugs to gain preference even if they could not compete across multiple indications. Further details on the Express Scripts program can be found here.

A second option is to consider some form of outcome-based payment, in which rebates or refunds are linked to outcomes. As part of the Express Scripts program, plan sponsors will receive a refund of up to $6,000 if patients discontinue a preferred auto-immune medication within the first 90 days. As part of any refund program of this type it should be explored whether refunds to patients for their out-of-pocket payments can also be included.

Co-payment and/or co-insurance for therapies should be based on prices net of discounts and rebates instead of list price.

Higher out-of-pocket costs put patients at high risk of coverage loss, bankruptcy, and inability to access effective treatment necessary to control a chronic disease. As shown in our report, rebates and discounts are substantial for most psoriasis drugs. However, patient out-of-pocket payments are based on the list price for these medications. Insurers should seek ways to calculate patient contributions based on the negotiated price, allowing patients to share in savings from cost-effective treatment pathways, especially if part of a step therapy protocol.

Manufacturers

Foster transparency in the rationale for price increases.

As noted in our report, some of the classes of psoriasis drugs have seen significant price increases in the past few years. Presently, discounted prices appear to be well-aligned with patient value for these drugs. If price increases continue at their current pace, however, this alignment will not continue for long. Manufacturers should seek to keep prices at a level that reflects the added benefit to patients, be mindful of the overall impact on health care costs of the growing use of targeted immunomodulators, and recognize the potential for lower prices to be linked to greater access for all patients. In addition, manufacturers should be transparent about the rationale for any future price increases, including new clinical evidence, improvements in therapy delivery or tolerability, and other considerations.

Release treatment-specific quality-of-life data.

Health economists are often frustrated by a lack of available data on disease-specific quality of life. When evaluated, information is often provided at the condition level, without data on the effect of treatment on quality of life measures. As an example, data from the commonly-used EuroQol (EQ)-5D was available for the psoriasis model, but was not

stratified by treatment group. Quality-of-life assumptions were therefore driven primarily by model structure rather than actual, trial-based data on treatment effect. To address this concern, manufacturers should release both summarized and treatment-stratified quality-of-life information.

Researchers and Manufacturers

Conduct research that directly compares real-world treatment options and sequential treatment effectiveness for both naïve and treatment-experienced patients.

As noted in the report, head-to-head clinical trial data were sparse and focused on only a few comparisons. There is also little information on how each targeted immunomodulator performs in early- versus later-line use. Patients, clinicians, and payers would benefit from real-world data comparing multiple treatment options, sequences, and combinations. For example, first-line use of targeted immunomodulators could be compared to other systemic therapies like methotrexate to evaluate their effectiveness and durability of benefit. In addition, within-class comparisons could be performed to identify advantages for particular agents. Finally, use of specific sequences of targeted immunomodulator therapy should be evaluated to identify the optimal treatment strategy for specific groups of patients, and to assess the possible decreased benefit for medications in early- versus later-line use.

Generate additional information on the treatment durability of IL-17A agents.

Since the IL-17A inhibitors are the newest class of drugs for plaque psoriasis, data on clinical benefits and potential harm are relatively short-term. There have been anecdotal reports suggesting that skin clearing wanes over time with IL-17A inhibitors. It is therefore important that manufacturers and researchers begin research on the longer-term effects of the IL-17A inhibitors including benefits, harms, and durability-of-response.

Patient Advocacy Groups, Clinicians, and Researchers

Patients and patient organizations should take a leadership role in the design of clinical trials and all stakeholders should advocate for rigorous study in diverse populations evaluating real-world comparative treatments.

Given the evolution of new therapies for moderate-severe plaque psoriasis, patients and clinicians often lack information on comparative clinical effectiveness of different treatment options that is necessary to help them tailor care for the individual patient. Clinical experts

noted, for example, that patients who have not yet taken a targeted immunomodulator are under-represented in many US-based clinical trials. Patient groups can help by encouraging patients to participate in clinical trials and by taking a leadership role in identifying treatment strategies and outcome measures that matter most to patients. Clinicians should also encourage patients to consider participating in research, and should develop the practice infrastructure needed to make that participation as seamless as possible. Researchers should work directly with patient groups and clinicians to ensure that trial design and implementation present the lowest barriers possible to participation.

Lead research efforts to evaluate heritability of psoriasis and the impact of managing plaque psoriasis on caregivers and families.

Patients groups describe the quality-of-life impacts of plaque psoriasis as extending well beyond the challenges and stigma faced by individual patients—there are substantial effects on family members and caregivers. Patients expressed concern about genetic factors associated with psoriasis onset and the likelihood of "passing the disease on" to future generations. Research on the impact of psoriasis on caregivers, family members, and the heritability of psoriasis would help broaden the understanding of the impact of psoriasis and capture the value of new treatments.

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Appendices

Appendix A. Evidence Review Methods and Results

Table A1. PRISMA 2009 Checklist

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

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

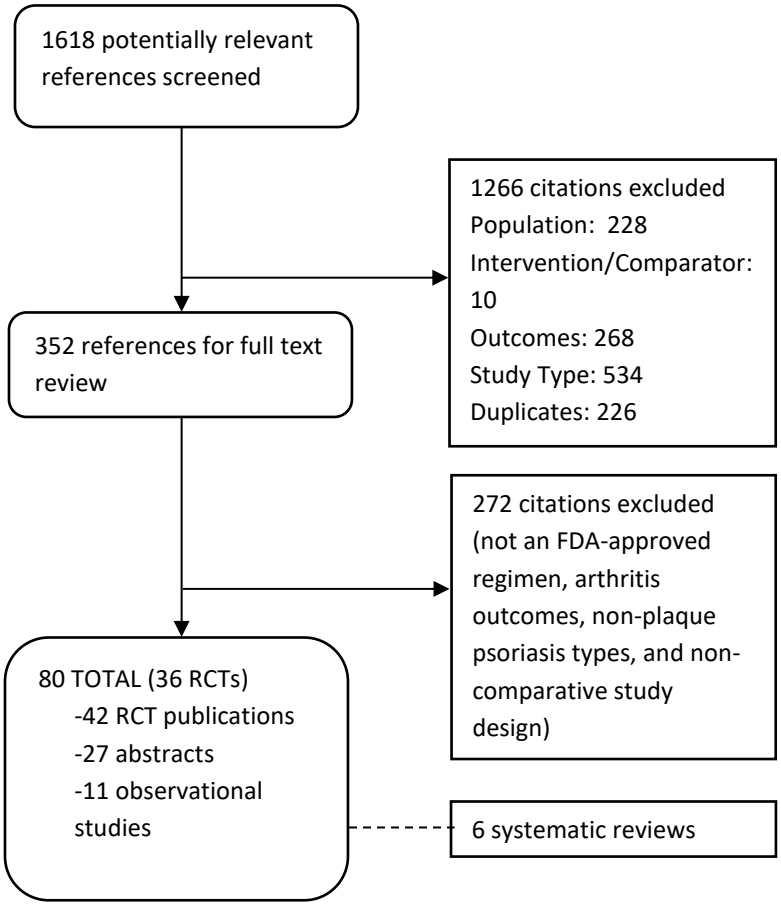
Table A2. Search Strategy of Medline 1996 to Present with Daily Update, EBM Reviews - Cochrane Database of Systematic Reviews, EBM Reviews - Cochrane Central Register of Controlled

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

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

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

Figure A1. PRISMA Flow Chart Showing Results of Literature Search



Appendix B. Evidence Summary Tables

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Publication *Piaserico, 2014* *Fair quality*	*Observational, prospective study* *Adjustment:* *for the presence of comorbidities, smoking, steroid use* *and disease severity*	*1) 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* *Exclusion:*	Age, mean 71.3 Male, % 58.3 White, % NR Duration of PsO, yr 22.1 Previous biologic therapy, % 26.2 PASI, mean (SD) 1)14.9 (6.4) 2)14.3 (4.1) 3)14.8 (5.7)	PASI 75 at week 12, % 1) 64 2) 65 3) 93 4) 100	Serious AEs, % 1)7.2 2)0 3)12.5 4)0

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

					IXE Q2W, +5.2 **SF-36 PCS, mean score:** Placebo, -1.1 IXE Q4W, +5.1 IXE Q2W, +5.4 *IXE groups vs. placebo for all outcomes, p<0.001*	
IXORA-S, 2016 (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, contraindication, or intolerability of at least 1 systemic therapy Baseline PASI ≥10 Exclusion: Prior use of ustekinumab, prior	**NR**	**PASI 75 (%):** 1)91% 2)69% **PASI 90 (%):** 1)75 2)42 **PASI 100(%);** 1)37 2)15	NR

			participation of other study with ixekizumab or IL-17A or IL12/23 antagonists, concurrent or recent use of biologics within washout periods, ongoing or serious infection.		**sPGA of 0 (%):** 1)43 2)18 **DLQI of 0/1 (%):** 1)63 2)45	
Brodalumab						
Papp, 2012 (NCT00975637) *Good quality publication*	Phase II RCT Double-blind Multicenter 23 international sites ITT	N=198 1) brodalumab 70mg (n=39) 2) brodalumab 140mg (n=39) 3) brodalumab 210mg (n=40) 4) placebo (n=38) 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	**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	Primary outcomes at week 12: **PASI 75 (%):** 1) 33, 2) 77, 3) 82, 4) 0 **PASI 50 (%):** 1) 51, 2) 90, 3) 90, 4) 16 **PASI 90 (%):** 1) 18*, 2) 72, 3) 75, 4) 0 **sPGA score of 0/1 (%):**	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

			Exclusion: patients could not have received biologic agents within 3 months, and no previous treatment with ustekinumab or etanercept	**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	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	**Deaths: NR**

					2 vs. placebo, p<0.05; 3 vs. placebo, p<0.01 ***Other outcomes reported: Mean % BSA***	
Gordon, 2013 (NCT00975637) *Good quality publication*	Secondary analysis of Phase II data evaluating quality of life	See above	See above	See above	Primary outcomes at week 12: **PSI total score = 0 (%):** 1) 18, 2) 41, 3) 55, 4) 0 2 and 3 vs. 4, p<0.0001; 1 vs. 4 p=0.006 **PSI change:** 1) 8.5, 2) 15.8, 3) 16.2, 4) 4.8 2 and 3 vs. 4, p<0.0001; 1 vs. 4, p=0.042 Other outcomes reported: Includes	NR

					further breakdown of PSI and DLQI components at weeks 2, 4, 8	
Papp, 2014 (NCT00975637) *Fair quality publication*	Secondary analysis of Phase II data evaluating subgroups with and without PsA and with and without previous biologic use Subgroups were not compared statistically due to low statistical power	1) PsA- yes (n=46) 2) PsA- no (n=152) 3) Biologic use- yes (n=70) 4) Biologic use- no (n=158) a) placebo b) brodalumab 140mg c) brodalumab 210mg	See original trial	**Age (years):** 1) 89.7, 2) 90.1, 3) 93, 4) 21.3 **PsO duration (years):** 1) 24.3, 2) 17.3, 3) 21.4, 4) 17.6 **PASI:** 1) 26.6, 2) 22.9, 3) 26.5, 4) 22.2 **DLQI:** 1) **PsA (%)** 1) 100, 2) 0, 3) 24.3, 4) 22.7 **Previous biologics (%):**	Primary outcomes at week 12: **PASI 75 (%):** 1a) 0, 1b) 82, 1c) 92 2a) 0, 2b) 75, 2c) 79 3a) 0, 3b) 70, 3c) 88 4a) 0, 4b) 60, 4c) 79 **PASI 90 (%):** 1a) 0, 1b) 73, 1c) 83 2a) 0, 1b) 71, 2c) 71 3a) 0, 1b) 70, 1c) 81 4a) 0, 1b) 72, 3c) 71 **DLQI response:** 1a) 0, 1b) 100, 1c) 100 2a) 42, 2b) 75, 2c) 79	AEs of any grade were higher among patients who received brodalumab versus placebo and were similar among subgroups (data NR)

				Anti-TNF- 1) 32.6, 2) 21.7, 3) 68.6, 4) 0 Ustekinumab- 1) 4.3, 2) 13.8, 3) 32.9, 4) 0	3a) 33, 3b) 80, 3c) 94 4a) 35, 4b) 83, 4c) 79 **PSI score ≤8, with no item having a score >1 (%):** 1a) 14, 1b) 100, 1c) 94 2a) 13, 2b) 86, 2c) 79 3a) 8, 3b) 100, 3c) 86 4a) 15, 4b) 94, 4c) 79 *All BROD groups vs. placebo were SS* Outcomes not compared between subgroups ***Other outcomes reported: PASI 100***	
Papp, 2015 (NCT00975637)	Secondary analysis of Phase II data evaluating subgroups	1) Biologic use- yes (n=70)	See original trial	See original trial	Primary outcomes at week 12:	**AEs at week 12 (%):** 1) brodalumab (combined) – 79%

Abstract	with and without previous biologic use	2) Biologic use- no (n=158) a) brodalumab 70mg b) brodalumab 140mg c) brodalumab 210mg d) placebo			**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	placebo – 67% 2) brodalumab (combined) – 70% placebo – 60%
Papp, 2016 (NCT01708590) AMAGINE 1 *Good quality publication*	Phase III RCT Double-blind Multicenter 73 sites in the US, Canada, and Europe	N=661 1) brodalumab 140mg Q2W (n=219) 2) brodalumab 210mg Q2W 3) placebo (n=222) Patients who achieved sPGA success (≥2) at	Inclusion: 18 - 75years BSA ≥10%, PASI ≥12 sPGA ≥3 ≥6 months of plaque psoriasis diagnosis	**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	Primary outcomes 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	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

	ITT (all randomized patients)	week 12 were rerandomized to their induction doses of brodalumab or placebo	Candidates for phototherapy or systemic therapy Exclusion: A washout period was required for patients receiving specific drugs (reported in supplementary appendix)	**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	**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 At week 52:	**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)

					PASI 90 (%): BROD 210/BROD 210, 78.3 BROD210/placebo, 0.0 BROD 140/BROD 140, 66.7 BROD140/placebo, 3.4 **PASI 100 (%):** BROD 210/BROD 210, 67.5 BROD210/placebo, 0.0 BROD 140/BROD 140, 43.9 BROD140/placebo, 1.7 **sPGA score ≥2 (%):** BROD 210/BROD 210, 83.1	

					BROD210/placebo, 0.0 BROD 140/BROD 140, 70.2 BROD140/placebo, 5.1 *All BROD vs. placebo, p<0.001* ***Other outcomes reported: sPGA score of 0***	
Strober, 2016 (NCT01708590) AMAGINE 1 *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 (%)**	NR

					1) 17, 2) 22, 3) 1 *All BROD groups vs. placebo, p<0.001* PSI responder data same as Papp, 2016	
Lebwohl, 2015 NCT01708603 AMAGINE-2 *Good quality publication*	Phase III RCT Double-blind Multicenter 142 international sites (US, Canada, Europe, Australia) ITT	N=2,492 1) placebo (n=309) 2) ustekinumab (n=300) 3) brodalumab 140mg Q2W (n=610) 4) brodalumab 210mg Q2W (n=612) At week 12, patients receiving brodalumab underwent rerandomization to receive one of four brodalumab	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	Primary outcomes at week 12: **PASI 75 (%)** 1) 8, 2) 70, 3) 67, 4) 86 **PASI 90 (%)** 1) 3, 2) 47, 3) 49, 4) 70 **PASI 100 (%)** 1), 2, 2) 22, 3) 26, 4) 44 **sPGA score of 0 or 1 (%)** 1) 4, 2) 61, 3) 58, 4) 79 **p1 (%)** 1) 7, 2) 55, 3) 51, 4) 68	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

		maintenance regimens		**DLQI:** NR **PsA (%):** 1) 17, 2) 17, 3), 21, 4) 19 **Previous biologics (%):** 1)29, 2) 28, 3) 29, 4) 29	*All BROD groups vs. placebo, p<0.001* *BROD 210mg was SS better than UST in both trials on PASI 75, 90, 100 and sPGA score of 0/1 (p-values in Table 2; no comparison b/w BROD and UST for PSI)* ***Other outcomes reported: sPGA score of 0*** At week 52 (after switching to brodalumab 210 mg): **PASI 75 (%)** 1) 94, 2) 91 **PASI 100 (%)**	**1 attempted suicide** in the brodalumab 210mg group **1 death** in the brodalumab 210mg group (cerebral infarction) **AE outcomes at week 52:** Based on number of patients with exposure-emergent adverse events per 100 patient-years (reported in supplementary appendix) **2 additional attempted suicides** in the same patient as the induction period and 1 in the UST group

					1) 62, 2) 46 **sPGA score of 0/1 (%)** 1) 87, 2) 73 **PSI score ≤8, with no item having a score >1 (%)** 1) 81, 2) 84	
Lebwohl, 2015 (same as above) (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:**	Primary outcomes at week 12: **PASI 75 (%)** 1) 69, 2) 85*, 3) 69, 4) 6 **PASI 90 (%)** 1) 2, 2) 48, 3) 52, 4) 69 **PASI 100 (%)** 1) 0.3, 2)19, 3) 27, 4) 37 **sPGA score of 0/1 (%):** 1) 6), 2) 69, 3) 69, 4) 85	**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

				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	**PSI score ≤8, with no item having a score >1 (%)** 1) 6, 2) 52, 3) 53, 4) 61 *All BROD groups vs. placebo, p<0.001* *BROD 210mg was SS better than UST in both trials on PASI 75, 90, 100 and sPGA score of 0/1 (p-values in Table 2; no comparison b/w BROD and UST for PSI) ***Other outcomes reported: sPGA score of 0*** At week 52 (after switching to brodalumab 210 mg): **PASI 75 (%)**	adverse events per 100 patient-years (reported in supplementary appendix) **No attempted suicides at any point during the study**

					1) 93 2) 92 **PASI 100 (%)** 1) 68 2) 40 **sPGA score of 0/1 (%)** 1) 90 2) 70 **PSI score ≤8, with no item having a score >1 (%)** 1) 86 2) 73	
Anti IL-12/13 Agent						
Ustekinumab (Stelara)						
Griffiths, 2010 (NCT00454584)	Phase III RCT Multicenter	N=903 1) ustekinumab 45mg (n=209)	Inclusion: ≥18 years BSA ≥10%,	**Age (years):** 1) 45.1, 2) 44.8, 3) 45.7 **% male:**	Primary outcomes at wk 12: **PASI 75 (%)** 1) 67.5 2) 73.8, 3) 56.8	Primary outcomes at week 12: **AEs ≥1 (%):**

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*	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	1) 63.6, 67.4, 3) 70.9 **Weight (kg):** 1) 90.4, 2) 91.0, 3) 90.8 **PsO duration (years):** 1) 18.9, 2) 18.7, 3) 18.8 **PASI:** 1) 20.5, 2) 19.9, 3) 18.6 **DLQI:** NR **PsA (%):** 1) 29.7, 2) 27.4, 3) 27.4 **Previous biologics (%):** 1) 12.4, 2) 10.4, 3) 11.8	*1 vs. 3, p=0.01* *2 vs. 3, p<0.001* **PASI 90 (%)** 1) 36.4, 2) 44.7, 23.1 **sPGA score of 0/1 (%)** 1) 65.1, 2) 70.6, 3) 49.0 *Both UST groups vs. ETN, p<0.001* Patients who did not respond on ETN and crossed over to UST 90mg: **PASI 75 (%)**: 48.9 **PASI 90 (%):** 23.4 **PGA- cleared or minimal (%):** 40.4 ***Other outcomes reported: PGA cleared***	1) 66.0, 2) 69.2), 3) 70.0 **URIs (%):** 1) 6.2, 2) 6.3, 3) 5.8 **SAEs ≥1 (%):** 1) 1.9, 2) 1.2, 3) 1.2 **Infections (%):** 1) 30.6, 2) 29.7, 3) 29.1 **Discontinuation due to AEs (%):** 1) 1.9, 2) 2.0, 3) 2.3 **3 deaths**, 1 in each active treatment arm **Common AEs at wk 64:** adverse events were similar in the lower-dose and higher-dose ustekinumab groups

						and also before and after crossover from etanercept to ustekinumab
Leonardi, 2008 (NCT00267969) PHOENIX 1 *Good quality publication*	Phase III RCT Double-blind Multicenter 48 sites in the US, Canada, and Belgium ITT with NRI	N=766 1) ustekinumab 45mg (n=255) 2) ustekinumab 90mg (n=256) 3) placebo (n=255) Ustekinumab patients with PASI ≥75% improvement re-randomized at wk 40 1) maintenance (n=162) 2) withdrawal (n=160)	Inclusion: ≥18 years PASI ≥12 BSA ≥10% ≥6 months of plaque psoriasis diagnosis Candidates for phototherapy or systemic therapy Exclusion: previous treatment with any agent that targets IL-12 or -23, received biological or investigational agents within previous 3 months, had received conventional systemic psoriasis therapy, or	**Age:** 1) 44.8, 2) 46.2, 3) 44.8 **% male:** 1) 68.6, 2) 67.6, 3) 71.8 **Weight (kg):** 1) 93.7, 2) 93.8, 3) 94.2 **PsO duration (years):** 1)19.7, 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	Primary outcomes at wk 12: **PASI 75 (%)** 1) 67.1, 2) 6 6.4, 3) 3.1 **PASI 50 (%)** 1) 83.5, 2) 85.9, 3) 10.2 **PASI 90 (%)** 1) 41.6, 2) 36.7, 3) 2.0 *All UST groups vs. placebo, p<0.0001*	Primary outcomes at week 12: **AEs ≥1 (%):** 1) 57.6, 2) 51.4, 3) 48.2 **URIs (%):** 1) 7.1, 2) 6.3, 3) 6.3 **SAEs (%):** 1) 0.8, 2) 1.6, 3) 0.8 **Infections (%):** 1) 31.4, 2) 25.9, 3) 26.7 No dose response was seen in the rates of adverse events, serious adverse events, or adverse

		Cross-over to ustekinumab 45 or 90 mg at week 12	phototherapy within the previous 4 weeks, or had received topical psoriasis treatment within the previous 2 weeks	**PsA:** 1) 29.0, 2) 36.7, 3) 35.3 **Previous biologics (%):** 1) 52.2, 2) 50.8, 3) 50.2	**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* ***Other outcomes reported: PGA clear and marked or severe and DLQI mean change also reported at week 12 and 28,***	events leading to study agent discontinuation Similar AEs in withdrawal phase AEs also reported wk 12-40 (crossover) and wk 40-74 (withdrawal) **3 deaths**, 1 in the 45mg and 2 in the placebo groups

					DLQI mean change reported at wk 28	
Kimball, 2013 PHOENIX 1	5-year long-term safety extension of PHOENIX 1	N=517 (those who received one dose of ustekinumab) 1) ustekinumab 45mg (n=259) 2) ustekinumab 90mg (n=258)	See above	Similar to original trial	At wk 244: **PASI 75 (%)** 1) 63.4, 2) 72.0 **PASI 90 (%)** 1) 39.7, 2) 49.0 **PASI 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 PHOENIX 2	Phase III RCT Double-blind Multicenter	N=766 1) ustekinumab 45mg (n=409) 2) ustekinumab 90mg (n=411)	Inclusion: ≥18 years PASI ≥12 BSA ≥10%	**Age (years):** 1) 45.1, 2) 46.6, 3) 47.0 **% male:**	Primary outcomes at wk 12: **PASI 75 (%):** 1) 66.7, 2) 75.7, 3) 3.7	Primary outcomes at week 12: **AEs ≥1 at wk 12 (%):** 1) 53.1, 47.9, 3) 49.8

Good quality publication	70 sites in Europe and North America ITT with NRI	3) placebo (n=410) *Partial responders (i.e., patients achieving ≥50% but <75% improvement from baseline in PASI) were re-randomized at week 28*	≥6 months of plaque psoriasis diagnosis Exclusion: patients who had received treatment with any agent that specifically targeted IL-12 or -23, had received biological or investigational agents within the previous 3 months	1) 69.2, 2) 66.7, 3) 69.0 **Weight (kg):** 1) 90.3, 2) 91.5, 3) 91.1 **PsO duration (years):** 1) 19.3, 2) 20.3, 3) 20.8 **PASI:** 1) 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	**PASI 50 (%):** 1) 83.6, 2) 89.3, 3) 10.0 **PASI 90 (%):** 1) 42.3, 2) 50.9, 3) 0.7 **PGA, cleared/minimal (%):** 1) 68.0, 2) 73.5, 3) 4.9 **DLQI, score of 0/1 (%):** 1) 55.3, 2) 56.4, 3) 3.2 *All UST groups vs. placebo, p<0.0001* ***Other outcomes reported: PGA clear and marked or severe and DLQI mean change also reported at week 12 and 28,***	**URIs (%):** 1) 4.4, 2) 2.9, 3) 3.4 **SAEs (%):** 1) 2.0, 1.2, 3) 2.0 **Infections (%):** 1) 21.5, 2) 22.4, 3) 20.0 **Discontinuation due to AEs (%):** NR *Patients not achieving PASI 50 at wk 28 discontinued the study* **AEs at wk 52:** No dose response had been observed in rates of adverse events, serious adverse events, or adverse events leading to treatment discontinuation.

				Baseline characteristics for partial responders at wk 28 also reported	***DLQI mean change reported at wk 28*** ***PASI 50, 90, 100 scores also reported at week 28***	**1 death (cardiac-related)**
Langley, 2015 PHOENIX 2	5-year long-term safety extension of PHOENIX 2 Also compared dose adjusters to non-adjusters after wk 28	N=1212 1) ustekinumab 45mg (n=606) 2) ustekinumab 90mg (n=606) 3) combined N=1112 a) adjusters (n=544) b) non-adjusters (n=568) c) combined	See above	**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	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

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

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

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

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

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

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

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

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

				1) 1.6, 2) 0.0, 3) 0.0	*p=NR* ***Other outcomes reported: DLQI mean change, SF-36 summary, MCS, and PDI scores also included through wk 64***	
Tsai, 2011 PEARL *Good quality publication*	Phase 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:**	Primary outcomes at wk 12: **PASI 75 (%):** 1) 67.2, 2) 5.0 *1 vs. 2, p<0.001* **PASI 50 (%):** 1) 83.6, 2) 13.3 *1 vs. 2, p<0.001* **PASI 90 (%):** 1) 49.2, 2) 1.7 *1 vs. 2, p<0.001* **PASI 100 (%):**	Primary outcomes at wk 12: **AEs ≥1 (%):** 1) 65.6, 2) 70.0 **SAEs (%):** 1) 0.0, 2) 3.3 **URIs (%):** 1) 11.5, 2) 11.7 **Discontinuation from AEs (%):** 1) 0.0, 2) 5.0 **Infections (%):**

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

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

					28 by weight (≤70kg vs. >70kg)	
Zhu, 2013 LOTUS *Good quality publication*	Phase III RCT Double-blind *14 sites in China* ITT with NRI	N=322 1) ustekinumab 45mg (n=160) 2) placebo (n=162) Placebo patients crossed over to receive ustekinumab for wks 12-16	Inclusion: ≥18 years PASI ≥12 BSA ≥10% ≥6 months of plaque psoriasis diagnosis	**Age (years):** 1) 40.1, 2) 39.2 **% male:** 1) 78.1, 2) 75.9 **Weight (kg):** 1) 69.9, 2) 70.0 **PsO duration (years):** 1) 14.6, 14.2 **PASI:** 1) 23.2, 2) 22.7 **DLQI:** 1) 13.7, 2) 13.1 **PsA (%):** 1)8.8, 2)8.6 **Previous biologics (%):**	Primary outcomes at wk 12: **PASI 75 (%):** 1) 82.5 2) 11.1 **PASI 50 (%):** 1) 91.3 2) 19.8 **PASI 90 (%):** 1) 66.9 2) 3.1 **PGA, cleared/minimal (%)** 1) 78.8 2) 14.8 *All UST groups vs. placebo, p<0.001*	**At week 12:** AEs (%) 1) 42.5, 2) 38.5 SAEs (%) 1) 0.6 2) 0.6 Infections (%) 1) 19.3 2) 25.6 Discontinuation due to AEs (%) 1) 1.2 2) 1.9

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

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

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

					recommended treatment frequency *Adjusted for sex, race, ethnicity, body mass index, skin type, frequency of topical use, practice setting of dermatologist, marital status, income, and insurance	
Gniadecki, 2011 DERMBIO *Publication* *Good quality*	Database of Danish patients to evaluate long-term drug survival (time to drug 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	**Age (years):** 1) 44.4, 2) 46.3, 3) 45.5, 4) 44.6 **% male:** 1) 63.8, 2) 65.9, 67.6, 4) 60.6 **Weight (kg):** 1) 87.4, 2) 88.6, 3) 92.0, 4) 89.6 **PsO duration (years):** 1) 18.7, 2) 19.5, 3) 18.7, 4) 17.9	***OR for treatment termination:** 1 vs. 4: 1.77, 95% CI 1.39-2.26, p<0.0001 2 vs. 4: 2.55, 95% CI 1.98-3.29, p<0.0001 3 vs. 4: 1.99, 95% CI 1.5-2.63, p<0.0001 2 vs. 1: 1.42, 95% CI, 1.20-1.68, p<0.0001 2 vs. 3: 1.30, 95% CI 1.04-1.61, p=0.02	NR

			The choice of drug *was the decision of the physician*	**PASI:** 1) 12.5, 2) 12.6, 3) 15.8, 4) 11.4 **DLQI:** 1) 12.6, 2) 11.9, 3) 13.9, 4) 11.5 **PsA (%):** 1) 38.1, 2) 39.6, 3) 43.8, 4) 14.1 **Previous biologics (%):** NR	Bio-naïve vs. bio-exposed: 1.24, 95% CI 1.05-1.46, 0.011 Male vs. female: 1.51, 95% CI 1.31-1.74, p<0.0001 *Adjusted for covariates*	
Goren, 2015 *Publication* *Fair quality*	Web-based survey from a US claims database study evaluating differences between ustekinumab and adalimumab for patients previously or not previous on 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	Significantly higher proportion of bio-naïve ustekinumab users reported a score of 0 on the DLQI compared with bio-naïve adalimumab users (45.2% vs 19.2%, p<0.05). After adjusting for covariates in multivariable models,	NR

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

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

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

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

Strober, 2016 PSOLAR *Publication* *Fair quality*	Multicenter, longitudinal, psoriasis-based registry study evaluating effectiveness of biologics in a real-world setting (June 20, 2007, through August 23, 2013)	N=2076 (patients initiating a new biologic) 1) UST (n=1041) 2) ETN (n=116) 3) ADA (n=662) 4) INF (n=257)	Inclusion: Patients may have been bio-naive or may have been exposed before enrollment to a biologic other than their newly initiated treatment in the registry Excluded: Patients restarting a biologic received before enrollment	**Age (years):** 1) 46.3, 2) 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 (6 months also reported): **PGA of 0/1 (%):** 1) 59.9, 2) 57.6, 3) 56.5, 4) 42.0 ***Odds of achieving a PGA score of 0/1 (logistic regression):** 1 vs. 4: OR 0.449, 95% CI 0.260-0.774, p=0.040 *No other comparisons to UST were SS* ***DLQI mean improvement (least mean square):** 1 vs. 2: -5.011, 1.917 (95% CI 0.909-2.925), p=0.0002 1 vs. 3: -6.185, 0.743 (95% CI 0.025-1.492), p=0.427	NR

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

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

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

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

Papp, 2013 (NCT00773734) Phase IIb *Abstract*	Reporting of symptom measures	See above	See above	See above	At wk 24 (those continuing apremilast): **Pruritus VAS, mean change (%):** 2) -36.7, 3) -41.5, 4) -41.0 p=NR ***Other outcomes reported: MCID between groups for pruritus VAS***	NR
Papp, 2015 (NCT01194219) ESTEEM 1 *Good quality publication*	Phase III RCT Double-blind Multicenter 72 sites in the US, Canada, and Europe	N=844 1) placebo (n=282) 2) apremilast 30mg BID (n=562)	Inclusion: ≥18 years BSA ≥10%, PASI ≥12 sPGA ≥3 ≥6 months of plaque psoriasis diagnosis	**Age (years):** 1) 46.5, 2) 45.8 **% male:** 1) 68.8, 2) 67.4 **Weight (kg):** 1) 93.7, 2) 93.2 **PsO duration (years):** 1) 18.7, 2) 19.8	Primary outcomes at week 16: **PASI 50 (%):** 1) 17.0, 2) 58.7ǂ **PASI 75 (%)*:** 1) 5.3, 2) 33.1ǂ **PASI 90 (%):** 1) 0.4, 2) 9.8	Primary outcomes at week 16: **AEs ≥1 (%):** 1) 55.7, 2) 69.3 **SAEs ≥1 (%):** 1) 2.8, 2) 2.1 **Discontinuation due to AEs (%):**

	ITT with LOCF and NRI results		Candidates for phototherapy or systemic therapy Exclusion: use of biologics within 12 to 24 weeks	**PASI:** 1) 19.4, 2) 18.7 **DLQI:** 1) 12.1, 2) 12.7 **PsA (%):** NR **Previous biologics (%):** 1) 28.4, 28.8	**sPGA score of 0/1 with ≥2-point reduction (%)*:** 1) 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* *LOCF for missing data (NRI also reported) *Patients remaining on APR over 52 weeks maintained or*	1) 3.2, 2) 5.3 **Deaths (n):** 1) 1, 2) 1 At week 52: **AEs ≥1 (%):** Apremilast- 78.7 **SAEs ≥1 (%):** Apremilast- 4.2 **Discontinuation due to AEs (%):** Apremilast- 7.3 **Deaths (n):** Apremilast- 1

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

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

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

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

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

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

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

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

					1) 59.4, 2) 75.7, 3) 71.2	

Appendix C. Previous Systematic Reviews and Technology Assessments

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

Reich 2011

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

Lin 2012

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

adalimumab [Odds Ratio (OR) 1.84], etanercept (OR 2.07), but lower than infliximab (OR 0.36), all treatments given according to the FDA-approved dosing (table x in this report). Previous experience with biologics was not found to be a statistically significant predictor of PASI response in the adjusted model.

Signorovitch 2014

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

Gomez-Garcia 2016

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

Zweegers 2016

The authors conducted a literature review of prospective and retrospective observational studies from 1990 to 2014 on the daily practice biologics and conventional systemic therapies. A total of 32 studies were identified, among which two retrospective and two prospective studies compared PASI responses of biologics of our interest, including adalimumab, infliximab, etanercept, and ustekinumab. Only one of these four studies found a statistically significant difference between biologics: percentage improvement in PASI at 24 weeks was greater with infliximab compared to etanercept (89% vs. 75%, p=0.02). The other studies either did not conduct statistical tests or found non-statistically significant results. The authors identified the gap in the availability of direct evidence on effectiveness between agents.

NICE HTA submissions

The apremilast NICE submission[125] showed apremilast to dominate its comparator, which in this case, was a treatment sequence starting with adalimumab. The NICE ERG noted that the manufacturer 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, as well as other measures, the ERG's final guidance slated apremilast had an incremental cost-effectiveness ratio versus adalimumab of about £30,300/QALY in the DLQ1>10 population and £60,000/QALY in the DLQ1<10 population. The secukinumab NICE submission resulted in an incremental cost-effectiveness of £2,515/QALY versus etanercept and £7,231/QALY versus supportive care.[157] Additionally, secukinumab dominated all other biologics in the analysis. Key differences between this model and our analysis are 1) treatment non-responders move to supportive care, while in our model non-responders move to a 'pooled' biologic treatment – the latter representing a more real-world scenario; 2) a discontinuation rate of 11.7% for patients who stopped biologic treatment and moved to PASI<50 and receiving supportive care, and an all-cause discontinuation rate of 20%, versus in our model where discontinuation rate varied by targeted immunomodulator. The ERG committee also stated that the resource utilization and associated costs for hospitalization during supportive care were not plausible.

The adalimumab NICE submission[126] reported an incremental cost-effectiveness of £30,538/QALY for adalimumab versus supportive care. The number of hospitalization days avoided influenced model outcomes significantly, ranging from £60,600/QALY for no days avoided to £4,800/QALY for 39 days avoided. The ERG noted this to be a key factor driving model results and expressed uncertainty of this model input. The infliximab NICE submission[127] reported infliximab to be cost-effective over etanercept at £26,095/QALY. This model reflects a lack of clarity on the patient population the it includes – the model population is defined as those in the fourth quartile of DLQ1, which does not clearly state if these patients fall under the moderate-to-severe psoriasis category. The model also had significant uncertainty related to the assumed cost offsets associated with

hospitalization. The ustekinumab NICE submission[128] resulted in an incremental cost-effectiveness of £29,587/QALY for ustekinumab versus supportive care. The model assumed that 80% of the population was less than 100kgs and thus received a 45mg dose of ustekinumab, while the remaining patients received a 90mg ustekinumab. The manufacturer, while submitting the evidence, proposed a patient access scheme (PAS), discounting the price of the 90mg dose to that of the 45mg dose. Doubling the price to the listed 90mg dose resulted in ustekinumab no longer dominating its comparators at the UK threshold of £20,000/QALY to £30,000/QALY.

Appendix D. Ongoing Trials

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

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

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

A Study Comparing Different Dosing regimens of Ixekizumab (LY2439821) in Participants with Moderate to Severe Plaque Psoriasis (IXORA-P) **NCT02513550**	Phase III RCT	1) Ixekizumab 160mg initial dose, 80mg Q2W 2) Ixekizumab 160mg initial dose, 80mg Q4W 3) 160 mg ixekizumab initial dose, 80mg ixekizumab Q4W with step-up to Q2W 4) Placebo	N = 1227, ages ≥18 **Inclusion criteria:** - 10% BSA, PGA ≥ 3, PASI ≥ 12, PsO duration ≥ 6 months **Exclusion criteria:** - No concurrent/recent use of biologic agent	PASI 75 and sPGA score of 0 or 1 at week 52 Selected secondary outcomes: PASI 90, 100; sPGA score of 0, DLQI, Itch NRS, EQ-5D, VAS-skin pain	September 2017
A Study of Ixekizumab (LY2439821) in Participants with Moderate-to-Severe Plaque Psoriasis (IXORA-S) **NCT02561806**	Phase III RCT	1) Ixekizumab 160mg initial dose, 80mg Q2W 2) Ustekinumab 45 or 90mg (weight-dependent)	N = 300, ages ≥18 **Inclusion criteria:** - PASI ≥ 12, PsO duration ≥ 6 months - Failure, contraindication, or intolerability to at least 1 systemic therapy (including cyclosporine, methotrexate, or phototherapy) **Exclusion criteria:** - No concurrent/recent use of biologic agent - No prior use or contraindication to ustekinumab - No previous TX with ixekizumab or other IL-	≥ PASI 90 at week 12 Selected secondary outcomes: SF-36, PGA, EQ-5D, WPAI	May 2017

			17A or IL-12/23 antagonists		
A Study in Japanese Participants with Moderate-to-Severe Psoriasis (UNCOVER-J) **NCT01624233**	Phase III (extension study)	Ixekizumab 160mg initial dose, 80mg Q2W until week 12, Q4W until week 52, and up to 192 weeks following relapse during drug-free period	N = 90, ages ≥20 **Inclusion criteria:** - 10% BSA, PGA ≥ 3, PASI ≥ 12, PsO duration ≥ 6 months **Exclusion criteria:** - No prior use of etanercept - No concurrent/recent use of biologic agents	PASI at week 12 Selected secondary outcomes: PGA, PROs, efficacy in patients with PsA	December 2016
Brodalumab – no ongoing studies identified					
Apremilast					
A Phase 4 Study of Efficacy and Safety of Apremilast in Subjects With Moderate Plaque Psoriasis (UNVEIL) **NCT02425826**	Phase IIII RCT	1) Apremilast 30mg BID 2) Placebo After week 16, all subjects take apremilast 30mg until week 52	N = 197, ages ≥18 **Inclusion criteria:** - 5-10% BSA, sPGA=3, PASI ≥ 12, PsO duration ≥ 6 months **Exclusion criteria:** - No prior exposure to systemic or biologic treatment for psoriatic arthritis, psoriasis, or other indications that could impact psoriasis assessment - No prior apremilast treatment	Mean percentage change in BSA multiplied by sPGA at week 16 Selected secondary outcomes: PASI 50, 75; DLQI, TSQM, AEs	November 2016

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

Appendix E. Comparative Clinical Effectiveness Supplemental Information

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

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" (see Appendix Table F2) [51] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

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

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

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

Table E1. Table PASI outcomes by trial

Trial	treatment	Time point (weeks)	N	%PASI 75	P value	%PASI 50	P value	%PASI 90	P value	%PASI 100	P value
Head-to-head trials											
Griffiths 2010 ACCEPT	Etanercept	12	347	57		NR		23		NR	
	Ustekinumab 45 mg	12	209	68	0.01	NR		36	P<0.001	NR	
	Ustekinumab 90 mg	12	347	74	<0.001	NR		45	P<0.001	NR	
Langley 2014 FIXTURE	Etanercept	12	326	44		NR		21		4	
	Secukinumab 300 mg	12	327	77	P<0.001	NR		54	P<0.001	24	P<0.001
Griffiths 2015	Etanercept	12	358	42		NR		19		5	
UNCOVER 2	Ixekizumab	12	351	90	P<0.0001	NR		71	P<0.0001	41	P<0.0001
Gordon 2015	Etanercept	12	382	53		NR		26		7	
UNCOVER 3	ixekizumab	12	385	87	P<0.0001	NR		68	P<0.0001	38	P<0.0001
Thaci 2015	Etanercept	12	339	79		NR		53		26	
IXORA-S	Ixekizumab	12	136	91	P<0.001	NR		75	P<0.001	37	P<0.001
	Ustekinumab	12	166	69				42		15	
CLEAR	Secukinumab 300 mg	12	337	91	P<0.0001	NR		73	P<0.0001	39	P<0.0001
	Ustekinumab WBD	16	339	83		NR		58		28	
	Secukinumab 300 mg	16	337	93	P=0.0001	NR		79	P<0.0001	44	P<0.0001
Lebwohl 2015	Ustekinumab WBD	12	300	70		NR		47		22	
AMAGINE 2	Brodalumab 210 mg	12	612	86	0.08	NR		70	P<0.001	44	P<0.001
Lebwohl 2015	Ustekinumab WBD	12	313	69		NR		48		19	
AMAGINE 3	Brodalumab 210 mg	12	624	85	0.007	NR		69	P<0.001	37	P<0.001
Placebo-controlled trials											
Sauret 2008	Adalimumab	16	108	80		88		52		17	
CHAMPION	placebo	16	53	19	P<0.001	30	P<0.001	11	P<0.001	2	P<0.01
Menter 2008	Adalimumab	16	814	71		NR		45		20	
REVEAL	placebo	16	398	7	P<0.001	NR		2	P<0.001	1	P<0.01
Papp 2005	Etanercept	12	203	46		72		19		NR	
	placebo	12	204	3	P<0.001	9	P<0.001	<1	P<0.001	NR	
Leonardi 2003	Etanercept	12	164	49		71		22		NR	
	placebo	12	166	4	P<0.001	14	P<0.001	1	P<0.001	NR	
Tyring 2006	Etanercept	12	300	47		74		21		NR	
	placebo	12	300	5	P<0.001	14	P<0.001	1	P<0.001	NR	
Bagel 2012	Etanercept	12	62	59		85		25		NR	
	placebo	12	62	5	P<0.001	7	P<0.001	2	P<0.001	NR	
Gottlieb 2011	Etanercept	12	141	56		NR		23		7	
M10-114	placebo	12	68	7	P<0.001	NR		1	P<0.001	0	NR
Strober 2011	Etanercept	12	139	40		NR		14		6	
M10-315	placebo	12	72	7	P<0.001	NR		4	P<0.001	0	NR
Bachelez 2015	Etanercept	12	335	59		80		32		NR	
	placebo	12	107	6	P<0.001	21	P<0.001	1	P<0.001	NR	
Griffiths 2016	Etanercept	12	241	75		NR		NR		NR	
EGALITY	Erelzi	12	239	73.4	NS	NR		NR		NR	
Reich 2015	Infliximab	10	301	80		91		57		NR	
	placebo	10	77	3	P<0.001	8	p<0.001	1	P<0.001	NR	
Menter 2007	Infliximab	10	314	76		NR		45		NR	
	placebo	10	208	2	P<0.001	NR		1	P<0.001	NR	

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

Appendix F. Network Meta-Analysis Methods and Results

Network Meta-Analysis Methods

In addition to summary evidence tables, we performed quantitative indirect comparisons using Bayesian network meta-analysis (NMA) for PASI outcomes.[158] A ordinal multinomial model with a probit link for PASI 50, PASI 75, and PASI 90 was used. This model assumes the treatment effect is the same regardless of the PASI cut-off and allowed us to use the data efficiently when some PASI outcomes were missing. All the analyses were conducted in WINBUGS 1.4,3 using code from the NICE DSU technical support document. Review of the deviance information criterion (DIC) statistics as well as comparison of the residual deviance (resdev) to the number of unconstrained data points was used to assess the best model fit under multiple alternative assumptions.[159] Given the expectation of at least some degree of heterogeneity in patient populations and/or study design, there is a general preference for a random-effects approach. A total of 50,000 iterations each were employed for both "burn-in" (for model convergence) and model (for model results) simulations. Relative risks and probabilities of patients having a given PASI response state was generated.

We conducted a sensitivity analysis to assess ustekinumab 45 mg and 90 mg doses separately by excluding a head-to-head trial where the two doses were combined. We also conducted a sensitivity analysis in which placebo response rate in each trial was adjusted as a covariate in the above described model. The median and credible interval of the adjustment coefficient (β) of placebo response from a previous network meta-analysis was used as input to our model. The adjustment coefficient (β) was tested against zero.[49]

Table F1. Basecase NMA. Relative risks and credible intervals of treatments compared to placebo on PASI outcomes from the NMA

treatment	PASI 75	CrI	PASI 50	CrI	PASI 90	CrI
ixekizumab	17.89	12.68-25.94	7.359	5.619-9.884	75.22	47.87-121.7
brodalumab 210	17.25	11.94-25.39	7.232	5.49-9.75	69.85	40.62-118.9
infliximab	16.72	11.75-24.34	7.13	5.442-9.576	64.84	39.78-106.8
secukinumab 300	15.37	10.93-22.17	6.844	5.246-9.148	54.63	34.57-87.98
ustekinumab 45/90	13.99	10.02-20.0	6.509	5.014-8.654	45.62	29.37-72.65
adalimumab	13.01	8.977-19.27	6.242	4.74-8.418	40.16	23.6-69.32
secukinumab 150	12.98	9.116-18.79	6.241	4.773-8.325	39.97	24.45-65.41
etanercept	9.57	6.943-13.54	5.196	4.046-6.839	23.89	15.63-37.58
Erelzi	8.92	4.465-15.46	4.95	3.062-7.278	21.5	7.749-49.13
apremilast	6.148	3.807-9.804	3.874	2.731-5.473	12.14	6.179-23.34

Table F2. Base case NMA. Probabilities of patients having a given PASI response state at the end of induction period

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

Erelzi	35.0	20.5	24.7	19.9

Table F3. Base case NMA: league table of PASI 75 response

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

Table F4. Base case NMA: league table of PASI 50 response

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

Table F5. Base case NMA: league table of PASI 90 response

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

Table F6. Sensitivity analysis NMA. Ustekinumab 45 mg and 90 mg separately, relative risks

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

Table F7. Sensitivity analysis NMA. Ustekinumab 45 mg and 90 mg separately, probabilities

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

Table F8. Sensitivity analysis NMA. Placebo response adjustment, relative risks

treatment	PASI 75	CrI	PASI 50	CrI	PASI 90	CrI
infliximab	17.7	12.78-25.21	6.962	5.39-9.221	70.9	46.21-111.9
brodalumab 210	17.35	12.41-24.91	6.896	5.339-9.152	68.17	42.56-110.0
ixekizumab	17.28	12.59-24.25	6.894	5.353-9.069	67.21	45.22-102.5
secukinumab 300	16.29	11.97-22.62	6.712	5.247-8.771	59.4	40.43-89.26
ustekinumab 45/50	14.38	10.78-19.58	6.312	4.999-8.139	46.8	32.62-68.38
secukinumab 150	14.08	10.45-19.42	6.24	4.933-8.077	45.09	30.48-68.1
adalimumab	11.96	8.533-16.81	5.698	4.459-7.39	33.99	20.86-54.34
etanercept	9.801	7.616-12.84	5.077	4.144-6.329	24.41	17.7-34.21
Erelzi	9.202	5.01-14.82	4.864	3.245-6.753	22.2	8.962-45.5
apremilast	5.284	3.366-7.948	3.395	2.466-4.555	9.609	5.113-17.04

Table F9. Sensitivity analysis NMA. Placebo response unadjustment, probabilities

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

Appendix G. Comparative Value Supplemental Information

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. 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 G5. 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 G6. 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 G7. 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 G1. Incremental costs of ixekizumab versus non-targeted therapy

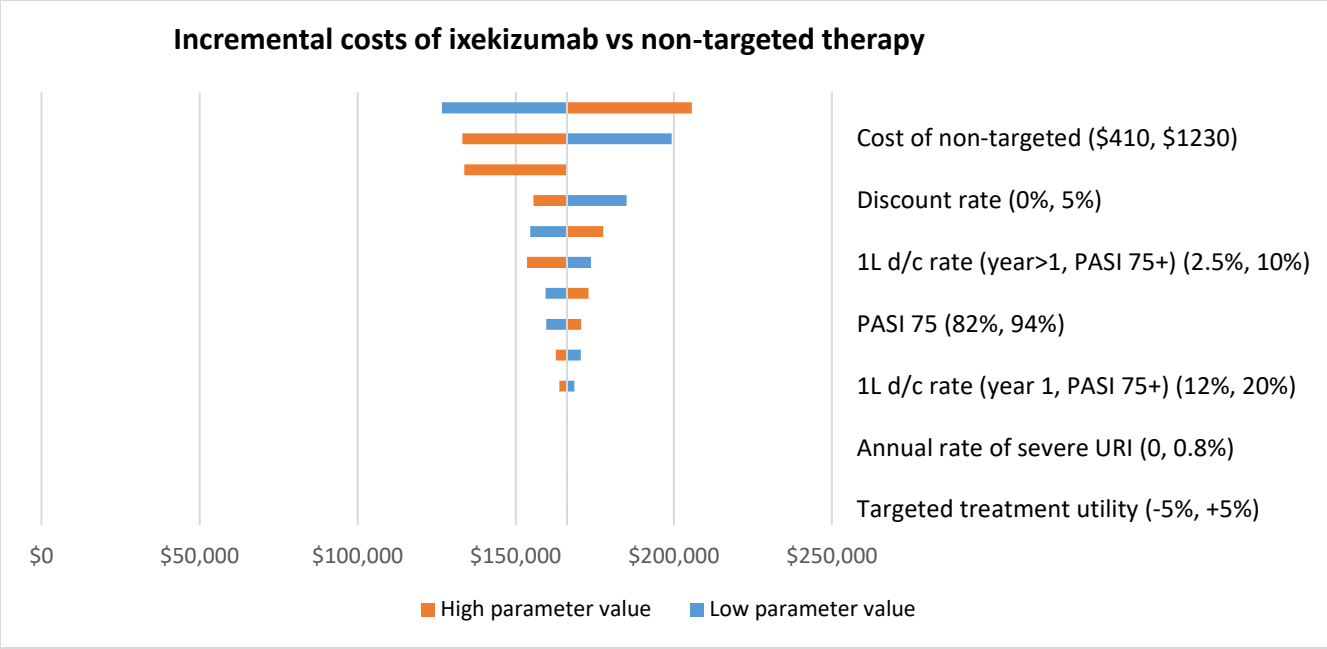


Figure G2. Incremental QALYs of ixekizumab versus non-targeted therapy

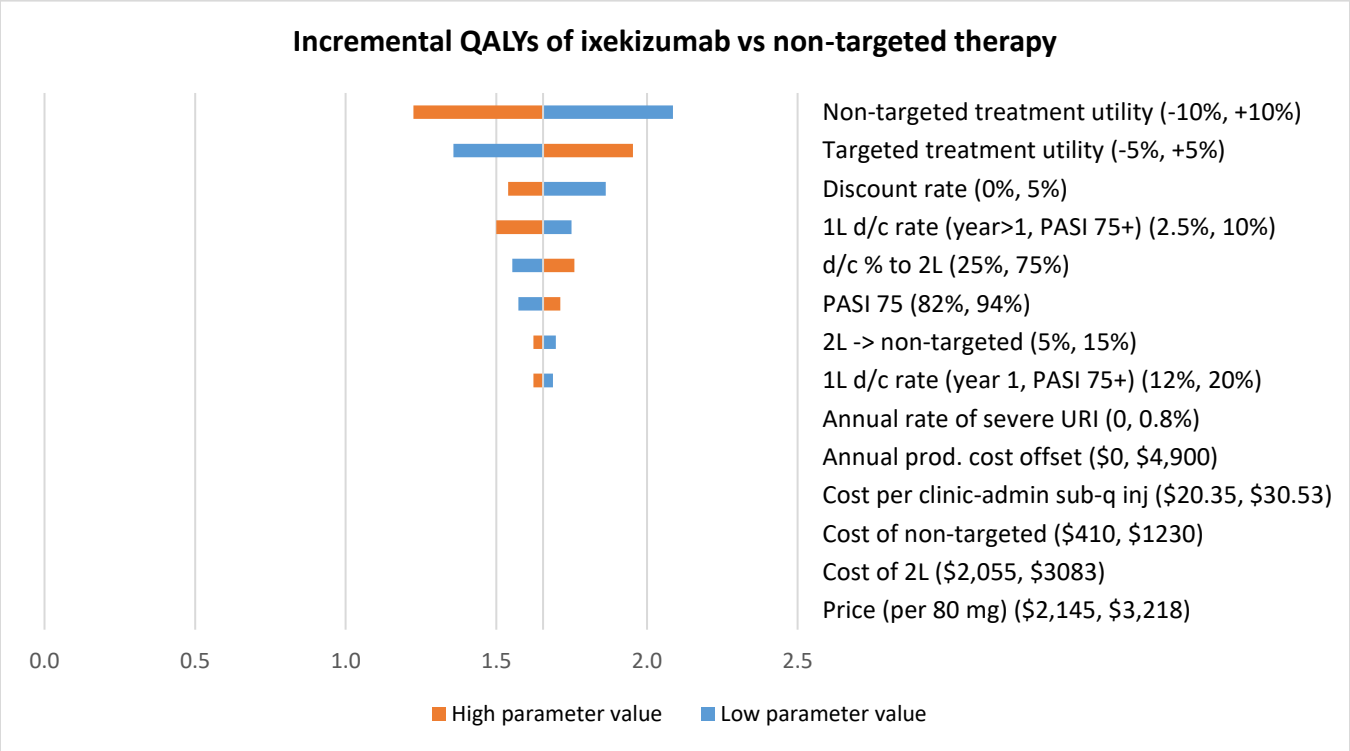


Figure G3. Incremental costs of infliximab versus non-targeted therapy

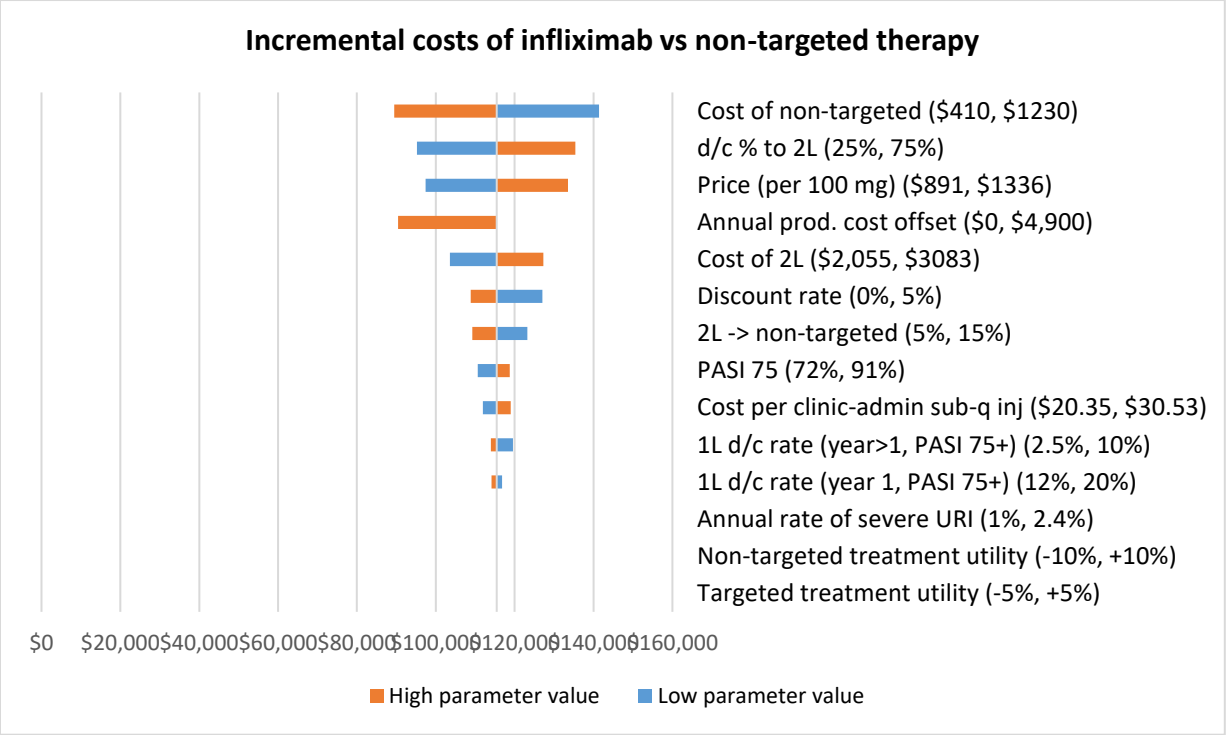


Figure G4. Incremental QALYs of infliximab versus non-targeted therapy

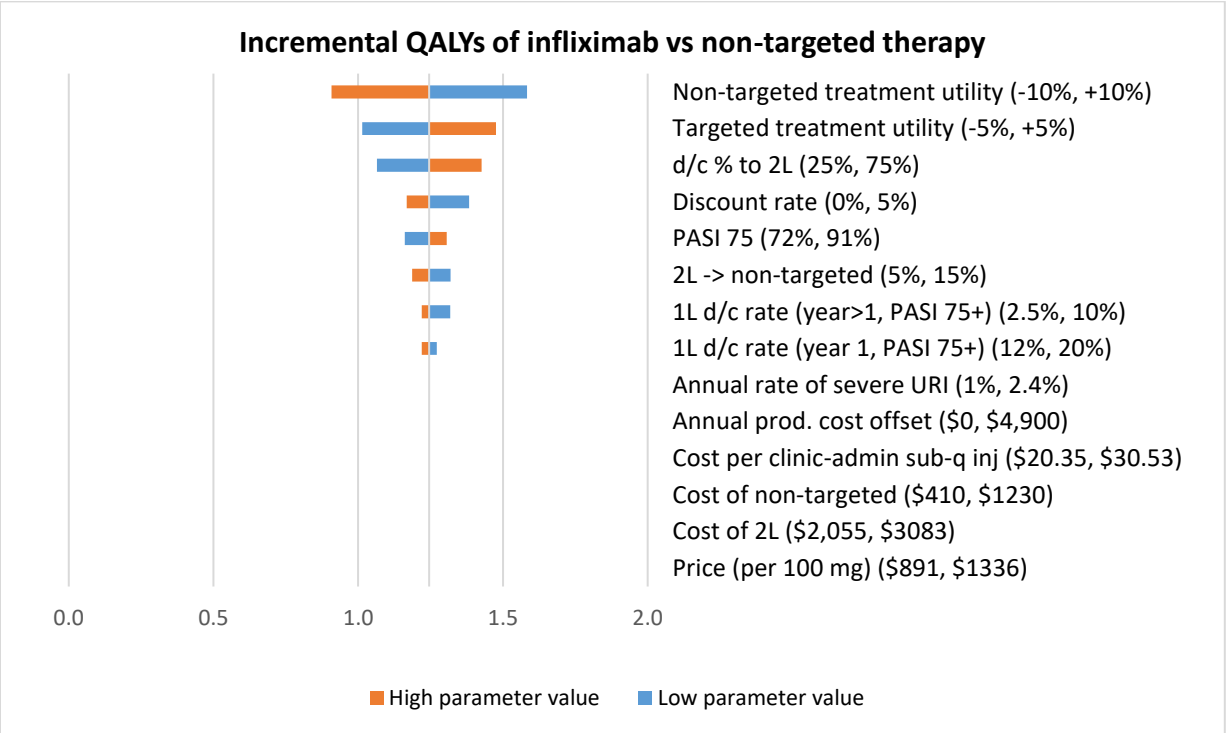


Figure G5. Incremental costs of ixekizumab versus infliximab

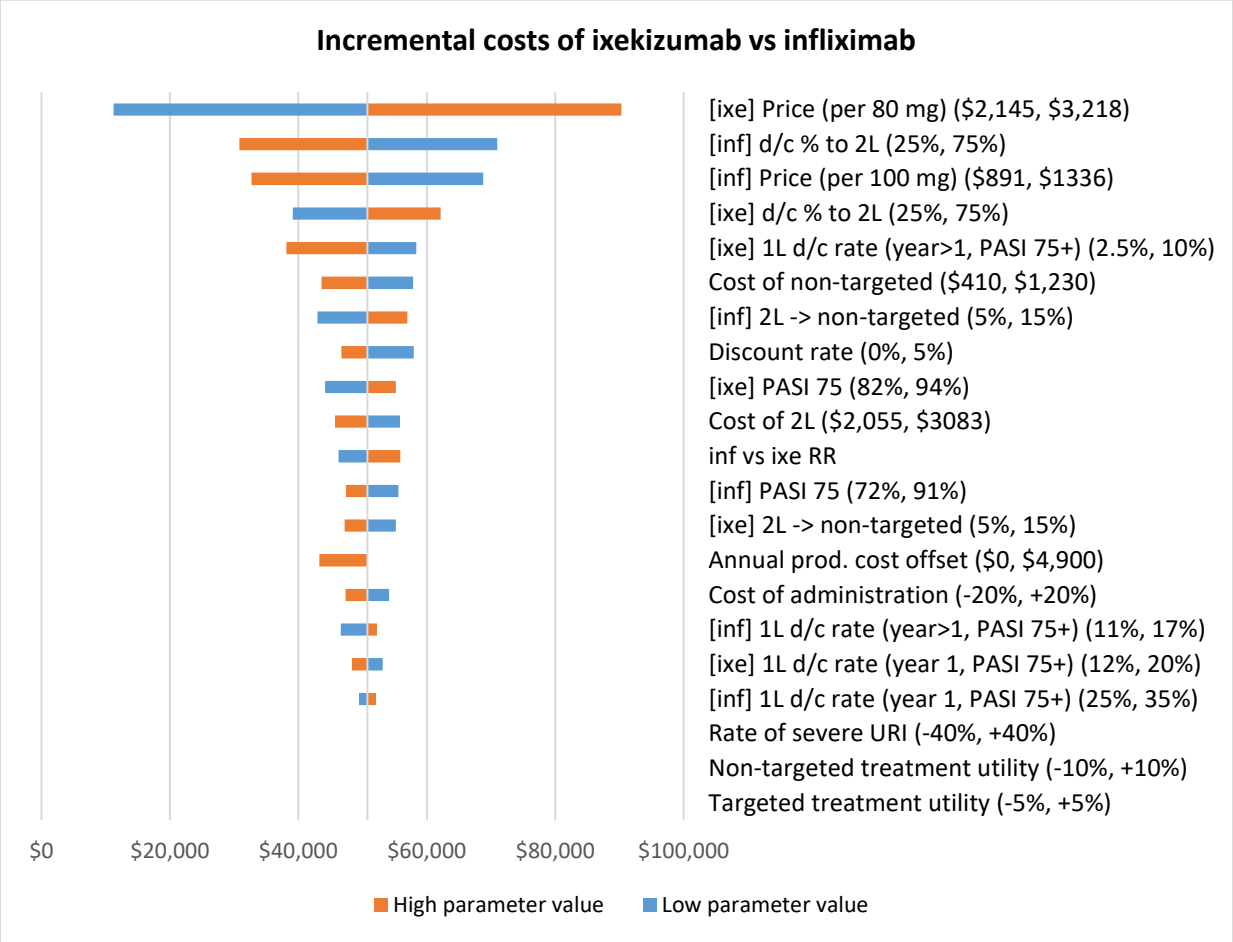


Figure G6. Incremental QALYs of ixekizumab versus infliximab

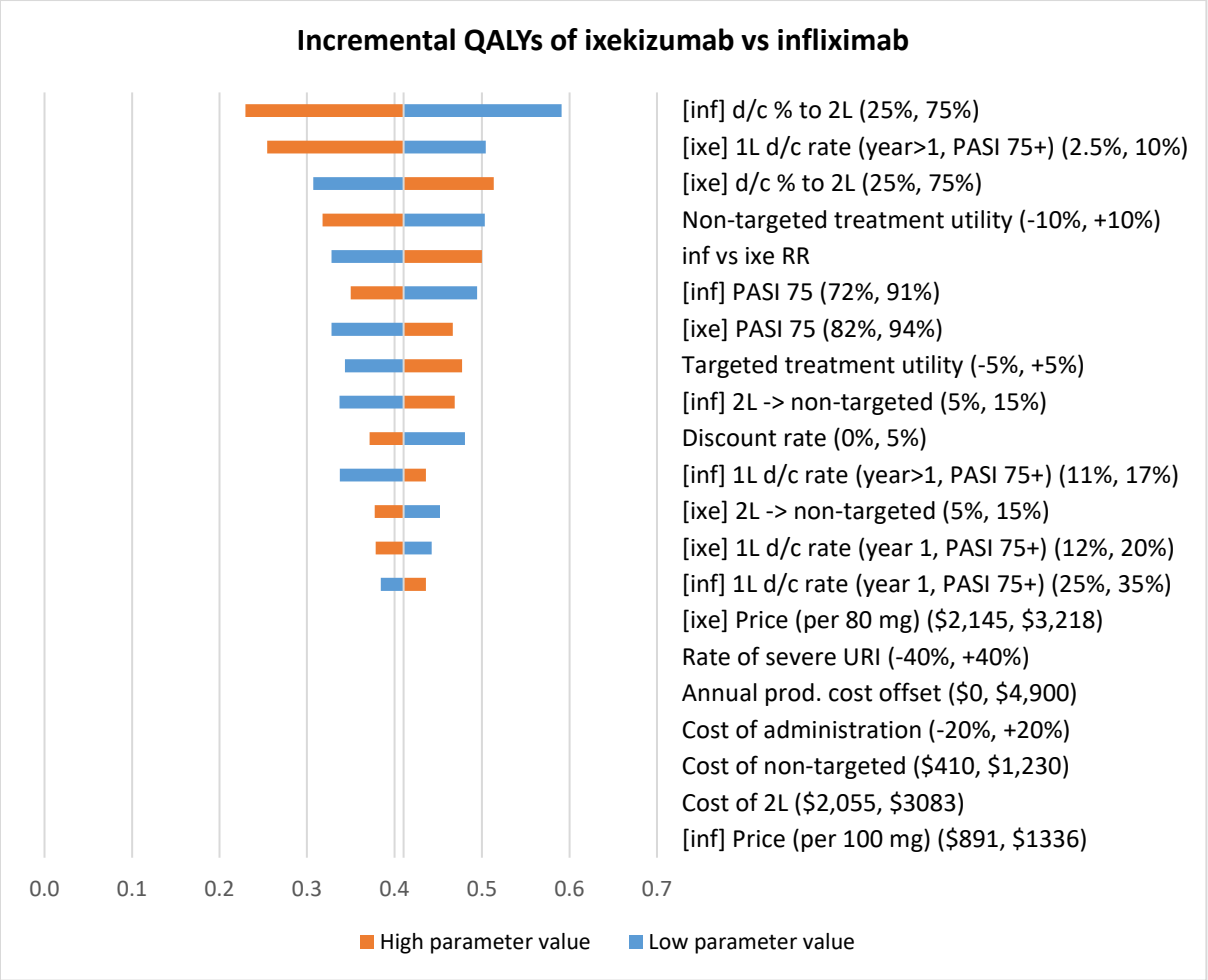


Figure G7. Incremental costs of etanercept versus ixekizumab

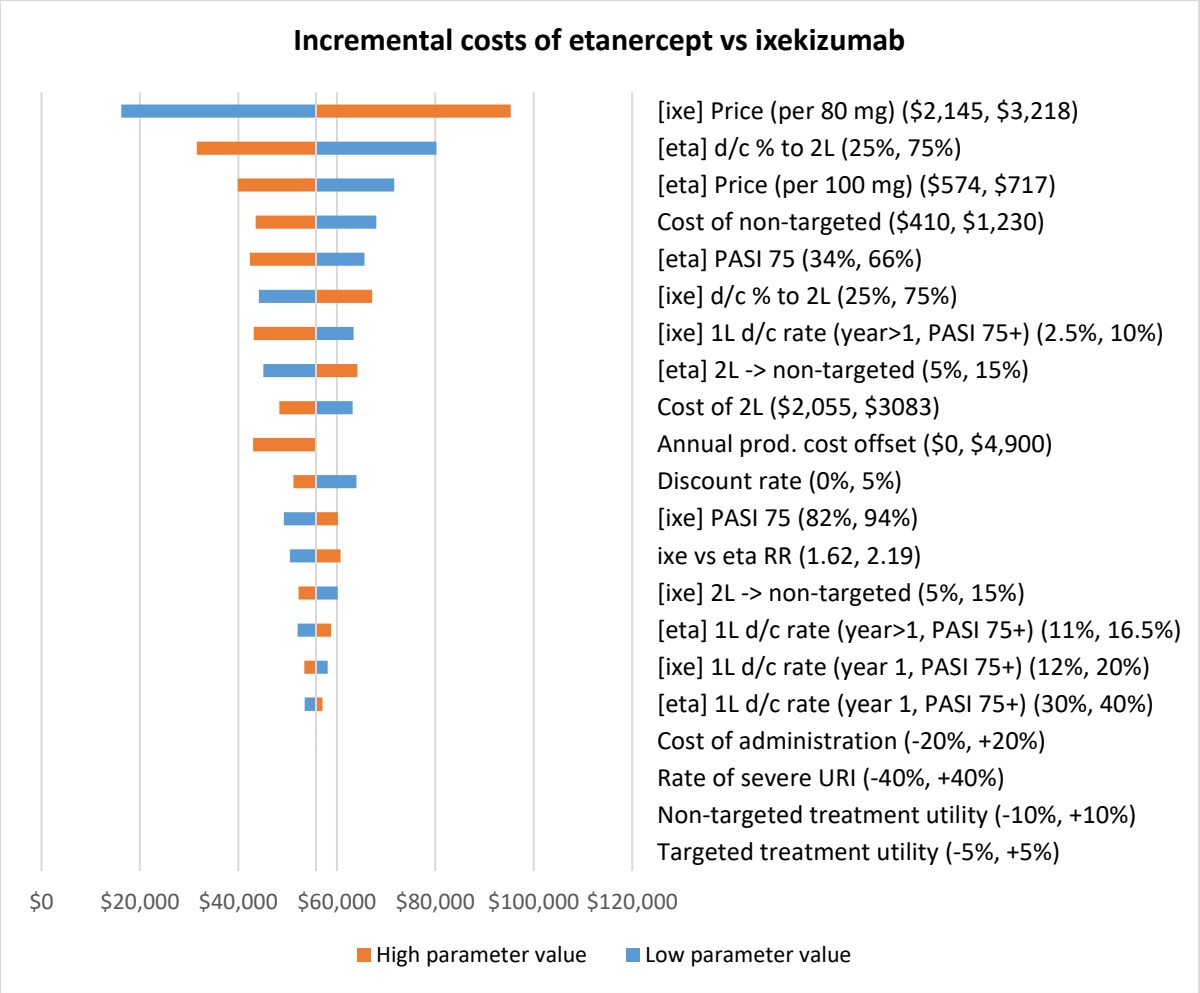
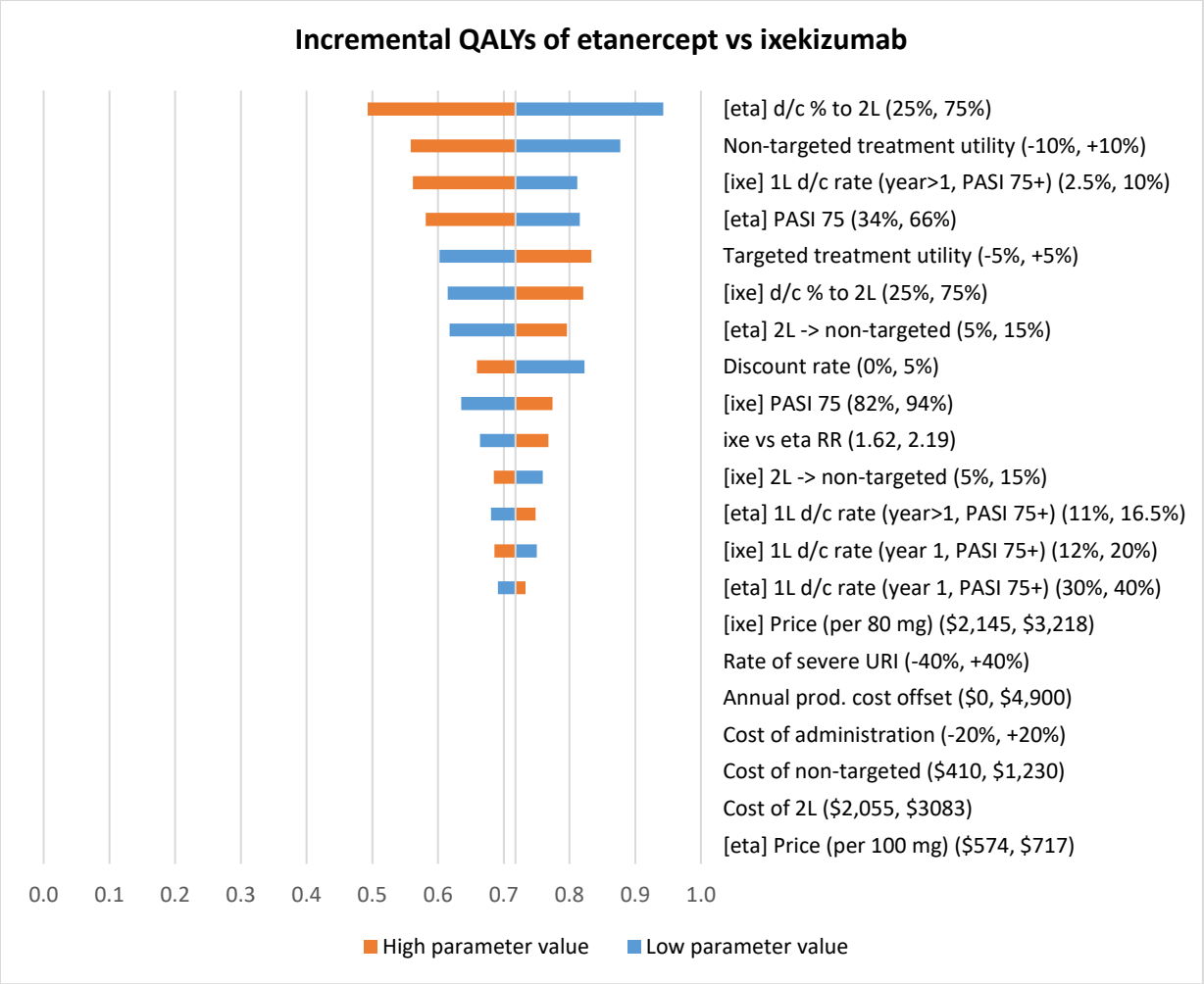


Figure G8. Incremental QALYs of etanercept versus ixekizumab



Scenario analysis

Table G8: 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 G9: 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

Appendix H. Public Comments.

This section includes summaries of the public comments prepared for the New England CEPAC Public Meeting on November 18, 2016 in Boston, MA. These summaries were prepared by those who delivered the public comments at the meeting and are presented in order of delivery. Frank Zhang, Global Head of Pricing and Market Access of Celgene Corporation, declined to submit a summary of his remarks.

A video recording of these comments can be found on our site here, at minute 1:27:14. Conflict of interest disclosures are included at the bottom of each statement.

Jonathan Wilcox, Patients Rising
Co-Founder and Policy Director

I know that those representing ICER feel strongly about what they are doing. I appreciate that. But the intense reaction you are feeling is not unlike psoriasis itself: roiling underneath the surface, misunderstood, and its origin well out of your sight.

The major crisis at hand and ahead for patients has less to do with the very real flaws in drug-pricing and more to do with insurance and regulatory practice that is, every day, overriding doctor decisions and blocking patients from getting treatments.

With all that we know is wrong in the system, this is truly health care's secret scandal.

I ask you today to hear another voice. Stronger than mine. Apart from mine. It is a quiet voice. It is a specific voice. It is the patient voice of value.

We all hope in this room that there is a chance that a deeper dialogue may occur that will advance the truth that patient access should drive value frameworks, not the other way around.

And those speaking today should say nothing that might impact that chance.

But after all of this time and all of this sacrifice and all of this support there is still no reform in this deeply flawed approach, then we say and patients say and their doctors say and their families say the time has come for the design and the development and the delivery of a new patient-friendly, patient-focused, patient-centered value framework ideal not tied to the mistakes and the policies of the past.

Conflict of Interest Disclosure. *Patients Rising receives financial support from Amgen, Bristol-Meyers Squibb, Celgene Corporation, Genentech, PhRMA*

Dr. Michael Siegel, National Psoriasis Foundation
Vice President, Research Programs

On behalf of the National Psoriasis Foundation (NPF), thanks to ICER for engaging with our organization, patients, and leading psoriatic disease researchers and clinicians during the assessment of psoriasis treatments. We appreciate the attention ICER has given to our comments and concerns throughout the process, and are pleased to see that the analysis has evolved to more appropriately note the value advanced therapies provide to individuals living with psoriatic disease.

As Vice President of Research of the largest advocacy organization serving patients with psoriasis, I will focus on the heterogeneity, complexity, and uncertainty facing the 8.3 million Americans living with this disease. Psoriasis has a heterogeneous genetic foundation, complex immunological pathogenesis, and uncertain environmental triggers. Symptoms are heterogeneous, there is complexity in disease progression, and uncertainty around the development of comorbidities. Finally, there is heterogeneity of treatment efficacy, complexity determining appropriate treatment, and uncertainty around access. These issues are compounded by the fact that psoriasis is a chronic disease, affecting patients throughout life.

Given these challenges, NPF is committed to the preservation of patient-provider dialog driving all treatment decisions. We believe that broad treatment access is central to the individual patient's success.

Much uncertainty exists for patients living with psoriasis. What we know is that most patients say psoriasis is a problem in everyday life, are dissatisfied with treatment, and are not treating to the level dictated by their disease severity. We urge ICER to consider these challenges and ensure recommendation do not disrupt the sanctity of the patient-provider relationship.

Conflict of Interest Disclosure. *The National Psoriasis Foundation receives financial support from: Amgen, Abbvie, Celgene, Eli Lilly, Janssen, Leo, Novartis, Pfizer, Wisconsin Pharmaceuticals, Valeant Pharmaceuticals, Alva Amco Pharmaceuticals*

Dr. Jerry Bagel, Psoriasis Treatment Center of New Jersey
Director

My initial involvement of treating psoriasis decades ago was on the inpatient unit at Columbia-Presbyterian where I cared for 30 patients with severe psoriasis who were hospitalized for one month. They would receive daily crude coal tar applications for 3 hours, coal tar baths for one hour, petrolatum for 2 hours, and then increasing doses of UVB light. Clear after one month they would invariably return one year later for re-treatment.

Fortunately, over the last 15 years there have been FDA approved medications that significantly improve the quality of life of psoriatics. These medications differ in mechanics, route of administration, efficacy, and safety. The TNF inhibitors have increased risk with demyelination and congestive heart failure. The IL-17 inhibitors may have a risk with inflammatory bowel disease. Apremilast allows for oral administration but has a risk for depression and a lower efficacy but no risk for infections. Ustekinumab allows for every three month subcutaneous administration. Ixekizumab reveals data which shows complete clearing of 40% of the patients within twelve weeks.

These medications, however, are not a one size fits all proposition. Some patients have high risk/benefit tolerance, others low risk/benefit tolerance. There is also an increased frequency of depression, anxiety, loss of self-esteem, suicidal ideation that affects not only the individual but also transcends the family unit. Psoriasis also correlates with is an increase in metabolic syndrome, obesity, diabetes, hyperlipidemia, cigarette smoking and alcoholism. There is a fivefold increase of myocardial infarction frequency in young severe psoriatics – which some studies have shown treating with biologics decreases. In addition to the average life span of an individual with psoriasis being reduced by four years, severe psoriatic is also tied to higher rates of poverty. Unfortunately, individuals with severe psoriasis indicate they would gladly sacrifice four years of life in exchange for normal skin.

Despite advancements in care, and all we know about the value of treating, over 50% of people with moderate-to-severe psoriasis are not adequately treated (i.e. they receive either topical or no treatment). It seems the Product Benefit Managers, specialty pharmacies, and in fact the pharmaceutical and insurance industry by being more transport could decrease the cost of some of these medications to allow more access to the patients that require them. In my opinion, the goal needs to be for all parties to be more transparent and cooperative in order for more psoriatics to have an improved quality of life.

***Conflict of Interest Disclosure**. Dr. Jerry Bagel is a speaker, consultant and investigator with AbbVie, Novartis, Eli Lilly, Celgene, and Leo Pharmaceuticals. He is a consultant and investigator with Amgen. He is a consultant with Sun Pharmaceuticals.*

Dr. Bradley Stolshek, Amgen
Director, Global Health Economics

Amgen's commitment to psoriasis patients began over 20 years ago with Enbrel in development, which continues to maintain an important place in psoriasis therapy.

While Amgen believes ICER's revised report for plaque psoriasis has several issues, it nonetheless shows that biologics, including Enbrel, are good value (below ICER's $150K/QALY threshold when using market-based discounts). Amgen disagrees with ICER's methodology: lack of full transparency, narrow use of CE analysis, arbitrary thresholds, and no acknowledgement of patient experience.

In addition, Enbrel would achieve greater value with inclusion of safety, impact of psoriatic arthritis, and flexible treatment options.

- Safety and comorbidities were not adequately included in ICER's evaluation. Enbrel has an established safety profile and over 14 years of use in psoriatic arthritis.
- Flexibility in treatment options based on individualized patient response is not incorporated. Enbrel is efficacious in naïve patients and as an alternative option to previous therapies.
- ICER's Evidence Ratings lack consistency. NMA comparisons with point estimates above zero with significant credible intervals were rated "Comparable", yet the Enbrel:Apremilast comparison is rated "Insufficient." Consistent application of methodology would lead to a "Comparable Plus" rating for Enbrel.

Enbrel's recent approval as the only treatment of moderate-to-severe plaque psoriasis for pediatric patients aged 4-17 broadens its value beyond adults.

All of these important aspects should be taken into account. We expect ICER to recognize the full value of Enbrel and recommend that payers provide broad access at equal co-payments for biologic treatment options so psoriasis patients can cope with this lifelong, burdensome condition.

Conflict of Interest Disclosure*. Dr. Bradley Stolshek is an employee of Amgen.*

Dr. Matthew Frankel, Novartis
Vice President and Head, Immunology & Dermatology Medical Unit

Secukinumab, indicated for ***moderate to severe plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis***, is an example of Novartis' commitment to innovation. ICER's findings

support secukinumab's value as the most cost-effective agent for plaque psoriasis versus non-targeted therapy.[160]

The ICER report is an important step in determining the relative value of psoriasis medicines, but still has key limitations. ICER should improve on transparency of methods used in network meta-analyses, cost-effective analyses and net price calculations. Moreover, we have an obligation to consider critical patient concerns:

(1) Patients suffering this lifelong chronic disease need effective, safe, and durable therapies: Up to half of those individuals with psoriasis are dissatisfied with treatment.[161]

- Secukinumab is the only IL-17A inhibitor with demonstrated sustained efficacy up to 4 years for PASI 90 and 100[162]. Secukinumab also has demonstrated sustained superiority compared to ustekinumab and etanercept for up to one year.[20,163]
- Secukinumab's safety profile has been consistent over 4 years of treatment.[162]

(2) The total impact of plaque psoriasis goes beyond the skin: A great concern for individuals with psoriasis is high emotional, psychological, and social burden.[164]

- Secukinumab has demonstrated early and sustained superior improvement in patient-reported symptoms, skin related quality of life, and work productivity compared to etanercept and ustekinumab.[20,165-167]

(3) Location matters: Patients with psoriasis in hard-to-treat areas such as palms, soles, nails and scalp have different needs.

- Secukinumab is the only IL-17A inhibitor that has dedicated studies for plaque psoriasis in these hard-to-treat areas, and has demonstrated sustained superior efficacy relative to placebo.[168-170]

Conflict of Interest Disclosure. Dr. Matthew Frankel is an employee of Novartis.