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CADTH Reimbursement Review

Biologics in Plaque Psoriasis

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Streamlined Drug Class Review

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Abbreviations

AE	adverse event
AMSTAR 2	A MeaSurement Tool to Assess Systematic Reviews 2
CI	confidence interval
IL	interleukin
PASI	Psoriasis Area and Severity Index
PASI 75	75% reduction in Psoriasis Area Severity Index score
PASI 90	90% reduction in Psoriasis Area Severity Index score
pCPA	pan-Canadian Pharmaceutical Alliance
PGA	Physician Global Assessment
QoL	quality of life
RCT	randomized controlled trial
RR	risk ratio
SAE	serious adverse event
SMD	standardized mean difference
SUCRA	surface under the cumulative ranking
TNF	tumour necrosis factor

Executive Summary

Context: Biologics, categorized as old-generation (anti–tumour necrosis factor [TNF] and anti–interleukin [IL]-12/23 drugs) and new-generation (anti–IL-17 and anti–IL-23 drugs), are commonly used to treat moderate to severe plaque psoriasis. Recent evidence, including a CADTH integrated technology review, suggested that the appropriate use of biologics for the treatment of plaque psoriasis may favour new-generation biologics over old-generation biologics:

- New-generation biologics for plaque psoriasis consistently demonstrated greater efficacy than old-generation biologics in recent head-to-head trials as well as in indirect comparisons (i.e., network meta-analyses).
- Despite access to new-generation biologics, there is still significant use of old-generation biologics in Canada; about 44% of patients newly initiating a biologic across public and private drug plans in the country were prescribed an old-generation biologic in 2020.
- The annual real-world drug cost (based on list prices) per patient is, on average, higher for old-generation originator biologics; it was estimated that a policy that would prioritize new-generation biologics for all new patients (versus the status quo) would result in budget neutrality or modest savings in 1 year.
- All old-generation biologics for plaque psoriasis have now lost their exclusivity status, with most having been launched before the pan-Canadian Pharmaceutical Alliance (pCPA) era. In addition, biosimilar versions of the old-generation biologics have had limited uptake and delayed launches in Canada that have spanned multiple years, suggesting a significant opportunity cost paid for these drugs after loss of exclusivity (it is estimated that Canadian public drug plans spent more than $3 billion from 2016 to 2020 on old-generation originator biologics indicated for plaque psoriasis after loss of exclusivity).

Approach: A CADTH Streamlined Drug Class Review aims to provide a timely appraisal of the current evidence by leveraging the most comprehensive and rigorously conducted systematic reviews and network meta-analyses that address the policy and research questions. For this review, CADTH also sought stakeholder engagement for feedback on the project scope, receiving input from patient organizations, clinician organizations, and industry. Finally, CADTH conducted a brief economic analysis consisting of a cost comparison and summary of real-world utilization from a Canadian public payer perspective.

- This review will identify and summarize the best available evidence regarding the efficacy of new-generation biologics compared to old-generation biologics for the treatment of moderate to severe plaque psoriasis; as such, a literature search of published systematic reviews with network meta-analysis was performed. The most recent and comprehensive systematic review with meta-analysis that included all intervention and comparator drugs of interest was selected to avoid primary study redundancy. One systematic review with network meta-analysis that examined systemic treatments for plaque psoriasis was included. The Cochrane systematic review by Sbidian et al. (2023) compared the efficacy and safety of nonbiologic systemic drugs, small molecules, and biologics for the

treatment of moderate to severe plaque psoriasis using a network meta-analysis and provided a ranking of these treatments according to their benefits and harms.

- CADTH contacted patient and clinician associations in Canada with a likely interest in this drug class review of biologics in plaque psoriasis to describe the purpose and scope of the project, and to outline future opportunities for involvement. In addition to a patient member on the CADTH Formulary Management Expert Committee, there was an opportunity for a person with lived experience of plaque psoriasis and treatment with biologics to interact with the expert committee. CADTH also contacted each of the companies that hold a Canadian licence for branded versions of the drugs included in the class review.
- The economic analysis consisted of a cost comparison table and a previously published real-world utilization analysis in a Canadian setting and a 1-year economic impact analysis of a policy that prioritized the use of new-generation biologics versus status quo.

Findings:

- Input from patient organizations and clinician groups highlighted a need for treatments in plaque psoriasis that are easy to administer, affordable, provide quick and full relief of symptoms, and have minimal adverse effects. Feedback from industry was generally supportive of the scope of this project.
- At a class level, anti–IL-17 treatments showed better effectiveness for reaching 90% or 100% skin clearance compared to all other classes of systemic interventions tested (anti-TNF alpha, anti–IL-12/23, anti–IL-23 biologics, and nonbiologic drugs, as well as small molecules).
- The most effective biologic drugs for reaching 90% or 100% skin clearance when compared to placebo were infliximab (an anti-TNF alpha), bimekizumab (an anti–IL-17), ixekizumab (an anti–IL-17), and risankizumab (an anti–IL-23). The clinical effectiveness of these drugs was similar when compared against each other.
- There were no significant differences in the number of serious adverse events (SAEs) for all systemic treatments tested when compared to placebo.
- The annual cost of new-generation biologics is comparable to old-generation biologics (based on list prices and branded versions). Real-world utilization demonstrated a lower average cost per patient for new-generation biologics. Therefore, a policy that would prioritize the use of new-generation biologics (compared to the status quo) demonstrated budget neutrality and/or modest savings.

Implications for decision-making: Based on current best available evidence from randomized controlled trials, new-generation classes of biologics show better efficacy for the treatment of moderate to severe plaque psoriasis compared to old-generation classes of biologics. Old-generation originator biologics may be more costly than new-generation biologics. Taken together, if new-generation biologics have superior efficacy and lower or comparable costs to old-generation biologics, a policy that prioritizes the use of new-generation drugs could result in better patient outcomes without requiring higher expenditures. A review of the combined clinical and economic evidence and of new- and old-generation biologics in the context of current evidence standards is needed to optimize the use of biologics for plaque psoriasis.

Background

Plaque Psoriasis

Plaque psoriasis is a common chronic inflammatory skin disorder that affects 2% to 4% of the population in western countries.[1] Approximately 1 million people in Canada are affected with psoriasis.[2] It occurs equally in men and women, with a mean onset age of 33 years.[3] It can present earlier in women, with a bimodal onset at the age of 16 to 22 years and 55 to 60 years, associated with 2 different subtypes based on genetic and immunological features: early onset, before the age of 40 years (75% of cases), and late onset, after the age of 40 years.[4] Gene-environment interactions play a central role in the etiology of psoriasis. The disease often manifests in the presence of environmental triggers, such as stress, infection (e.g., streptococcal), alcohol consumption, smoking, exposure to drugs (e.g., lithium, antimalarials), nonsteroidal inflammatory drugs, and, in some cases, sunlight.[4] Weight gain and obesity are both risk factors and triggers, and potentially a consequence of living with psoriasis.[5]

There are several forms of psoriasis, including plaque, guttate, inverse, pustular, and erythrodermic. Plaque psoriasis is the most common type, affecting 90% of patients with psoriasis.[2] Symptoms can include dry or red areas of skin usually covered with silver-white scales, itching and skin pain, joint pain, swelling or stiffness, and nail abnormalities.[2] Psoriasis is considered a systemic disease and may also affect the joints and other organ systems. Patients with psoriasis may have other comorbidities and chronic systemic diseases, including inflammatory arthritis, type 2 diabetes, cardiovascular disease, gastrointestinal disease, and chronic kidney disease.[6-8] Approximately one-third of patients with psoriasis are also affected by psoriatic arthritis.[9] Psoriasis is associated with a substantial disease burden due its chronic nature and multitude of symptoms. Without appropriate treatment, patients with psoriasis experience impaired physical and psychologic functioning that leads to poor quality of life (QoL) and work productivity.[10-12]

The diagnosis of psoriasis is made based on clinical findings and the Psoriasis Area Severity Index (PASI) score is used to grade the severity of the disease based on induration, erythema, and scaling.[13] The severity of psoriasis may be classified as mild, moderate, or severe based on the extent of body surface area affected, with 10% or more of body surface area affected generally considered more severe disease.[14] However, for patients with involvement of the hands, feet, scalp, face, or genital area, or those experiencing significant physical discomfort or emotional impacts from the disease, psoriasis may also be considered severe, regardless of body surface area affected.[14] Approximately 30% of people with psoriasis have moderate to severe disease.[3]

Treatments

The treatment strategy for plaque psoriasis is guided by disease severity, location, and comorbid conditions (including psoriatic arthritis), as well as previous treatments and patient preferences.[3,14] Treatments can be classified as topical, phototherapeutic, and systemic. In patients with mild psoriasis, topical treatments (e.g., corticosteroids, vitamin D3 analogues, retinoids, anthralin, and tars) and phototherapy may be sufficient to control the disease, but for patients with moderate to severe psoriasis, systemic therapies may also be needed to control symptoms.[15] Patients suitable for systemic therapy generally meet at least 1 of 3 criteria:

more than 10% of body surface area is affected, psoriasis at special sites (scalp, face, palms and soles, or genitalia), and lack of response to topical therapy.[3] There are 3 types of systemic treatments to treat psoriasis: nonbiologic systemic therapies, small molecules or target therapies, and biologic therapies.

Biologic Therapies

Biologics are mostly recombinant monoclonal antibodies or receptor fusion proteins, either fully human, humanized, or human-mouse chimeric, and target specific inflammatory mediators. Biologics are grouped into 4 main classes based on their mechanism of action in targeting the critical immune-mediated pathways involved in the pathogenesis of psoriasis.[3] These include anti-TNF alpha, anti–IL-12/23, anti–IL-17, and anti–IL-23 treatments. Biologic therapies have revolutionized the treatment of moderate to severe psoriasis because of their efficacy and low risk of end-organ toxicity, which allows for long-term treatment to allow sustained control of symptoms.

Health Canada has approved 12 biologics for the treatment of adults with moderate to severe plaque psoriasis. Anti-TNF alpha (etanercept, infliximab, adalimumab) and anti–IL-12/23 (i.e., ustekinumab) drugs were the first classes of biologics to be approved for plaque psoriasis. The new-generation biologics approved in 2015 or later include anti–IL-17 (i.e., secukinumab, ixekizumab, brodalumab, and bimekizumab) and anti–IL-23 (i.e., risankizumab, tildrakizumab, and guselkumab) drugs (refer to Table 1). Certolizumab pegol, an anti-TNF alpha was approved in 2018. CADTH has reviewed and provided a recommendation for reimbursement for all new-generation biologics, secukinumab (2014),[16] ixekizumab (2016),[17] brodalumab (2018),[18] guselkumab (2018),[19] risankizumab (2019),[20] tildrakizumab (2021),[21] and bimekizumab (2022)[22] and all the old-generation biologics except infliximab.[23-25]

Table 1: Biologics for Plaque Psoriasis Approved in Canada

Generic name	Brand name	Manufacturer	NOC date for psoriasis	Data protection expiry	Patent end date
Adalimumab	Humira	AbbVie Corporation	January 23, 2008	NA[a]	November 11, 2031
	Amgevita (biosimilar)	Amgen Canada Inc.	November 4, 2020	NA	NA
	Hadlima (biosimilar)	Samsung Bioepis Co., Ltd.	May 8, 2018	NA	NA
	Hulio (biosimilar)	BGP Pharma ULC	November 24, 2020	NA	NA
	Hyrimoz (biosimilar)	Sandoz Canada Inc.	November 4, 2020	NA	NA
	Idacio (biosimilar)	Fresenius Kabi Canada Ltd.	October 30, 2020	NA	NA
	Abrilada (biosimilar)	Pfizer Canada ULC	April 9, 2021	NA	NA
	Simlandi (biosimilar)	Alvotech Jamp Pharma Co.	January 5, 2022	NA	NA

Generic name	Brand name	Manufacturer	NOC date for psoriasis	Data protection expiry	Patent end date
	Yuflyma (biosimilar)	Celltrion Healthcare Co., Ltd.	December 24, 2021	NA	NA
Certolizumab pegol	Cimzia	UCB Canada Inc.	August 16, 2018	August 12, 2017	June 5, 2021
Etanercept	Enbrel	Amgen Canada Inc.	December 20, 2005	NA	February 27, 2023
	Brenzys (biosimilar)	Samsung Bioepis Co., Ltd. Merck Canada Inc.	August 19, 2020	NA	NA
	Erelzi (biosimilar)	Sandoz Canada Inc.	June 9, 2020	NA	NA
Infliximab	Remicade	Janssen Inc.	June 7, 2006	NA[a]	August 1, 2017[b]
	Avsola (biosimilar)	Amgen Canada Inc.	March 12, 2020	NA	NA
	Inflectra (biosimilar)	Celltrion Healthcare Co., Ltd. Pfizer Canada ULC	January 15, 2014	NA	NA
	Remsima (biosimilar)	Celltrion Healthcare Co., Ltd.	January 15, 2014	NA	NA
	Renflexis (biosimilar)	Samsung Bioepis Co., Ltd.	December 1, 2017	NA	NA
Ustekinumab	Stelara	Janssen Inc.	December 12, 2008	December 12, 2016	August 7, 2021
Brodalumab	Siliq	Bausch Health, Canada Inc.	March 6, 2018	March 6, 2026	January 12, 2031
Ixekizumab	Taltz	Eli Lilly Canada Inc.	May 25, 2016	November 25, 2024	March 1, 2033
Secukinumab	Cosentyx	Novartis Pharmaceuticals Canada Inc.	February 17, 2015	August 27, 2023	October 7, 2031
Bimekizumab	Bimzelx	UCB Canada Inc.	February 14, 2022	February 14, 2030	January0 11, 2032
Guselkumab	Tremfya	Janssen Inc.	November 10, 2017	November 10, 2025	December 28, 2026
	Tremfya One-Press	Janssen Inc.	April 18, 2019	—	—
Risankizumab	Skyrizi	AbbVie Co.	April 17, 2019	April 17, 2027	November 2, 2031
Tildrakizumab	Ilumya	Sun Pharma Global FZE	May 19, 2021	May 19, 2029	February 21, 2028

NA = not applicable; NOC = Notice of Compliance.

[a]NOCs for adalimumab, etanercept, and infliximab were issued before the enactment of the data protection regulations in 2006.

[b]The longest patent (which was filed for the originator infliximab) was found to be infringed by the biosimilar launch. The only other patent filed for infliximab expired March 18, 2012.[31]

Rationale and Policy Issues

The treatment landscape for plaque psoriasis has drastically changed in the past 10 years with the emergence of novel classes of biologic drugs that have expanded systemic treatment options for plaque psoriasis. New biologics have continued to emerge, with 5 being approved in Canada since 2018 (Table 1). Many older biologics used today have met or are approaching loss of data exclusivity, at which point biosimilar drugs can be used. However, the development of biosimilars for these drugs is challenging due to complex molecular structures, proprietary manufacturing processes, and regulatory issues. Biologics are also 1 of the highest expenditures in public drug programs. A recent CADTH report on the formulary management of biologics in plaque psoriasis found that although several old-generation biologics for plaque psoriasis have lost exclusivity, they represent a significant portion of expenditures in Canada.[26] Older biologics often predate pCPA agreements, which could imply disparate product listing agreements across public drug plans, whereas new-generation biologics have negotiated prices under pCPA agreements. New-generation biologics are also less costly on average per patient at list price compared with the most used old-generation biologic (ustekinumab).[26]

Newer-generation biologics, anti–IL-17 and anti–IL-23 classes of drugs, have demonstrated generally more favourable efficacy compared to old-generation biologics in head-to-head trials, as reported in a previous CADTH Rapid Review.[27] Clinical evidence for most of the new-generation biologics includes direct evidence demonstrating better efficacy outcomes compared with the active comparator of the old-generation biologics. For example, adalimumab was an active comparator in trials of bimekizumab, risankizumab, and guselkumab.[19,20,22] Secukinumab, ixekizumab, and tildrakizumab were compared against etanercept,[16,17,21] and brodalumab and guselkumab were compared against ustekinumab.[18,19] However, despite access to newer and more effective treatments, older-generation biologics comprise a considerable proportion of prescriptions to patients newly initiating a biologic for plaque psoriasis. A 2022 CADTH report showed that in 2020, approximately 44% of patients newly initiating a biologic across public and private drug plans in Canada were prescribed an old-generation biologic. The average annual cost per new patient was typically higher for old-generation originator biologics (range = $11,645 to $16,047) versus new-generation biologics (range = $8,303 to $15,229) across public payers. Gross expenditure across public and private spending for originator biologics beyond exclusivity was $9 billion.[28]

Given the evolving landscape of biologic treatments for moderate to severe plaque psoriasis, and the availability of newer, potentially less costly treatment options, a class review of place in therapy for biologic drugs is essential to inform decision-makers in optimal formulary management and could improve patient outcomes. To optimize treatment pathways, the efficacy and safety of therapies relative to each other should be determined. Although many randomized controlled trials (RCTs) have compared biologic therapies against placebo, few head-to-head trials have compared biologics against each other. In the absence of some direct evidence of comparative efficacy for some biologics, network meta-analyses may help fill some of the evidence gaps.

This Streamlined Drug Class Review is intended to provide a timely means to identify, summarize, and appraise the best available evidence by leveraging existing published systematic reviews with network

meta-analyses of direct and indirect evidence on the comparative efficacy and safety of different classes of biologics for plaque psoriasis. This report is the final of several related CADTH reports[26-30] that point to a need for an expert committee review of the clinical evidence and costs of different classes of biologics for plaque psoriasis in the context of current place in therapy and reimbursement practices.

Policy Question

Does current evidence support the improved benefit-risk profile of new-generation biologics (i.e., anti–IL-17 and anti–IL-23 drug classes) compared to old-generation biologics (i.e., anti-TNF alpha and anti–IL-12/23 drug classes) for the treatment of patients with moderate to severe plaque psoriasis?

Research Questions

1. What is the clinical efficacy of new-generation biologics compared to old-generation biologics in adults with moderate to severe plaque psoriasis?
2. What are the harms of new-generation biologics compared to old-generation biologics in adults with moderate to severe plaque psoriasis?
3. How do costs compare across new- and old-generation biologics for the treatment of adults with moderate to severe plaque psoriasis?

Objectives

The objective of this report is to identify and summarize:

- the best available evidence regarding the efficacy and safety of new-generation biologics (i.e., anti–IL-17 and anti–IL-23 drug classes) compared to old-generation biologics (i.e., anti-TNF alpha and anti–IL-12/23 drug classes) for the treatment of patients with moderate to severe plaque psoriasis
- stakeholder feedback from patient, health care practitioner, and manufacturer perspectives on the needs for therapies in plaque psoriasis and scope of the drug class review
- an economic analysis that compares costs of biologics used to treat plaque psoriasis, based on product monograph dosing and real-world utilization.

Stakeholder Engagement

CADTH involves clinicians, patients, patient and clinician groups, and industry to improve the quality and significance of our work. It also allows those affected by our reviews to have an opportunity to learn about and contribute to them. Within the International Association for Public Participation Spectrum, our engagement activities can be described as “Involve” as we interact with stakeholders multiple times during

our process to ensure concerns and aspirations are consistently understood and considered. Our aim is that all stakeholders find engaging with CADTH to be a productive and worthwhile experience.

Stakeholders were given the opportunity to comment on the proposed project scope and the evidence that informed this report. They were also given the opportunity to provide feedback on the draft report and the recommendations.

Methods

Clinicians: Two dermatologists were involved as specialist members for this class review, in addition to the pharmacist, endocrinologist, gerontologist, and 2 oncologists who are core members of the CADTH Formulary Management Expert Committee. Specialist members are selected by CADTH and have clinical experience with the drugs in the class review, in addition to expertise in health research or health policy. Specialist members work directly with the CADTH team and expert committee to evaluate the therapeutic value and cost of the drugs under review, answer clinical questions related to their practical experience in diagnosing and managing treatment for plaque psoriasis, actively involve in committee deliberations, and vote on the recommendations. The names and backgrounds of the 2 specialist members will be shared at the conclusion of the review to discourage attempts to directly lobby the specialists.

Associations: In May and June of 2023, CADTH contacted patient and clinician associations in Canada with a likely interest in this class review of biologics in plaque psoriasis to describe the purpose and scope of the project, and to outline future opportunities for involvement. Early notification is especially valued by not-for-profit organizations, which often have limited staff and/or volunteers to contribute to projects. CADTH met with the Canadian Dermatology Nurses' Association, the Canadian Psoriasis Network, the Canadian Skin Patient Alliance, and the Canadian Association of Psoriasis Patients to answer questions related to the review, to identify important perspectives from past patient and clinician input most relevant to this class review, and to support a person living with plaque psoriasis speak with the expert committee.

Patients: In addition to a patient member on the CADTH Formulary Management Expert Committee, there was an opportunity for a person with lived experience of plaque psoriasis and treatment with biologics to interact with the expert committee. The aim was to enable a deeper understanding by committee members of the lived experience of receiving treatment in Canada. An opportunity for patients and caregivers to present to expert committees making reimbursement recommendations has long been requested from CADTH; however, sharing difficult stories can feel one-sided, voyeuristic, and triggering if the person is not appropriately supported. The person with lived experience will be acknowledged by name for their insights and offered honorariums. While compensation is not a motivator in and of itself for many people to participate in an engagement, it does signal that the person's time and knowledge is valued by the organization. An emotional support person was available for debrief and the associations that helped identify the person with lived experience also attended the committee meeting in a supporting role. CADTH staff briefed and debriefed the person with lived experience, as well as the patient and clinician associations.

Industry: In June 2023, CADTH contacted each of the companies that hold a Canadian licence for branded versions of the drugs included in the class review. Companies were told that the class review and

recommendations from the CADTH Formulary Management Expert Committee may include updates to previous reimbursement review recommendations issued by CADTH for those drugs. We also offered the manufacturers the opportunity to meet with CADTH staff to discuss the project and ask questions.

All stakeholders: CADTH provides 10 business days for stakeholders to provide feedback at the following stages: proposed project scope (available June 22, 2023), draft summary report (available July 20, 2023), and draft recommendations (available September 14, 2023). Feedback opportunities were communicated through the CADTH Weekly Summary emails to subscribers. Any interested stakeholders are welcome to contact CADTH to learn more about this class review.

Summary of Patient and Clinician Associations Input

The Canadian Psoriasis Network, the Canadian Skin Patient Alliance, and the Canadian Association of Psoriasis Patients had previously contributed patient input to CADTH for many of the biologics included in the class review. More recently, the Canadian Dermatology Association, the Ontario Dermatology Association, the Fraser Health Dermatology Group, and the Atlantic Provinces Dermatology Association contributed input to CADTH.

CADTH reread past patient and clinician input and categorized major ideas relevant to the class review into the following themes:

- need for psoriasis medications to be easy to administer
- need for medications that are accessible (as affordability is key to access)
- need for medications that provide quick and full symptom relief
- need for minimal adverse effects
- variability of success provided by biologics.

Additional ideas were explored when CADTH met with the Canadian Psoriasis Network, the Canadian Skin Patient Alliance, and the Canadian Dermatology Nurses Association (on July 7, 2023) and these ideas were further expanded upon in the associations' feedback to the project scope.

The patient and clinician associations noted the emotional impact of therapy change. CADTH heard about the emotional impact on a person whose disease reached a stage in which a biologic was needed, and that there is additional emotional impact to patients each time a medication is changed.

As noted by the Canadian Dermatology Nurses Association, IL-23 inhibitors are often a first choice biologic when a patient is biologic naive because they offer fewer injections, fewer potential adverse events (AEs), good efficacy, and superior patient support. However, there is no predicting who will or will not respond to a particular class of biologics. When switching drugs, patients worry about insurance coverage, out-of-pocket expenses, lack of effectiveness, and new AEs.

The patient associations suggested that FMEC consider which biologics are indicated for the treatment of both plaque psoriasis and psoriatic arthritis.

They also suggested considering which biologics should be avoided in patients who have, or are at higher risk of developing, certain comorbidities. For example, the Canadian Dermatology Nurses Association noted that its members have witnessed that IL-17s can exacerbate Crohn disease. The patient associations emphasized that people with psoriasis often live with other conditions, including atherosclerotic diseases, metabolic diseases, mental health conditions, and joint diseases, in part due to the inflammation underlying plaque psoriasis. The patient association also suggested considering which biologics and prerequisite therapies are indicated for pregnancy, breastfeeding, and individuals who may become pregnant. Pregnancy and breastfeeding can greatly impact a person's psoriasis. Methotrexate is contraindicated in pregnancy, as are retinoids. A gap of 2 to 3 years between stopping oral retinoids and becoming pregnant is recommended. In contrast, in their 2021 Baring It All report, the patient associations found that more than a quarter (28%) of their 400 survey participants who identified as a woman and had arthritis and psoriatic disease did not discuss having a child with their health care provider until they were pregnant. The patient associations encouraged CADTH to consider enlarging the project scope to include an evaluation of the safety and efficacy of these newer biologics compared to the prerequisite therapies.

CADTH heard that phototherapy may not be available to all patients in Canada, particularly those in rural areas. This may also be the case in urban or suburban areas. As a result, some people who may benefit from this treatment option will not pursue it because they aren't able to travel to sessions 2 to 3 times per week, or their employers will not permit them that time away from work.

Additionally, consider special sites such as the genital area, hands, and face. The associations explained that patients with plaques on genital areas, hands, and face benefit from reimbursement criteria that currently expedites access to biologics, as topical corticosteroids cannot be used on these areas. The associations urge continuation of these criteria to enable people with plaque psoriasis in these hard-to-treat areas to access biologics.

The GRIPP2 Short Form 19 reporting checklist was used to outline the process of engagement and where and how stakeholders' contributions were used in the review.

Table 2: Stakeholder Involvement in CADTH's Streamlined Drug Class Review of Biologics for Plaque Psoriasis

Topic	Item	Reported
Aim	CADTH involves clinicians, patients, associations, and industry to improve the quality and significance of our work.	—
Methods	Four associations and 5 pharmaceutical companies provided feedback on the project scope. Two dermatologists provided peer review, answered the CADTH team's questions, and will be involved in the deliberation and voting of the Formulary Management Expert Committee on August 24, 2023.	—
Engagement results	Past patient and clinician input emphasized the need for psoriasis medications that are easy to administer, affordable, and provide quick and full symptom relief with minimal adverse events. CADTH heard the emotional impact of therapy change.	Table 2 of the Project Scope Summary Report

Topic	Item	Reported
	Outcomes explored in CADTH's class review are response rate (clear skin at 24 weeks), maintenance of response at 52 weeks, quality of life measured by a validated scale, and adverse events. Clinician and patient associations asked CADTH to: • consider which biologics are indicated for the treatment of both plaque psoriasis and psoriatic arthritis • consider which biologics should be avoided in patients who have, or are at higher risk of developing, certain comorbidities • consider which biologics and prerequisite therapies are indicated for pregnancy, breastfeeding, and individuals who may become pregnant • consider enlarging the project scope to include an evaluation of the safety and efficacy of these newer biologics compared to the prerequisite therapies • consider special sites such as the genital area, hands, and face.	
Discussion and conclusions	Dialogue between CADTH and the associations helped build trust and a greater understanding of each other's goals. CADTH explained its aim for patients with plaque psoriasis to start on the most effective drugs. Although this class review does not focus on cost, CADTH shared that newer-generation biologics are typically less expensive compared to older-generation biologics across many regions of Canada. CADTH confirmed that the class review is limited to adults and the recommendations will accordingly only be applied to adults with plaque psoriasis. The associations applauded CADTH for a new proactive approach to engagement; they expect that the outcomes of this class review will help people making policy or clinical practice decisions have a wider and more human view of the factors patients consider and the challenges they face when seeking biologic treatment for moderate to severe plaque psoriasis.	–
Reflections and critical perspective	Combining dialogue with patient and clinician associations enabled greater integration of perspectives and allowed participants to learn from each other. We have missed the voices and perspectives of those who are not members of patient or clinician associations.	–

Summary of Industry Input

CADTH prepared this section based on input provided by industry stakeholders on the project scope and the draft summary report.

Industry input was submitted by 8 manufacturers: AbbVie Corporation, Amgen Canada Inc., Bausch Health Canada Inc., Eli Lilly Canada Inc., Sandoz Canada Inc., Sun Pharma Inc., Novartis Pharmaceuticals Inc., and UCB Canada Inc.

The general feedback from industry was supportive of the project scope and the proposed research question and it agreed that health care providers and policy-makers would benefit from an enhanced understanding of the role of older biologics in the treatment of patients who are newly diagnosed and eligible for advanced therapy. One manufacturer suggested conducting comparative cost-effectiveness of biologics and some pointed to the availability of biosimilars that have lower prices that originator biologics. One

manufacturer suggested expanding the scope to include oral systemic therapies as additional comparators and some suggested supplementing the review with other studies, such as a cost-per-responder analysis, other indirect comparisons, and real-world data. There was a suggestion to include long-term extension studies, including those presented as conference abstracts, which may not be included in meta-analyses or indirect comparisons. One manufacturer directly endorsed the use of the Cochrane review, while another highlighted concerns with using any indirect comparisons due to a lack of head-to-head trials and reliance on a naive comparison of PASI scores to determine relative drug efficacy given the variability in interpretation, reproducibility, and sensitivity of PASI scores in clinical trials. They suggested that in lieu of head-to-head comparisons, feedback regarding clinical practice and real-world experience from clinicians in Canada be taken into consideration to provide a more comprehensive review of the use of biologics for plaque psoriasis. The clinical experts consulted by CADTH did not express concern regarding interobserver reliability and reproducibility of PASI such that it precludes cross trial comparisons. While real-world studies may help fill the gaps in evidence, they are observational with varying methodologies and are prone to different biases. RCTs are considered the highest level of evidence; they provide the most reliable evidence on the effectiveness of interventions by minimizing the risk of confounding factors through randomization. Given the large number of head-to-head trials comparing different biologics for the treatment of plaque psoriasis, the Streamlined Drug Class Review will include only evidence from RCTs. Some manufacturers recommended not limiting comparisons at the class level (anti–IL-17 and anti–IL-23 versus anti-TNF and anti–IL-12/23) as efficacy and harms differ between treatments at the class level.

Clinical Review

Many systematic reviews and meta-analyses have evaluated the comparative efficacy and safety of systemic drugs, including biologics, for the treatment of moderate to severe plaque psoriasis. Network meta-analyses combine both direct and indirect evidence to determine the relative efficacy of different treatment options and help fill the gap in evidence arising from the lack of direct treatment comparisons needed to inform practice. The approach chosen for this drug class review was guided by the need to provide a timely appraisal of the evidence regarding comparative efficacy and safety of biologics for plaque psoriasis in this rapidly changing treatment landscape. The approach taken is a best evidence summary with critical appraisal, leveraging the most comprehensive and rigorously conducted systematic reviews and network meta-analyses that address the policy and research questions of this drug class review.

Methods

Search

An information specialist performed the literature search for clinical studies, using a peer-reviewed search strategy according to CADTH's *PRESS Peer Review of Electronic Search Strategies* checklist.[32] Published literature was identified by searching the following bibliographic databases: MEDLINE via Ovid and Embase via Ovid. All Ovid searches were run simultaneously as a multifile search. Duplicates were removed using Ovid deduplication for multifile searches, followed by manual deduplication in EndNote. The search strategy

comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the PICOS (population, intervention, comparison, outcomes, and study) framework and the research questions. The main search concepts were plaque psoriasis and new-generation biologics, including specific drug names as well as general terms for these drugs. CADTH-developed search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, or indirect treatment comparisons. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. Refer to Appendix 1 for the detailed search strategies. The initial search was completed on May 17, 2023. Regular alerts updated the search until June 28, 2023.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from CADTH's Grey Matters: A Practical Tool For Searching Health-Related Grey Literature.[29] Included in this search were the websites of regulatory agencies (US FDA and European Medicines Agency). Google was used to search for additional internet-based materials. Refer to Appendix 1 for more information on the grey literature search strategy.

Selection Criteria

The selection criteria for the evidence summary are outlined in Table 3. We included published systematic reviews with network meta-analysis that compared the efficacy and/or safety of new- and old-generation biologics.

Selection Process

In the first level of screening, a single reviewer scanned titles and abstracts; potentially relevant articles were retrieved and their full texts were examined. Decisions about final inclusion were made by a single reviewer. This included reviewing the primary studies included in the systematic reviews and meta-analyses to determine primary study overlap.

Appendix 2 presents the flow chart of the study selection. The literature search identified 628 records. Then, the full text of 49 records were reviewed. Twelve studies reported did not include a network meta-analysis and were excluded. Thirty-seven systematic reviews with network meta-analyses met the inclusion criteria. The characteristics of these studies, including number of studies included in the network meta-analysis and number of patients included, as well as source of funding, were extracted. There was extensive overlap of primary studies across the systematic reviews and network meta-analyses. To avoid overlap in primary studies, the most recent and comprehensive systematic review with network meta-analysis that included all of the intervention and comparator drugs of interest was included (i.e., systematic reviews and network meta-analyses in which all relevant composing primary studies were captured in another more recent analysis were sequentially excluded). Excluded studies are listed in Appendix 3.

One systematic review with network meta-analysis that examined systemic treatments for plaque psoriasis was included: *Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis*. This systematic review with network meta-analysis from Cochrane was first published in 2017 and was subsequently updated as a living systematic review to maintain the currency of the evidence included.[33-37]

The last update to this systematic review was published on July 12, 2023.[37] This network meta-analysis is the most comprehensive and up-to-date synthesis of direct and indirect evidence regarding the comparative efficacy of biologics (and other systemic treatments) for plaque psoriasis and forms the evidence base for this CADTH report.

Table 3: Study Selection Criteria

Criteria	Description
Population	Adult patients (18 years and older) with moderate to severe plaque psoriasis
Interventions	**New-generation biologics** • Anti–IL-17: secukinumab, ixekizumab, brodalumab, bimekizumab • Anti–IL-23: risankizumab, tildrakizumab, guselkumab
Comparators	**Old-generation biologics** • Anti-TNF alpha: etanercept, adalimumab, certolizumab pegol, infliximab • Anti–IL12/23: ustekinumab
Outcomes	**Efficacy:** • Response rate measured by PASI 90, PASI 100 (proportion of patients who achieved clear or almost clear skin at the end of the induction phase) • Physician Global Assessment • Health-related quality of life measured by a disease-specific validated scale (i.e., DLQI, Skindex, PDI, or PSI) • Maintenance of response (proportion of patients who achieved PASI 75 and proportion of patients who achieved PASI 90 at 52 weeks) **Safety:** • Any adverse events • Serious adverse events • Notable harms (i.e., serious infection, malignancy, respiratory tract infection, injection site reactions, mucocutaneous candidiasis, exacerbation of inflammatory bowel disease)
Study design	Published systematic reviews of RCTs with network meta-analysis
Publication date	Any

DLQI = Dermatology Life Quality Index; IL = interleukin; PASI 75 = 75% reduction in Psoriasis Area Severity Index score; PASI 90 = 90% reduction in Psoriasis Area Severity Index score; PASI 100 = 100% reduction in Psoriasis Area Severity Index score; PDI = Psoriasis Disability Index; PSI = Psoriasis Symptoms Inventory; RCT = randomized controlled trial; TNF = tumour necrosis factor.

Summary of Results

Description of the Included Systematic Review With Network Meta-Analysis

The Cochrane systematic review by Sbidian et al. (2023) compared the efficacy and safety of nonbiological systemic drugs, small molecules, and biologics for the treatment of moderate to severe psoriasis using a network meta-analysis and provided a ranking of these treatments according to their benefits and harms. An overview of the methods of this systematic review and network meta-analysis is given in the following.

Methods

Phase II, III, and IV RCTs that included adults with moderate to severe plaque psoriasis (i.e., those who needed systemic treatment) or psoriatic arthritis whose skin had been clinically diagnosed with moderate to severe psoriasis and who were at any stage of treatment were considered. The last search of the earlier published version (October 2021)[36] was updated monthly up to October 6, 2022.

Trials that assessed systemic treatments regardless of dose and duration of treatment, compared with placebo, or with an active comparator were considered. Different drugs (n = 20) and different classes of drugs (n = 6) were considered. Systemic therapies included nonbiological systemic drugs, small molecules, and biologics: anti-TNF alpha drugs (i.e., etanercept, infliximab, adalimumab, certolizumab), anti–IL-12/23 drugs (i.e., ustekinumab), anti–IL-17 drugs (i.e, secukinumab, ixekizumab, brodalumab, bimekizumab, sonelokimab, netakimab), and anti–IL-23 drugs (i.e., guselkumab, tildrakizumab, risankizumab). Active comparators were any of the systemic drugs of interest as well as additional treatments used for the network synthesis (e.g., topical treatment, phototherapy).

The primary outcomes were the proportion of patients who achieved clear or almost clear skin (i.e., at least a 90% reduction in Psoriasis Area Severity Index score [PASI 90] at induction phase) and the proportion of patients with SAEs at induction phase. SAEs included death, life-threatening events, initial or prolonged hospitalization, and AEs requiring intervention to prevent permanent impairment or damage (as defined by the International Conference for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use). Secondary outcomes were the proportion of patients who achieved a 75% reduction in Psoriasis Area Severity Index score (PASI 75) at induction phase, the proportion of patients who achieve a Physician Global Assessment (PGA) value of 0 or 1 at induction phase, QoL measured by a specific validated scale (e.g., Dermatology Life Quality Index [DLQ], Skindex, Psoriasis Disability Index [PDI], or Psoriasis Symptom Inventory [PSI] at induction phase, the proportion of patients with AEs at induction phase, the proportion of patients who achieve PASI 75 at 52 weeks, and the proportion of participants who achieve PASI 90 at 52 weeks.

The induction phase was defined as an evaluation at 8 to 24 weeks after randomization. In cases of multiple time points, the longest time point was chosen (Table 4).

Data Analysis

The authors conducted pairwise meta-analyses of trials comparing 1 of the treatments against placebo or 2 treatments against each other. Pairwise meta-analyses were done for all outcomes and comparisons using a random-effects model if at least 2 studies were available.

A network meta-analysis was then performed using random effects models for all outcomes and comparisons to estimate the relative effects for all possible comparisons between any pair of treatments within a frequentist framework. The authors used the total number of studies and participants as a denominator to calculate the proportion of trials and participants used for the quantitative synthesis of each outcome. Risk ratios (RR) with 95% confidence intervals (CIs) were used as a measure of treatment effect

for each pairwise comparison and each dichotomous outcome at each time point. For continuous variables (e.g., QoL scales), standardized mean difference (SMD) with a 95% CI were used.

Treatment hierarchy was determined using the surface under the cumulative ranking curve (SUCRA). The ranking probabilities of being at each possible rank for all outcomes was estimated. SUCRA was expressed as a percentage between 0 and 100%.

Table 4: Primary Study Selection Criteria — Sbidian et al. (2023)

Criteria	Description
Population	Adult patients (18 years and older) with moderate to severe plaque psoriasis or psoriatic arthritis whose skin had been clinically diagnosed with moderate to severe psoriasis and who are at any stage of treatment

Interventions	• Nonbiologic treatments
	  ◦ FAEs
	  ◦ Acitretin
	  ◦ Ciclosporin
	  ◦ Methotrexate
	• Small molecules
	  ◦ Apremilast
	  ◦ Deucravacitinib
	• Biologic treatments
	  ◦ Anti-TNF alpha
	  ▪ Infliximab
	  ▪ Etanercept
	  ▪ Adalimumab
	  ▪ Certolizumab
	  ◦ Anti–IL-12/23
	  ▪ Ustekinumab
	  ◦ Anti–IL-17
	  ▪ Secukinumab
	  ▪ Brodalumab
	  ▪ Ixekizumab
	  ▪ Bimekizumab
	  ▪ Sonelokimab
	  ▪ Netakimab
	  ◦ Anti–IL-23
	  ▪ Tildrakizumab
	  ▪ Guselkumab
	  ▪ Risankizumab

Active comparators	Any of the intervention drugs or any treatment not of primary interest but used for the network synthesis (e.g., topical treatment or phototherapy)

Criteria	Description
Outcomes	**Primary outcomes** • Proportion of patients who achieved clear or almost clear skin (i.e., at least PASI 90) at induction phase • The proportion of patients with SAEs at induction phase **Secondary outcomes** • Proportion of patients who achieved PASI 75 at induction phase • Proportion of patients who achieved a PGA value of 0 or 1 at induction phase • Quality of life measured by a specific validated scale (DLQI, Skindex, PDI, or PSI at induction phase) • Proportion of patients with AEs at induction phase • Proportion of patients who achieved PASI 75 at 52 weeks • Proportion of patients who achieved PASI 90 at 52 weeks
Study designs	Phase II, III, and IV RCTs
Search dates	Up to October 2022

AE = adverse event, DLQI = Dermatology Life Quality Index; FAE = fumaric acid ester; IL = interleukin; PASI 75 = 75% reduction in Psoriasis Area Severity Index score; PASI 90 = 90% reduction in Psoriasis Area Severity Index score; PDI = Psoriasis Disability Index; PGA = Physician Global Assessment; PSI = Psoriasis Symptom Inventory; RCT = randomized controlled trial; SAE = serious adverse event; TNF = tumour necrosis factor.

Source: Sbidian E, Chaimani A, Guelimi R, et al. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. Cochrane Database Syst Rev. 2023. Copyright © 2023 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd. Reprinted with permission from John Wiley & Sons, Ltd.[37]

Assessment of Heterogeneity

The authors planned to undertake meta-analyses only if they judged participants, interventions, comparisons, and outcomes to be sufficiently similar as outlined in the Cochrane Handbook for Systematic Reviews of Interventions. Potential sources of heterogeneity included participants' baseline characteristics (i.e., weight, previous systemic treatment or not, treatment doses, cointerventions, and duration of treatment). The distributions of these characteristics across studies and treatment comparisons were used to assess the transitivity assumption. To further ensure the plausibility of the transitivity assumption, the authors included trials that did not involve cointerventions. As response to biologics is different depending on prior use of systemic treatment, the main analysis excluded trials of patients who were biologic naive.

In the classic meta-analyses, statistical heterogeneity was assessed by visual inspection of the forest plots, Q-test, and the I^2 statistic. The authors interpreted the I^2 statistic threshold (according to the Cochrane Handbook for Systematic Reviews of Interventions) as 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% represents considerable heterogeneity. In the network meta-analysis, the assessment of statistical heterogeneity in the entire network was based on the estimated heterogeneity variance parameter ($\tau 2$) estimated from the network meta-analysis models.

Assessment of Risk of Bias

Risk of bias in included studies was assessed by 2 review authors independently using the Cochrane's risk of bias tool, and a third author resolved any disagreements. Risk of bias domains were judged as “low,” “high,” or “unclear” for each of the following domains according to the general principles outlined in the Cochrane

Handbook for Systematic Reviews of Interventions: selection bias (random sequence generation and allocation concealment), performance and detection bias (blinding of participants and outcome assessors), attrition bias (incomplete outcome data), and reporting bias (selective outcome reporting).[38]

The authors determined the overall risk of bias and the quality of evidence to interpret the network results. The 6 risk of bias criteria (random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessor, incomplete outcome data, and selective outcome reporting) were used to classify each trial as having low risk of bias if none of the domains were rated as high risk of bias, and 2 or fewer as unclear risk. The trial was rated as having moderate risk of bias if 1 domain was rated as high risk of bias, 1 or fewer domains as unclear risk, or no domains as high risk of bias, but 3 or fewer were rated as unclear risk. All other scenarios were assumed to represent high risk of bias.

Assessment of the Certainty of the Evidence

The authors assessed the confidence of the evidence estimates using the Confidence in Network Meta-Analysis (CINeMA) approach, which is based on the contributions of the direct comparisons to the estimation in the network meta-analysis.[37] It is based on 6 domains: within-study bias (the impact of risk of bias in the included studies), across-studies bias (publication or reporting bias), indirectness (relevance to the research question and transitivity), imprecision (comparing the range of treatment effects included in the 95% CI with the range of equivalence), heterogeneity (predictive intervals), and incoherence (disagreement between estimates from direct and indirect evidence).[39] All comparison results for the 2 main outcomes (PASI 90 and SAEs) and the anticipated absolute effects and assessment of the certainty of evidence were presented using CINeMA. After confidence in each network meta-analysis RR_{AB} between any 2 given drug A and drug B was evaluated for 6 domains (rated as "major concern," "some concern," or "no concern" for each domain), the authors summarized the overall confidence in evidence for each RR between any 2 drugs into high, moderate, low, and very low. Starting with high confidence, they downgraded by 1 level for each "major concern" in any of the 6 domains; then by two-thirds of a level down for "some concerns" in "within-study bias"; and by one-third of a level down for each "some concerns" in any of the other 5 domains. The final level was obtained by rounding the number of downgrades to their nearest integer. Finally, the authors calculated the percentage of the 4 levels based on all comparisons including that drug for benefits and harms outcomes for each drug.

Critical Appraisal

The included systematic review and meta-analysis by Sbidian et al. (2023) was critically appraised by CADTH using A MeaSurement Tool to Assess Systematic Reviews 2 (AMSTAR 2) tool, an instrument used to assess the methodological quality of systematic reivews.[40] The systematic review and network meta-analysis by Sbidian. et al. scored "high" using the AMSTAR 2 checklist. A high AMSTAR 2 score indicates 0 or 1 noncritical weakness; that is, the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question. The Professional Society for Health Economics and Outcomes Research (ISPOR) checklist for indirect treatment comparisons was also used to assess the quality of the network meta-analysis (Appendix 5).

The authors of the systematic review used validated methods to assess risk of bias in individual studies. As described in the clinical review methods, risk of bias in included studies was assessed by 2 review authors independently, using the Cochrane risk of bias tool. Detailed assessments of risk of bias corresponding to each trial were outlined in a table of characteristics of included studies. The authors also assessed the confidence of the evidence estimates using the CINeMA tool. Assumptions for network meta-analyses were tested and discussed. To reassure the plausibility of the transitivity assumption, the authors only included trials not involving cointerventions and excluded trials that included patients who were naive to biologics as response to biologics is different depending on treatment status (i.e., biologic naive or not). The authors reported that the distribution of participant characteristics did not give any indication of important differences across comparisons; formal tests of heterogeneity in the meta-analysis and network meta-analysis did not identify important heterogeneity. Tests for incoherence (i.e., consistency between direct and indirect estimates) did not suggest serious incoherence.

An assessment of heterogeneity and inconsistency for all networks in all indirect comparisons were performed and considered in the evaluation of evidence. The authors discussed that they did not identify important heterogeneity either in direct meta-analyses or in network meta-analysis. They noted that the common outcome-specified network heterogeneity and the prediction intervals suggested the presence of low heterogeneity for all outcomes. The authors investigated differences in heterogeneity between class- and drug- level analysis, as well as differences in heterogeneity between primary and sensitivity analyses for the primary outcomes, noting similar results. The distribution of some patient characteristics (i.e., age, sex ratio, weight, severity of psoriasis) did not point to important differences in these characteristics across comparisons.

Summary of Results

Description of Included Studies

In total, 449 reports of 179 studies were included (n = 62,339). A total of 140 studies involving 54,815 patients (88% of the patients in the review) were included in the quantitative synthesis (i.e., network meta-analysis) for at least 1 of the outcomes. All trials used a parallel-group design. The mean sample size was 348 (range = 10 to 1,881).

A total of 100 trials compared systemic treatments with placebo, of which 65 trials compared biologic treatments versus placebo, including etanercept (n = 9), adalimumab (n = 7), infliximab (n = 6), certolizumab (n = 4), ustekinumab (n = 7), secukinumab (n = 13), ixekizumab (n = 3), brodalumab (n = 4), bimekizumab (n = 2), guselkumab (n = 2), tildrakizumab (n = 2), and risankizumab (n = 4). A total of 57 trials compared systemic treatments with systemic treatments; 19 trials with 3 parallel arms compared systemic treatments with systemic treatments and placebo; and 3 trials compared 3 systemic treatments. The dataset of 179 studies provided information on 317 direct comparisons between 37different drug dosages, 20 different drugs, 6 different drug classes, and placebo. Figure 4 in Appendix 4 depicts network diagrams for all the outcomes at the class level.

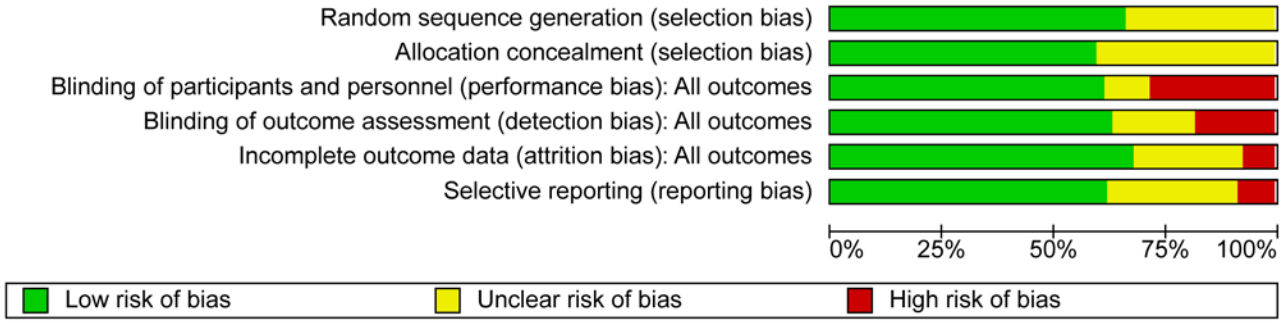
Out of 179 trials, 135 reported the number of patients with AEs and 147 reported the number of patients with SAEs.

The patients were reported to be between 27 and 56.5 years old, with an overall mean age of 44.6. There were more men (41,829) than women (19,805), the overall mean weight was 85.4 kg (range = 59 kg to 100.5 kg), and the overall mean PASI score at baseline was 20.4 (range = 9.5 to 39). The mean duration of psoriasis was 16.5 years (range = 4.5 to 21.5).

Risk of Bias in Included Studies

For overall risk of bias across studies, the authors categorized 90 (50%) trials as being at low risk of bias, and a third of the trials (65 out of 179, 36%) as being at high risk of bias. The remaining 24 studies were categorized as being at unclear risk of bias. The risk of bias assessments with review authors' judgment about each risk of bias item presented as percentages across all included studies is summarized in Figure 1.

Figure 1: Risk of Bias — Review Authors' Judgment About Each Risk of Bias Item Across All Included Studies



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Description of Findings

The following sections provide a summary of results of direct and indirect evidence of the analyses comparing 1 biologic drug versus another biologic drug only for primary and secondary outcomes.

Response Rate (PASI 90 or Better)

Direct Evidence

For reaching PASI 90, ustekinumab, secukinumab, infliximab, ixekizumab, and tildrakizumab were more effective than etanercept. Secukinumab, ixekizumab, brodalumab, risankizumab, and bimekizumab were more effective than ustekinumab. Guselkumab, risankizumab, and bimekizumab were more effective than adalimumab. Secukinumab and ixekizumab were more effective than guselkumab, and bimekizumab was more effective than secukinumab. No significant difference was observed between risankizumab and secukinumab, or between certolizumab and etanercept (Table 5).

Network Meta-Analysis

The summary relative effects from the network meta-analysis were reported for both drug-level and class-level analyses (refer to Figure 5 and Figure 6 in Appendix 4). The certainty of evidence for each comparison using CiNeMA was also reported (refer to Figure 5 in Appendix 4).

Table 5: Direct Evidence — PASI 90

Biologics	Number of studies N = 27	Number of participants	Effect size Risk ratio, M-H, random (95% CI)
Ustekinumab vs. etanercept	1	903	1.80 (1.45 to 2.24)
Secukinumab vs. etanercept	1	980	2.32 (1.85 to 2.92)
Infliximab vs. etanercept	1	48	9.20 (1.28 to 66.37)
Ixekizumab vs. etanercept	2	2,209	2.98 (2.24 to 3.98)
Tildrakizumab vs. etanercept	1	934	1.76 (1.39 to 2.23)
Certolizumab vs. etanercept	1	502	1.20 (0.90 to 1.61)
Secukinumab vs. ustekinumab	2	1,778	1.40 (1.30 to 1.50)
Ixekizumab vs. ustekinumab	1	302	1.41 (1.21 to 1.63)
Brodalumab vs. ustekinumab	2	3,088	1.27 (1.16 to 1.39)
Risankizumab vs. ustekinumab	3	965	1.67 (1.43 to 1.93)
Bimekizumab vs. ustekinumab	1	484	1.71 (1.46 to 2.01)
Guselkumab vs. adalimumab	3	1,658	1.43 (1.26 to 1.62)
Risankizumab vs. adalimumab	1	605	1.53 (1.33 to 1.75)
Bimekizumab vs. adalimumab	1	478	1.66 (1.42 to 1.94)
Ixekizumab vs. adalimumab	1	100	1.42 (1.10 to 1.85)
Ixekizumab vs. guselkumab	1	1,027	1.29 (1.18 to 1.42)
Risankizumab vs. secukinumab	1	327	1.12 (0.97 to 1.30)
Bimekizumab vs. secukinumab	1	743	1.15 (1.07 to 1.24)
Guselkumab vs. secukinumab	1	1,048	0.91 (0.84 to 0.98)
Sonelokimab vs. secukinumab	1	261	0.97 (0.77 to 1.21)

CI = confidence interval; M-H = Mantel-Haenszel; PASI 90 = 90% reduction in Psoriasis Area Severity Index score; vs. = versus.

Source: Sbidian E, Chaimani A, Guelimi R, et al. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. Cochrane Database Syst Rev. 2023. Copyright © 2023 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd. Reprinted with permission from John Wiley & Sons, Ltd.[37]

There was no significant difference between infliximab, bimekizumab, ixekizumab, and risankizumab in terms of reaching PASI 90. Bimekizumab and ixekizumab were significantly more likely to reach PASI 90 than secukinumab. Bimekizumab, ixekizumab, and risankizumab were significantly more likely to reach PASI 90 than brodalumab and guselkumab. Infliximab, anti–IL-17 drugs (bimekizumab, ixekizumab, secukinumab, and brodalumab), and anti–IL-23 drugs (i.e., risankizumab and guselkumab), except tildrakizumab, were significantly more likely to reach PASI 90 than ustekinumab, 3 anti-TNF alpha drugs (i.e, adalimumab,

certolizumab, and etanercept), and deucravacitinib. Ustekinumab was superior to certolizumab (RR = 1.43; 95% CI, 1.06 to 1.91). Adalimumab, tildrakizumab, and ustekinumab were superior to etanercept (RR = 1.67; 95% CI, 1.47 to 1.89; RR = 1.76; 95% CI, 1.40 to 2.20; and RR = 1.79; 95% CI, 1.60 to 2.01, respectively). The certainty of evidence based on CiNeMA was rated as high or moderate for most comparisons.

Ranking class level analysis suggested that the anti–IL-17 class had a better chance of reaching PASI 90 at class level (versus placebo: RR = 23.94; 95% CI, 20.19 to 28.40; SUCRA = 99.5), followed by anti–IL-23 drugs (versus placebo: RR = 20.76; 95% CI = 17.32 to 24.89; SUCRA = 83.8), anti–IL-12/23 drugs (versus placebo: RR = 16.60; 95% CI, 13.72 to 20.09; SUCRA = 66.7), then anti-TNF alphas (versus placebo: RR = 12.25; 95% CI, 10.33 to 14.52; SUCRA = 48.7) (refer to Table 11, and Figure 9 in Appendix 4).

Serious Adverse Events

Direct Evidence

There were no differences between biologic treatments and placebo in the number of patients with SAEs (Table 6).

Network Meta-Analysis

The summary relative effects from the network meta-analysis were reported for both drug-level and class-level analyses (refer to Figure 5 in Appendix 4 and Figure 6 in Appendix 4). The certainty of evidence for each comparison using CiNeMA was also reported (refer to Figure 5 in Appendix 4).

The authors found no significant differences between any of the interventions and placebo for the risk of SAEs. Results were similar after excluding flares of psoriasis as SAEs. There was no difference between all interventions in the number of participants with SAEs. The certainty of evidence using CINeMA was rated as moderate and low.

Table 6: Direct Evidence — SAEs

Biologics	Number of studies N = 27	Number of participants	Effect size Risk ratio M-H, random (95% CI)
Ustekinumab vs. etanercept	1	903	1.25 (0.38 to 4.11)
Secukinumab vs. etanercept	1	980	1.08 (0.41 to 2.82)
Infliximab vs. etanercept	1	48	0.92 (0.06 to 13.87)
Ixekizumab vs. etanercept	2	2,209	1.07 (0.55 to 2.06)
Tildrakizumab vs. etanercept	1	934	0.72 (0.28 to 1.87)
Certolizumab vs. etanercept	1	502	2.56 (0.30 to 21.74)
Secukinumab vs. ustekinumab	2	1,778	1.26 (0.70 to 2.30)
Ixekizumab vs. ustekinumab	1	302	0.73 (0.18 to 3.01)
Brodalumab vs. ustekinumab	2	3,088	1.51 (0.64 to 3.56)
Risankizumab vs. ustekinumab	3	965	0.57 (0.24 to 1.32)
Bimekizumab vs. ustekinumab	1	484	0.51 (0.15 to 1.73)

Biologics	Number of studies N = 27	Number of participants	Effect size Risk ratio M-H, random (95% CI)
Guselkumab vs. adalimumab	3	1,658	0.91 (0.45 to 1.84)
Risankizumab vs. adalimumab	1	605	1.12 (0.46 to 2.72)
Bimekizumab vs. adalimumab	1	478	0.50 (0.15 to 1.70)
Ixekizumab vs. guselkumab	1	1,027	1.10 (0.57 to 2.13)
Risankizumab vs. secukinumab	1	327	1.49 (0.54 to 4.09)
Ixekizumab vs. secukinumab	1	0	Not estimable
Guselkumab vs. secukinumab	1	1,048	0.86 (0.55 to 1.35)
Sonelokimab vs. secukinumab	1	261	2.84 (0.16 to 50.61)

CI = confidence interval; M-H = Mantel-Haenszel; SAE = serious adverse event; vs. = versus.

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In the ranking class-level analysis, small molecules had the highest SUCRA at class level for SAEs (versus placebo: RR = 0.75; 95% CI, 0.49 to 1.14; SUCRA = 76.2), followed by anti–IL-23s (versus placebo: RR = 0.79; 95% CI, 0.60 to 1.04; SUCRA = 74.3), then nonbiologic systemic treatments (versus placebo: RR = 0.80; 95% CI, 0.40 to 1.61; SUCRA = 60.8), anti-TNF alpha (versus placebo: RR = 0.92; 95% CI, 0.71 to 1.18; SUCRA = 45.2), anti–IL-17 (versus placebo: RR = 0.95; 95% CI, 0.76 to 1.20; SUCRA = 37.6), and anti-IL12/23 classes of drugs (versus placebo: RR = 0.99; 95% CI, 0.71 to 1.37; SUCRA = 31.4) (refer to Table 11, and Figure 9 in Appendix 4).

Response Rate (PASI 75)

Direct Evidence

Treatment estimates for pairwise meta-analyses are presented in Table 7.

Network Meta-Analysis

The summary relative effects from the network meta-analysis are reported for class-level and drug-level analyses (refer to Figure 6 and Figure 7 in Appendix 4).

At class level, the anti–IL-17 class of drugs was associated with a higher chance of reaching PASI 75 compared to the other classes, except for anti–IL-23 (refer to Figure 6). At drug level, infliximab, anti–IL-17 drugs (i.e., ixekizumab, bimekizumab, and secukinumab), and risankizumab were significantly more likely to reach PASI 75 than ustekinumab and other anti-TNF alpha drugs (i.e., adalimumab, certolizumab, and etanercept) (refer to Figure 7).

Ranking class-level analysis suggested that anti–IL-17s had a better chance of reaching PASI 75 (versus placebo: RR = 12.22; 95% CI, 10.95 to 13.64; SUCRA = 99.5), followed by anti–IL-23 (versus placebo: RR = 10.97; 95% CI, 9.75 to 12.35; SUCRA = 80.8), anti–IL-12/23 (versus placebo: RR = 10.39; 95% CI, 9.20 to 11.74; SUCRA = 69.8), and anti-TNF alpha (versus placebo: RR = 8.27; 95% CI, 7.45 to 9.18; SUCRA = 50) (refer to Table 11).

Table 7: Direct Evidence — PASI 75

Biologics	Number of studies N = 26	Number of participants	Effect size Risk ratio, M-H, random (95% CI)
Ustekinumab vs. etanercept	1	903	1.26 (1.13 to 1.40)
Secukinumab vs. etanercept	1	980	1.64 (1.44 to 1.88)
Infliximab vs. etanercept	1	48	2.07 (1.12 to 3.81)
Ixekizumab vs. etanercept	2	2,209	1.79 (1.43 to 2.24)
Tildrakizumab vs. etanercept	1	934	1.32 (1.16 to 1.50)
Certolizumab vs. etanercept	1	502	1.19 (1.01 to 1.40)
Secukinumab vs. ustekinumab	2	1,778	1.14 (1.10 to 1.19)
Ixekizumab vs. ustekinumab	1	302	1.11 (1.02 to 1.22)
Brodalumab vs. ustekinumab	2	3,088	1.10 (1.04 to 1.17)
Risankizumab vs. ustekinumab	3	965	1.23 (1.13 to 1.33)
Bimekizumab vs. ustekinumab	1	484	1.26 (1.14 to 1.39)
Guselkumab vs. adalimumab	3	1,658	1.23 (1.14 to 1.32)
Risankizumab vs. adalimumab	1	605	1.26 (1.17 to 1.37)
Bimekizumab vs. adalimumab	1	478	1.34 (1.20 to 1.49)
Ixekizumab vs. adalimumab	1	100	1.21 (1.00 to 1.45)
Risankizumab vs. secukinumab	1	327	1.15 (1.05 to 1.26)
Bimekizumab vs. secukinumab	1	743	1.02 (0.98 to 1.07)
Guselkumab vs. secukinumab	1	1,048	0.97 (0.94 to 1.01)
Sonelokimab vs. secukinumab	1	261	0.91 (0.82 to 1.01)

CI = confidence interval; M-H = Mantel-Haenszel; PASI 75 = 75% reduction in Psoriasis Area Severity Index score; vs. = versus.

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Physician Global Assessment

Direct Evidence

Treatment estimates for pairwise meta-analyses are presented in Table 8.

Table 8: Direct Evidence — Physician Global Assessment 0 or 1

Biologics	Number of studies N = 26	Number of participants	Effect size Risk ratio, M-H, random (95% CI)
Ustekinumab vs. etanercept	1	903	1.40 (1.24 to 1.58)
Secukinumab vs. etanercept	1	980	2.09 (1.73 to 2.53)
Infliximab vs. etanercept	1	48	2.50 (1.30 to 4.81)
Ixekizumab vs. etanercept	2	2,209	2.01 (1.74 to 2.31)
Tildrakizumab vs. etanercept	1	934	1.20 (1.05 to 1.37)
Secukinumab vs. ustekinumab	2	1,778	1.28 (1.19 to 1.38)
Ixekizumab vs. ustekinumab	1	302	1.23 (1.09 to 1.39)
Brodalumab vs. ustekinumab	2	3,088	1.17 (1.07 to 1.27)
Risankizumab vs. ustekinumab	3	965	1.37 (1.23 to 1.52)
Bimekizumab vs. ustekinumab	1	484	1.58 (1.35 to 1.83)
Guselkumab vs. adalimumab	3	1,658	1.26 (1.19 to 1.34)
Risankizumab vs. adalimumab	1	605	1.39 (1.25 to 1.54)
Bimekizumab vs. adalimumab	1	478	1.50 (1.30 to 1.72)
Ixekizumab vs. guselkumab	1	1,027	1.33 (1.21 to 1.46)
Risankizumab vs. secukinumab	1	327	1.23 (1.10 to 1.37)
Ixekizumab vs. secukinumab	1	54	1.01 (0.81 to 1.27)
Bimekizumab vs. secukinumab	1	743	1.09 (1.02 to 1.16)
Guselkumab vs. secukinumab	1	1,048	1.00 (0.95 to 1.05)
Sonelokimab vs. secukinumab	1	261	0.96 (0.82 to 1.14)

CI = confidence interval; M-H = Mantel-Haenszel; vs. = versus.

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Network Meta-Analysis

At class level, all the interventions appeared superior to placebo in terms of reaching PGA 0 or 1, and anti–IL-17s were associated with a better chance for this outcome compared to the other drug classes (refer to Figure 6 in Appendix 4). Results at the drug level are presented in Figure 8 in Appendix 4.

Ranking class-level analysis suggested that anti–IL-17 had a better chance of reaching PGA 0 or 1 at class level (versus placebo: RR = 13.44; 95% CI, 11.73 to 15.40; SUCRA = 100), followed by anti–IL-23 (versus placebo: RR = 10.92; 95% CI, 9.48 to 12.59; SUCRA = 81.2), anti–IL-12/23 drugs (versus placebo: RR = 9.94; 95% CI, 8.56 to 11.54; SUCRA = 68.8), and anti-TNF alpha drugs (versus placebo: RR = 7.86; 95% CI, 6.89 to 8.95; SUCRA = 50) (refer to Table 11, and Figure 9 in Appendix 4).

Health-Related Quality of Life

Direct Evidence

Treatment estimates for pairwise meta-analyses are presented in Table 9.

Table 9: Direct Evidence — Quality of Life

Biologics	Number of studies N = 9	Number of participants	Effect size Risk ratio, M-H, random (95% CI)
Ixekizumab vs. etanercept	2	2,209	−0.44 (-0.53 to −0.35)
Tildrakizumab vs. etanercept	1	932	−0.24 (-0.38 to −0.10)
Infliximab vs. etanercept	1	48	−0.67 (-1.25 to −0.08)
Guselkumab vs. adalimumab	2	1,407	−0.24 (-0.35 to −0.14)
Bimekizumab vs. adalimumab	1	478	−0.31 (-0.50 to −0.12)
Risankizumab vs. ustekinumab	2	799	−0.30 (-0.46 to −0.14)

CI = confidence interval; M-H = Mantel-Haenszel; vs. = versus.

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Network Meta-Analysis

At class level all classes of treatments appeared superior to placebo in terms of showing significant improvement on a QoL scale (refer to Figure 6 in Appendix 4). No differences were observed between the anti–IL-23, anti–IL-12/23, and anti–IL-17 classes. Anti–IL-23, anti–IL-17, and anti–IL-12/23 classes were more favourable than the anti-TNF class (refer to Figure 8 in Appendix 4).

Ranking class-level analysis suggested that the anti–IL-17 class had a better chance of improving QoL at class level (versus placebo: SMD = −1.50; 95% CI, −1.66 to −1.35; SUCRA = 96), followed by the anti–IL-23 (versus placebo: SMD −1.41; 95% CI, −1.56 to −1.27; SUCRA = 83.3) and anti–IL-12/23 classes (versus placebo: SMD = −1.31; 95% CI, −1.49 to −1.14; SUCRA = 70) (refer to Table 11, and Figure 9 in Appendix 4).

Adverse Events

Direct Evidence

Treatment estimates for pairwise meta-analyses are presented in Table 10.

Table 10: Direct Evidence — Adverse Events

Biologics	Number of studies N = 26	Number of participants	Effect size Risk ratio, M-H, random (95% CI)
Ustekinumab vs. etanercept	1	903	0.97 (0.89 to 1.06)
Secukinumab vs. etanercept	1	980	1.00 (0.89 to 1.12)
Ixekizumab vs. etanercept	2	2,209	1.06 (0.97 to 1.15)
Infliximab vs. etanercept	1	48	0.96 (0.86 to 1.08)
Tildrakizumab vs. etanercept	1	934	0.75 (0.65 to 0.86)
Certolizumab vs. etanercept	1	502	1.05 (0.86 to 1.28)
Secukinumab vs. ustekinumab	2	1,778	1.06 (0.98 to 1.16)
Ixekizumab vs. ustekinumab	1	302	0.92 (0.80 to 1.06)
Brodalumab vs. ustekinumab	2	3,088	1.00 (0.93 to 1.09)
Risankizumab vs. ustekinumab	3	965	0.97 (0.85 to 1.11)
Bimekizumab vs. ustekinumab	1	484	1.11 (0.93 to 1.32)
Guselkumab vs. adalimumab	3	1,658	0.98 (0.89 to 1.09)
Risankizumab vs. adalimumab	1	605	0.98 (0.85 to 1.13)
Bimekizumab vs. adalimumab	1	478	1.02 (0.90 to 1.16)
Ixekizumab vs. guselkumab	1	1,027	1.03 (0.92 to 1.15)
Risankizumab vs. secukinumab	1	327	1.00 (0.87 to 1.15)
Ixekizumab vs. secukinumab	1	54	1.04 (0.71 to 1.52)
Guselkumab vs. secukinumab	1	1,048	0.96 (0.90 to 1.02)
Sonelokimab vs. secukinumab	1	261	1.05 (0.77 to 1.42)

CI = confidence interval; M-H = Mantel-Haenszel; vs. = versus.

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Network Meta-Analysis

At class level, all classes of treatments had a more significant risk of AEs compared to placebo, except the anti–IL-23 class. Among biologics, the anti–IL-17 class had a higher risk of AEs compared with the anti–IL-23, anti–IL-12/23, and anti-TNF classes (refer to Figure 6 in Appendix 4). Results of comparisons between each of the drugs are available in Figure 7 in Appendix 4.

In ranking class-level analysis, placebo had the highest SUCRA (SUCRA = 95.1) at class level for all AEs, followed by the anti–IL-23 (versus placebo: RR = 1.02; 95% CI, 0.96 to 1.08; SUCRA = 85.5), anti-TNF (versus placebo: RR = 1.08; 95% CI, 1.03 to 1.12; SUCRA = 57.2), then anti–IL-12/23 classes (versus placebo: RR = 1.08; 95% CI, 1.02 to 1.14; SUCRA = 54.6) (refer to Table 11, and Figure 9 in Appendix 4).

Table 11: Ranking Findings for All Outcomes at Class Level

Class-level intervention	PASI 90		SAE		PASI 75		AE		PGA		Specific QoL scale	
	SUCRA	Rank	SUCRA	Rank	SUCRA	Rank	SUCRA	Rank	SUCRA	Rank	SUCRA	Rank
Anti–IL-17	99.5	1	37.6	5	99.5	1	25.1	6	100	1	96	1
Anti–IL-23	83.8	2	74.3	2	80.8	2	85.5	2	81.2	2	83.3	2
Anti–IL-12/23	66.7	3	31.4	6	69.8	3	54.6	4	68.8	3	70	3
Anti-TNF alpha	48.7	4	45.2	4	50	4	57.2	3	50	4	48	4
Small molecules	33.3	5	76.2	1	27.9	5	3.8	7	28.8	5	20.1	6
Nonbiologics	18	6	60.8	3	22.1	6	28.9	5	21.3	6	33	5
Placebo	0	7	24.4	7	0	7	95.1	1	0	7	0	7

AE = adverse event; IL = interleukin; PASI 75 = 75% reduction in Psoriasis Area Severity Index score; PASI 90 = 90% reduction in Psoriasis Area Severity Index score; PGA = Physician Global Assessment; QoL = quality of life; TNF = tumour necrosis factor; SAE: serious adverse events; SUCRA = surface under the cumulative ranking.

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Response Rate (PASI 90) at 52 Weeks

Direct Evidence

Treatment estimates for pairwise meta-analyses at the drug level are presented in Table 13.

Eleven head-to-head comparisons evaluated 2 different biologics; 7 compared 2 different dosages of secukinumab, guselkumab, ixekizumab, risankizumab, and apremilast, respectively. For reaching PASI 90 at 52 weeks, risankizumab was more effective than ustekinumab (RR = 1.73; 95% CI 1.46 to 2.05). Secukinumab was more effective than ustekinumab (RR = 1.23; 95% CI 1.15 to 1.31); ixekizumab was more effective than ustekinumab (RR = 1.30; 95% CI 1.11 to 1.52); bimekizumab was more effective than ustekinumab (RR = 1.47; 95% CI 1.27 to 1.70); risankizumab was more effective than secukinumab (RR = 1.52; 95% CI, 1.31 to 1.76); bimekizumab was more effective than secukinumab (RR = 1.19; 95% CI, 1.09 to 1.28); guselkumab was more effective than adalimumab (RR = 1.59; 95% CI, 1.40 to 1.81); guselkumab was more effective than secukinumab (RR = 1.21; 95% CI, 1.13 to 1.29), and ixekizumab was more effective than adalimumab (RR = 1.34; 95% CI 1.04 to 1.74).

Ixekizumab every other week was more effective than ixekizumab every 4 weeks (RR = 1.06; 95% CI, 1.01 to 1.11) and secukinumab 300 mg was more effective than secukinumab 150 mg (RR = 0.84; 95% CI, 0.78 to 0.91) in reaching PASI 90 at 52 weeks.

The authors did not conduct network meta-analyses because of the low number of studies for this outcome.

Table 12: Direct Evidence — PASI 90 at 52 Weeks

Biologics	Number of studies N = 17	Number of participants N = 8,729	Effect size Risk ratio, M-H, random (95% CI)
Secukinumab vs. ustekinumab	2	1,778	1.23 (1.15 to 1.31)
Risankizumab vs. ustekinumab	2	799	1.73 (1.46 to 2.05)
Ixekizumab vs. ustekinumab	1	302	1.30 (1.11 to 1.52)
Bimekizumab vs. ustekinumab	1	484	1.47 (1.27 to 1.70)
Risankizumab vs. secukinumab	1	327	1.52 (1.31 to 1.76)
Bimekizumab vs. secukinumab	1	743	1.19 (1.09 to 1.28)
Guselkumab vs. secukinumab	1	1,048	1.21 (1.13 to 1.29)
Guselkumab vs. adalimumab	1	663	1.59 (1.40 to 1.81)
Ixekizumab vs. adalimumab	1	100	1.34 (1.04 to 1.74)
Secukinumab 150 vs. secukinumab 300	3	1,017	0.84 (0.78 to 0.91)
Guselkumab 100 vs. guselkumab 50	1	128	1.03 (0.85 to 1.25)
Ixekizumab q.2.w. vs. Ixekizumab q.4.w.	1	1,227	1.06 (1.01 to 1.11)
Risankizumab 75 vs. risankizumab 150	1	113	0.93 (0.82 to 1.06)

CI = confidence interval; M-H = Mantel-Haenszel; q.2.w. = every 2 weeks; PASI 90 = 90% reduction in Psoriasis Area Severity Index score; q.4.w. = every 4 weeks; vs. = versus.

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Response Rate (PASI 75) at 52 Weeks

Direct Evidence

Treatment estimates for pairwise meta-analyses at the drug level are presented in Table 13.

Ten head-to-head comparisons evaluated 2 different biologics; 7 compared 2 different dosages of secukinumab, guselkumab, ixekizumab, risankizumab, and apremilast, respectively. For reaching PASI 75 at 52 weeks, risankizumab was more effective than ustekinumab (RR = 1.26; 95% CI, 1.12 to 1.41), secukinumab was more effective than ustekinumab (RR = 1.13; 95% CI, 1.04 to 1.22); ixekizumab was more effective than ustekinumab (RR = 1.16; 95% CI, 1.05 to 1.29); risankizumab was more effective than secukinumab (RR = 1.28; 95% CI, 1.14 to 1.44); bimekizumab was more effective than secukinumab (RR = 1.09; 95% CI, 1.02 to 1.16); guselkumab was more effective than secukinumab (RR = 1.06; 95% CI, 1.00 to 1.12); guselkumab was more effective than adalimumab (RR = 1.40; 95% CI, 1.28 to 1.54). No difference was observed for ixekizumab and adalimumab in reaching PASI 75 at week 52. Ixekizumab every other week was more effective than ixekizumab every 4 weeks (RR = 1.14; 95% CI 1.07 to 1.22) and secukinumab 300 mg was more effective than secukinumab 150 mg in reaching PASI 75 at 52 weeks (RR = 0.90; 95% CI, 0.85 to 0.94).

The authors did not conduct network meta-analyses because of the low number of studies for this outcome.

Table 13: Direct Evidence — PASI 75 at 52 Weeks

Biologics	Number of studies N = 16	Number of participants N = 8,245	Effect size Risk ratio, M-H, random (95% CI)
Secukinumab vs. ustekinumab	2	1,778	1.13 (1.04 to 1.22)
Risankizumab vs. ustekinumab	2	799	1.26 (1.12 to 1.41)
Ixekizumab vs. ustekinumab	1	302	1.16 (1.05 to 1.29)
Risankizumab vs. secukinumab	1	327	1.28 (1.14 to 1.44)
Bimekizumab vs. secukinumab	1	743	1.09 (1.02 to 1.16)
Guselkumab vs. secukinumab	1	1,048	1.06 (1.00 to 1.12)
Guselkumab vs. adalimumab	1	663	1.40 (1.28 to 1.54)
Ixekizumab vs. adalimumab	1	100	1.07 (0.89 to 1.27)
Secukinumab 150 vs. secukinumab 300	3	1,017	0.90 (0.85 to 0.94)
Guselkumab 100 vs. guselkumab 50	1	128	0.98 (0.88 to 1.09)
Ixekizumab q.2.w. vs. ixekizumab q.4.w.	1	1,227	1.14 (1.07 to 1.22)
Risankizumab 75 vs. risankizumab 150	1	113	0.98 (0.91 to 1.07)

CI = confidence interval; M-H = Mantel-Haenszel; PASI 75 = 75% reduction in Psoriasis Area Severity Index score; q.2.w. = every 2 weeks; q.4.w. = every 4 weeks; vs. = versus.

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Economic Analysis

This review is part of the CADTH Streamlined Drug Class Review program, in which an application filed by a sponsor is absent. CADTH does not have access to an economic model for biologics in moderate to severe plaque psoriasis from previous CADTH therapeutic or technology reviews. As a result, the economic review consisted of only a cost comparison for old-generation biologics compared with new-generation biologics for the treatment of moderate to severe plaque psoriasis.

CADTH Analyses

The comparators presented in Table 14 have been deemed to be appropriate based on feedback from clinical experts and drug plans. Recommended doses were based on each product's respective product monograph and validated by clinical experts. Existing product listing agreements are not reflected in the table; as such, the table may not represent the actual costs to public drug plans for all comparators. The price of comparators was based on public list prices from the Ontario Drug Benefit Formulary/Comparative Drug Index (accessed in July of 2023).

The annual maintenance costs for all branded publicly reimbursed biologics ranged from $16,770 to $42,250, with a median of $19,740, based on recommended dosages.

Table 14: CADTH Cost Comparison Table for Old- and New-Generation Biologics for the Treatment of Moderate to Severe Plaque Psoriasis

Treatment	Strength/concentration	Form	Price	Recommended dosage[a]	Annual cost
Adalimumab (biosimilars)	20 mg/0.4 mL 40 mg/0.4 mL 40 mg/0.8 mL 80 mg/0.8 mL	Prefilled syringe	$235.6350 $471.2700 $471.2700 $942.5400	80 mg at week 0 followed by 40 mg every 2 weeks starting 1 week after initial dose	First year = $12,724 Subsequent years = $12,253
Bimekizumab (Bimzelx)	160 mg/mL	1 mL prefilled syringe or autoinjector	$1,625.0000	320 mg at weeks 0, 4, 8, 12, 16 followed by 320 mg every 8 weeks (or every 4 weeks for those ≥ 120 kg)	First year: $29,250 Subsequent years = $21,125 **For ≥ 120 kg** First year = $42,250 Subsequent years = $42,250
Brodalumab (Siliq)	140 mg/mL	1.5 mL prefilled syringe	$645.0000	210 mg at weeks 0, 1, 2 followed by 210 mg every 2 weeks	First year = $17,415 Subsequent years = $16,770
Certolizumab pegol (Cimzia)	200 mg/mL	1 mL prefilled syringe	$664.5100[b]	400 mg at weeks 0, 2, 4 followed by 200 mg or 400 mg every 2 weeks	First year = $19,271 to $34,555 Subsequent years = $17,277 to $34,555
Etanercept (biosimilars)	25 mg/0.5 mL 50 mg/mL	Prefilled syringe or autoinjector	$120.5000 $241.0000	50 mg twice per week for 12 weeks followed by 50 mg per week	First year = $15,424 Subsequent years = $12,532
Guselkumab (Tremfya)	100 mg/mL	1 mL prefilled syringe or autoinjector	$3,059.7400[c]	100 mg at weeks 0 and 4 followed by 100 mg every 8 weeks	First year = $21,418 Subsequent years = $19,888
Infliximab (Renflexis & Avsola; biosimilars)	0.4 mg/mL	100 mg powder or solution for IV injection	$493.0000	5 mg/kg at weeks 0, 2, 6 followed by 5 mg/kg every 8 weeks	First year = $19,720 Subsequent years = $16,023
Infliximab (Inflectra; biosimilar)	0.4 mg/mL	100 mg powder or solution for IV injection	$525.0000	5 mg/kg at weeks 0, 2, 6 followed by 5 mg/kg every 8 weeks	First year = $21,000 Subsequent years = $17,063

Treatment	Strength/concentration	Form	Price	Recommended dosage[a]	Annual cost
Ixekizumab (Taltz)	80 mg	1 mL prefilled syringe	$1,723.8900	160 mg at week 0 followed by 80 mg at weeks 2, 4, 6, 8, 10, 12 followed by 80 mg every 4 weeks	First year = $29,306 Subsequent years = $22,411
Risankizumab (Skyrizi)	75 mg/0.83 mL 150 mg/1mL	Prefilled syringe	$2,467.5000 $4,935.0000	150 mg at weeks 0, 4 followed by 150 mg every 12 weeks	First year = $24,675 Subsequent years = $21,385
Secukinumab (Cosentyx)	150 mg/mL	1 mL prefilled syringe	$882.5900	300 mg at weeks 0, 1, 2, 3, 4 followed by monthly maintenance dosing	First year = $28,243 Subsequent years = $21,182
Tildrakizumab (Ilumya)	100 mg/mL	1 mL prefilled syringe	$4,935.0000	100 mg at weeks 0, 4 followed by 100 mg every 12 weeks	First year = $24,675 Subsequent years = $21,385
Ustekinumab (Stelara)	45 mg/mL; 90 mg/mL	0.5 mL prefilled syringe; 1 mL prefilled syringe	$4,593.1400	45 mg to 90 mg at weeks 0, 4, followed by 45 mg to 90 mg every 12 weeks	First year = $22,966 Subsequent years = $19,904

Notes: All prices are from the Ontario Drug Benefit Formulary (accessed July 2023), unless otherwise indicated, and do not include dispensing fees. For weight-based dosing, a weight of 89.6 kg was assumed based on pooled data from bimekizumab trials.[41]

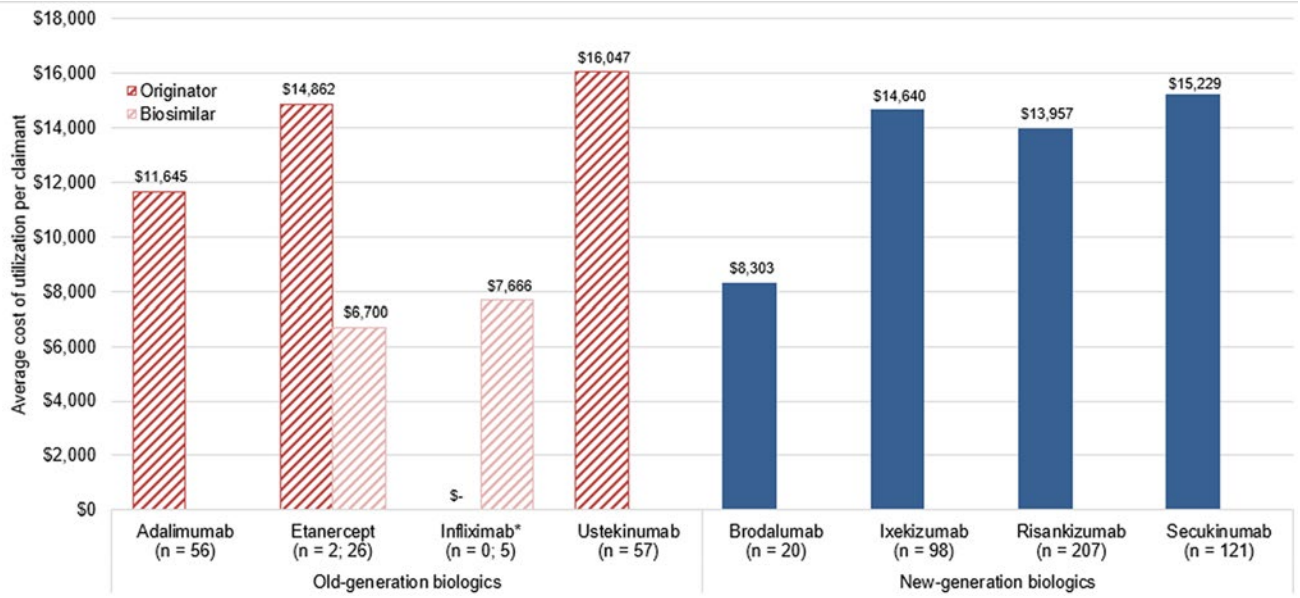
[a]Recommended dosages are from the respective product monographs.[42-52]

[b]Ontario Exceptional Access Program formulary (accessed July 2023).[53]

[c]IQVIA DeltaPA database (accessed July 2023).[54]

In addition to the cost table, CADTH revisited a previously published utilization analysis of biologics in plaque psoriasis.[28] Based on average costs for new claimants in 2020 (i.e., a new claimant was defined as a patient without any historical claims for other biologics), it appears that branded etanercept and branded ustekinumab were more costly than all 4 new-generation biologics (i.e., brodalumab, ixekizumab, risankizumab, and secukinumab). Biosimilar versions of etanercept and infliximab were the least costly options, whereas brodalumab was the least costly new-generation biologic. This real-world utilization may reflect more realistic cost comparisons, as, according to clinical experts, dose escalation with waning induction response is prevalent. It should be noted that these costs do not incorporate product listing agreements; therefore, net costs to payers may differ.

Figure 2: National Average Annual Cost of Utilization per Claimant for Plaque Psoriasis Biologics Among New Claimants With Plaque Psoriasis Across Public Drug Plans in Canada (2020)



n = number of claimants.

Notes: Blue (solid bars) indicate new-generation biologics and red (striped) bars indicate old-generation biologics. Costs do not reflect product listing agreements between drug plans and manufacturers. There were no claims for originator infliximab among new claimants with plaque psoriasis in 2020.

Source: Utilization of old-versus new-generation biologics for plaque psoriasis for public and private payers in Canada (health technology review). Ottawa (ON): CADTH; 2022.[28]

Based on these real-world drug costs, CADTH estimated (in a CADTH technology review) the first-year cost impact to Canadian public drug plans of a policy scenario whereby new-generation biologics were prioritized.[26] The analysis assumed that all new patients treated with biologics for moderate to severe plaque psoriasis initiated treatment with a new-generation therapy, versus the status quo of biologics use in 2020. The impact of a policy prioritizing new-generation biologics over old-generation biologics was estimated to reduce first-year expenditures for drug plans by approximately 7% across Canada, with the largest cost savings seen in British Columbia and Ontario.

Some limitations to this cost analysis should be noted. Given the unavailability of confidential negotiated prices, publicly available costs were used, which introduces uncertainty in the estimated cost impact. In addition, real-world utilization analysis and 1-year economic analysis were based on claims data from 2020 at which time several provinces had not yet adopted a biosimilar transition policy, and biosimilars in addition to their lower list prices have also undergone pCPA negotiations. As such, the data may not fully represent the current real-world utilization and costs. Most of the old-generation biologics, except certolizumab pegol, predated the pCPA, whereas all new-generation biologics have undergone (or are currently undergoing) pCPA negotiations, implying disparate product listing agreements across public drug plans for the old-generation biologics. Should these disparate product listing agreements for old-generation biologics result in higher

overall average net prices, additional cost savings are possible for a policy that prioritizes the use of new-generation biologics.

Issues for Consideration

- Some comparators are approved for differential dosing regimens based on weight, which would impact cost comparisons across the old- versus new-generation biologics for individual patients.
- Given the weight-based dosing for infliximab (5 mg/kg and 10 mg/kg), and at average weights seen in clinical trials, biosimilar versions of the drug may have comparable annual costs to the new-generation biologics. It is also important to note that the CADTH utilization analysis found that the market share of infliximab for new patients was low (0.8%).
- All old-generation biologics are now beyond their loss of exclusivity, yet biosimilar versions have had limited uptake and their delayed launches in Canada have spanned multiple years, suggesting a significant opportunity cost paid for these drugs after loss of exclusivity. There are currently no biosimilar options for certolizumab pegol and ustekinumab.
- Approximately 44% of patients newly initiating a biologic across public and private drug plans in Canada were prescribed an old-generation biologic in 2020.
- The use of new-generation biologics among patients with plaque psoriasis has increased over time across federal, provincial, and territorial drug plans, although their use is more prevalent among new claimants. These patterns are consistent across all jurisdictions. Among new claimants with plaque psoriasis in Canada, approximately 25% initiated treatment with an old-generation biologic in 2020, although this proportion was lower in Manitoba, Alberta, and Saskatchewan, which indicates that there is variation in prescribing patterns for new drug claimants with plaque psoriasis across jurisdictions.

Discussion

Summary of the Input and Evidence

Input from patient organizations and clinician groups highlighted a need for treatments in plaque psoriasis that are easy to administer, affordable, provide quick and full relief of symptoms, and have minimal adverse effects. Based on the evidence highlighted in the single included systematic review with network meta-analysis, it appears that new-generation biologics meet all these treatment criteria. Old-generation biologics generally meet these criteria, as well, though it can be argued that the IV formulation of infliximab is inconvenient. Feedback from industry was generally supportive of the scope of this project, but all suggestions for amending the study protocol (e.g., to include all systemic therapies or real-world data) were deemed to be out of scope at this time.

The Cochrane living systematic review[37] that forms the evidence base for this Streamlined Drug Class Review of biologics for plaque psoriasis provides the most up-to-date and comprehensive evidence regarding the clinical efficacy of new- and old-generation biologics for plaque psoriasis. The results of the

network meta-analysis showed that new-generation biologics were more effective than older biologics for achieving clear or almost clear skin (PASI 90 or better) after short-term (induction phase) treatments based on high-certainty evidence after 52 weeks of treatment. At class level, anti–IL-17 treatment showed a higher proportion of patients reaching PASI 90 compared to all the systemic interventions assessed (i.e., anti–IL-23, anti–IL-12/23, anti-TNF alpha, small molecule, and nonbiological systemic treatments). Among the biologics, compared with placebo, infliximab, ixekizumab, bimekizumab, and risankizumab were the most effective drugs for reaching PASI 90. The clinical effectiveness of these drugs was similar when compared against each other. The results for other efficacy outcomes (PASI 75 and PGA) were similar to the results for PASI 90. There were no significant differences between any of the interventions and placebo for risk of SAEs. When combining the anti–IL-17 and anti–IL-23 classes together into a group of new-generation biologics, they appear to be more efficacious compared to the remaining biologics (i.e., old-generation biologics). Although there was no significant difference between infliximab and 3 new-generation biologics (i.e., bimekizumab, ixekizumab, and risankizumab) for reaching PASI 90 in the network meta-analysis, there is some uncertainty with respect to its uptake in the real-world based on some published registry data.[55]

The economic analysis consisted of a cost comparison table, a real-world utilization analysis in a Canadian setting, and an economic impact analysis. In general, it appears that the cost of new-generation biologics is comparable to old-generation biologics (based on list prices and branded versions). There may be reason to believe that real-world utilization demonstrates a lower average cost per patient for new-generation biologics; therefore, a policy that would prioritize the use of new-generation biologics compared to the status quo demonstrated modest savings (or budget neutrality).

Limitations of the Evidence

The network meta-analysis is limited to induction therapy as most trials of the interventions included in the analysis assessed outcomes from 8 to 24 weeks after randomization. The small number of trials assessing long-term efficacy and safety did not allow a network meta-analysis and the evidence of comparative efficacy is based only on direct evidence of head-to-head trials (i.e., 11 trials for PASI 90 and 10 trials for PASI 75 at 52 weeks). Nonetheless, this long-term evidence (i.e., PASI 90 at 52 weeks) is consistent in showing that new-generation biologics are more efficacious than old-generation biologics beyond induction therapy. Data on QoL was often poorly reported and was absent for several of the trials (almost half of the population included in the network meta-analysis) and so the results of the network meta-analysis for QoL should be interpreted with caution in light of the potential for reporting biases.

Some limitations of the evidence based on clinical trials related to generalizability to the real-world population should be noted as participants selected for RCTs are generally different in many aspects of disease characteristics, including having fewer major comorbidities. The authors noted that almost all studies including 1 biological arm excluded patients with a history of infectious diseases or malignancies and signs of severe renal, cardiac, hepatic, demyelinating, or other disorders, which may affect the generalizability of these results for clinical practice. However, some participant characteristics (e.g., being overweight, presence of metabolic syndrome) were comparable to the population of patients with moderate to severe psoriasis in the observational studies reported in the literature. Participants in the included studies

had a mean age of 44.6 years and had moderate to severe psoriasis; more than 60% were males, with an overall mean PASI score at baseline of 20.4 (range = 9.5 to 39) and a duration of psoriasis of 16.5 years (range = 4.5 to 21.5). The authors of the Cochrane review noted that the young age and the high level of disease severity may not be typical of patients seen in daily clinical practice, or those who need a first-line systemic treatment.

Conclusions and Implications for Decision-Making

Current best evidence for the comparative efficacy and safety of different classes of biologics based on direct and indirect comparisons of clinical trial data of biologic interventions suggests superiority of the newer-generation biologic classes (i.e., anti–IL-17 and anti–IL-23) compared to the older-generation biologic classes (i.e., anti-TNF alpha and anti–IL-12/23). Three out of the 4 most effective drugs for reaching PASI 90 (i.e., bimekizumab, ixekizumab, and risankizumab) belong to the new-generation biologic classes (based on high-certainty evidence). The only old-generation biologic that showed similar efficacy to new-generation biologics for reaching PASI 90 in the network meta-analysis was infliximab, though there are limited clinical trials where infliximab was a comparator and real-world data suggest it may be comparable to other old-generation biologics. Given the chronic nature of plaque psoriasis, there is a need for effective drugs that may be administered long-term to manage symptoms. In addition to patient disease characteristics, treatment-related characteristics such as long-term efficacy and safety, convenience and ease of administration, acceptability by patients, and minimal drug-to-drug interactions are important considerations in the choice of long-term treatment. The patient and clinician input also emphasized the need for treatment options that are easy to administer and biologics that are indicated for both plaque psoriasis and psoriatic arthritis. They also pointed to the need to consider which biologics should be avoided in patients with certain comorbidities.

The clinical experts that CADTH consulted for this report indicated that all available biologics currently approved for plaque psoriasis have utility for a particular profile of patient and most may be used in all patients regardless of age, disease characteristics, and joint involvement (i.e., psoriatic arthritis). However, the clinical trials of some of the biologic drugs include data to support specific use in special patient populations (e.g., certolizumab pegol for patients who are pregnant); thus, they may be favoured over other biologics for use in specific populations. Treatment-related characteristics impact choice of treatment in clinical practice. For example, infliximab, a highly effective biologic treatment for plaque psoriasis, is the only biologic treatment that is administered by IV, which may be a barrier to its initiation or long-term use for some patients in clinical practice. Some biologics may offer unique benefits in terms of tailoring to patient needs. For example, biologics that have weight-based dosing, or those with the most convenient dosing regimens (e.g., only 4 injections per year), may make them the treatment of choice for some patients.

In terms of costs, new-generation biologics are less costly compared to the most used old-generation biologic (ustekinumab) on an average per patient basis at list price for patients with psoriasis newly initiating therapy. Based on product monograph standard dosing, annual maintenance costs are generally comparable across all branded biologics, with some exceptions. But when real-world utilization is considered, it appears that the new-generation biologics are consistently less costly than the branded versions of etanercept

and ustekinumab. The clinical experts consulted by CADTH for this review hypothesized that this could be a result of a higher incidence of dose escalation for old-generation drugs due to their lower likelihood of achieving the clinical standard of PASI 90 or PASI 100 clearance. Though these analyses were based on list prices and not on net prices after product listing agreements, all the new-generation biologics underwent pCPA negotiations, which was not the case for the old-generation drugs.

Overall, when conducting a cost analysis in new patients for psoriasis, a policy that prioritizes the use of new-generation biologics versus the status quo could result in budget neutrality or cost savings, and likely with better patient outcomes. An assessment of the clinical and economic value of old-generation biologics in the context of current evidence standards and promotion of new-generation biologics should be considered by payers to support the appropriate use of biologics in plaque psoriasis.

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Appendix 1: Literature Search Strategy

Note that this appendix has not been copy-edited.

Clinical Literature Search

Overview

Interface: Ovid

Databases:

- MEDLINE All (1946-present)
- Embase (1974-present)
- Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: May 17, 2023

Alerts: Bi-weekly search updates until project completion on June 28, 2023

Search filters applied: Systematic reviews; meta-analyses; network meta-analyses; health technology assessments.

Limits:

- Conference abstracts: excluded

Table 15: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
?	Truncation symbol for one or no characters only
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ot	Original title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Keyword heading word
.dq	Candidate term word (Embase)
.pt	Publication type

Syntax	Description
.mp	Mapped term
.rn	Registry number
.nm	Name of substance word (MEDLINE)
.jw	Journal title word (MEDLINE)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

Multi-Database Strategy

1. exp Psoriasis/
2. (psorias* or psoriatic* or pustulos* or pustular or palmoplantar* or parapsorias* or erythrodermic or guttate or Koebner or willan lepra or Andrew* disease* or pustular bacterid* or palmar plantar bacterid* or plantar palmar bacterid* or recalcitrant pustular eruption*).ti,ab,kf,ot.
3. or/1-2
4. (cosentyx* or secukinumab* or zafrez* or ain 457? or ain457? or DLG4EML025 or BLA 125-504 or bat 2306 or bat2306 or kb 03303a or kb03303a or scapho or ts 1808 or ts1808).ti,ab,kf,ot,hw,rn,nm.
5. (taltz* or ixekizumab* or LY2439821 or LY 2439821 or BTY1537600 or BTY 153760O). ti,ot,ab,kf,rn,hw,nm.
6. (brodalumab* or siliq* or kyntheum* or lumicef* or amg827 or amg 827 or KHK4827 or KHK-4827 or 6ZA31Y954Z).ti,ab,kf,ot,hw,rn,nm.
7. (bimekizumab* or Bimzelx* or ucb-4940 or ucb4940 or cdp-4940 or cdp4940 or WHO 9870 or WHO9870 or 09495UIM6V).ti,ab,kf,ot,hw,nm,rn.
8. (risankizumab* or skyrizi* or 655066-01 or ABBV-066 or ABBV066 or BI 655066 or BI655066 or 90ZX3Q3FR7).ti,ab,kf,ot,hw,nm,rn.
9. (ilumya* or tildrakizumab* or ilumetri* or MK3222 or MK-3222 or SCH900222 or SCH-900222 or SUNPG1622 or SUNPG-1622 or SUNPG1623 or SUNPG-1623 or DEW6X41BEK).ti,ab,kf,ot,hw,rn,nm.
10. (tremfya* or guselkumab* or cnto 1959 or cnto1959 or 089658A12D).ti,ab,kf,ot,hw,rn,nm.
11. Interleukin-17/ai [antagonists and inhibitors]
12. exp Interleukin-23/ai [antagonists and inhibitors]
13. ((interleukin 17* or IL-17* or IL17* or interleukin 23* or IL-23* or IL23*) adj3 (inhibit* or antagonist* or anti)).ti,ab,kf.
14. new biologic*.ti,ab,kf.
15. ((new generation* or new therapies or newer) adj3 biologic*).ti,ab,kf.
16. or/4-15
17. 3 and 16
18. 17 use medall

19. exp psoriasis/
20. (psorias* or psoriatic* or pustulos* or pustular or palmoplantar* or parapsorias* or erythrodermic or guttate or Koebner or willan lepra or Andrew* disease* or pustular bacterid* or palmar plantar bacterid* or plantar palmar bacterid* or recalcitrant pustular eruption*).ti,ab,kf,dq.
21. or/19-20
22. *secukinumab/
23. (cosentyx* or secukinumab* or zafrez* or ain 457? or ain457? or BLA 125-504 or bat 2306 or bat2306 or kb 03303a or kb03303a or scapho or ts 1808 or ts1808).ti,ab,kf,dq.
24. *ixekizumab/
25. (taltz* or ixekizumab* or LY2439821 or LY 2439821).ti,ab,kf,dq.
26. *brodalumab/
27. (brodalumab* or siliq* or kyntheum* or lumicef* or amg827 or amg 827 or BLA 761032 or KHK4827 or KHK-4827).ti,ab,kf,dq.
28. *bimekizumab/
29. (bimekizumab* or Bimzelx* or ucb-4940 or ucb4940 or cdp 4940 or cdp4940 or WHO 9870 or WHO9870).ti,ab,kf,dq.
30. *Risankizumab/
31. (risankizumab* or skyrizi* or 655066-01 or ABBV-066 or ABBV066 or BI 655066 or BI655066).ti,ab,kf,dq.
32. *tildrakizumab/
33. (ilumya* or tildrakizumab* or ilumetri* or MK3222 or MK-3222 or SCH900222 or SCH-900222 or SUNPG1622 or SUNPG-1622 or SUNPG1623 or SUNPG-1623).ti,ab,kf,dq.
34. *guselkumab/
35. (tremfya* or guselkumab* or cnto 1959 or cnto1959).ti,ab,kf,dq.
36. (interleukin 17/ or interleukin 23/) and cytokine receptor antagonist/
37. ((interleukin 17* or IL-17* or IL17* or interleukin 23* or IL-23* or IL23*) adj3 (inhibit* or antagonist* or anti)).ti,ab,kf,dq.
38. new biologic*.ti,ab,kf,dq.
39. ((new generation* or new therapies or newer) adj3 biologic*).ti,ab,kf,dq.
40. or/22-39
41. 21 and 40
42. (conference abstract or “conference review”).pt.
43. 41 not 42
44. 43 use oemezd
45. 18 or 44

46. (systematic review or meta-analysis).pt.
47. meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ or network meta-analysis/
48. ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf.
49. ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf.
50. ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf.
51. (data synthes* or data extraction* or data abstraction*).ti,ab,kf.
52. (handsearch* or hand search*).ti,ab,kf.
53. (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf.
54. (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf.
55. (meta regression* or metaregression*).ti,ab,kf.
56. (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
57. (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
58. (cochrane or (health adj2 technology assessment) or evidence report).jw.
59. (comparative adj3 (efficacy or effectiveness)).ti,ab,kf.
60. (outcomes research or relative effectiveness).ti,ab,kf.
61. ((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf.
62. (multi* adj3 treatment adj3 comparison*).ti,ab,kf.
63. (mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf.
64. umbrella review*.ti,ab,kf.
65. (multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kf.
66. (multiparamet* adj2 evidence adj2 synthesis).ti,ab,kf.
67. (multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kf.
68. or/46-67
69. 45 and 68
70. remove duplicates from 69

Grey Literature

Search dates: May 14 to 17,2023

Keywords: secukinumab, ixekizumab, brodalumab, bimekizumab, risankizumab, tildrakizumab, guselkumab, plaque psoriasis

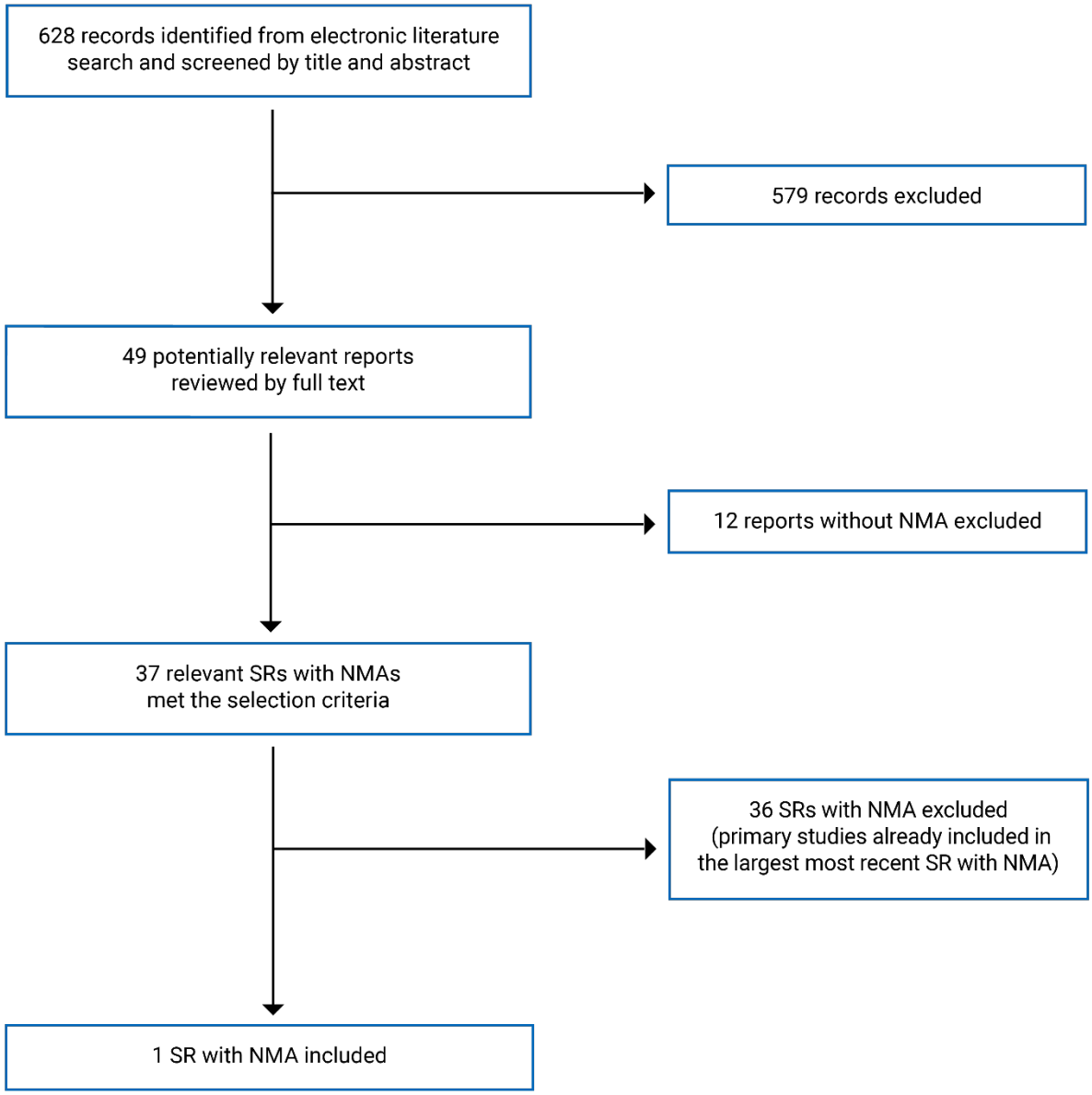
Limits: English language

Relevant websites from the following sections of the CADTH grey literature checklist Grey Matters: A Practical Tool for Searching Health-Related Grey Literature were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Health Statistics
- Internet Search
- Open Access Journals.

Appendix 2: Selection of Included Studies

Figure 3: Flow Chart of Selected Reports



NMA = network meta-analysis; SR = systematic review.

Appendix 3: List of Excluded Studies

Note that this appendix has not been copy-edited.

Table 16: Excluded Systematic Reviews With Network Meta-Analyses

Reference	Number of included studies	Number of studies in NMA	Number of included biologics	Number of patients	Funding
Sbidian et al., 2023[37]	179	140	14	62,339	Academic
Yasmeen et al., 2022[56]	88	28	8	5,054	Industry
Pan et al., 2022[57]	23	23	3	NR	Industry
Feng et al., 2022[58]	48	48	8	27,297	NR
Blauvelt et al., 2022[59]	18	18	10	NR	Industry
Armstrong et al., 2022[60]	14	14	9	NR	Industry
Armstrong et al., 2022[61]	86	86	12	34,476	Industry
Xu et al., 2020[62]	60	60	14	34,020	Academic
Singh et al., 2021[63]	7	7	3	2,243	Academic
Shear et al., 2021[64]	52	52	12	NR	Industry
Fahrback et al., 2021[65]	73	73	11	30,314	Industry
Armstrong et al., 2021[66]	71	71	11	NR	Industry
Almohideb et al., 2021[67]	9	9	2	2,673	Academic
Xue et al., 2020[68]	43	43	7	NR	Industry
Witjes et al., 2020[69]	8	8	2	3,767	Industry
Warren et al., 2020[70]	28	28	9	22,749	Industry
Warren et al., 2020[71]	34	34	11	27,574	Industry
Tada et al., 2020[72]	41	41	8	19,248	Industry
Shi et al., 2020[73]	14	13	4	8,402	Academic
Nartowicz et al., 2020[74]	43	43	8	19,161	Academic
Mahil et al., 2020[75]	62	62	11	31,899	Academic
Karpinska-Mirecka et al., 2020[76]	43	43	5	25,898	NR
Armstrong et al., 2020[77]	60	60	11	25,566	Industry
Xu et al., 2019[78]	54	54	13	13,657	Industry
Sawyer et al., 2019[79]	24	17	10	NR	Industry
Champs et al., 2019[80]	77	77	10	NR	Not funded
Bai et al., 2019[81]	28	28	7	19,840	Not funded
Lv et al., 2018[82]	75	75	9	25,108	Institutional
Loos et al., 2018[83]	34	34	8	22,892	Industry

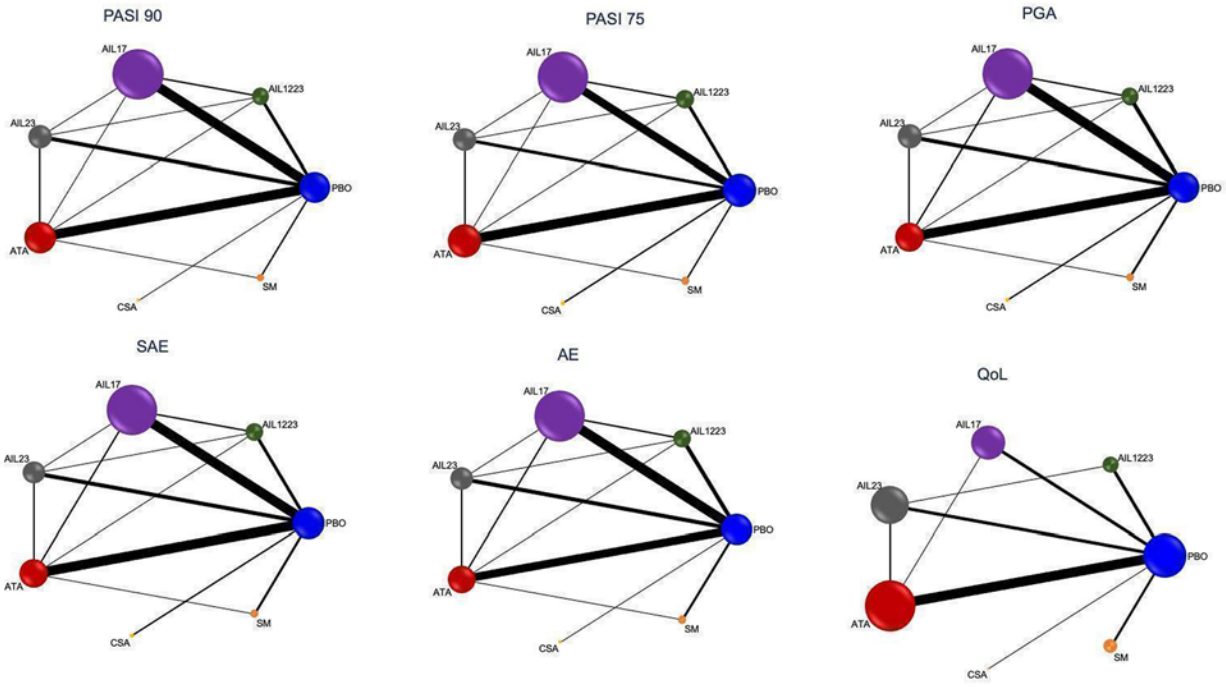
Reference	Number of included studies	Number of studies in NMA	Number of included biologics	Number of patients	Funding
Bilal et al., 2018[84]	24	24	6	NR	Not funded
Rungapiromnan et al., 2017[85]	38	38	6	18,024	Academic
Jabbar-Lopez et al., 2017[86]	41	41	6	20,561	Academic
Gomez-Garcia et al., 2017[87]	27	27	5	10,629	Academic
de Carvalho et al., 2017[88]	40	40	7	22,884	Not funded
Yiu et al., 2016[89]	32	32	5	13,359	Academic
Nast et al., 2015[90]	25	25	5	NR	Not funded
Ryan et al., 2011[91]	22	22	5	10,183	Academic

NMA = network meta-analysis; NR = not reported.

Appendix 4: Additional Results

Note that this appendix has not been copy-edited.

Figure 4: Network Plot for All Outcomes at Class Level



AIL12/23 = anti-IL12/23; AIL17 = anti-IL17; AIL23 = anti-IL23, ATA = anti-TNF alpha; CSA = non-biological conventional systemic agents; PBO = placebo; SM = small molecules AE = adverse events; PASI = Psoriasis Area and Severity Index; PGA = Physician Global Assessment; QoL = quality of life; SAE = serious adverse events.

Source: Sbidian E, Chaimani A, Guelimi R, et al. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. Cochrane Database Syst Rev. 2023. Copyright © 2023 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd. Reprinted with permission from John Wiley & Sons, Ltd.[37]

Figure 5: Relative Effects of the Interventions as Estimated From the Network Meta-Analysis Model for PASI 90 and SAEs

Number of participants (studies)	1693 (6)	1730 (4)	5775 (7)	3078 (10)	8459 (20)	313 (1)	4722 (5)	4467 (7)	11342 (16)	2217 (3)	5440 (11)	2173 (4)	1323 (5)	218 (2)	8464 (14)	4362 (9)	127 (1)	213 (1)	1130 (2)	-	
1693 (6)	IFX	2.28 (0.81, 6.37)	1.31 (0.57, 2.98)	1.72 (0.74, 3.99)	1.12 (0.51, 2.47)	0.96 (0.17, 5.55)	1.12 (0.46, 2.71)	1.32 (0.58, 2.98)	1.24 (0.56, 2.74)	1.49 (0.52, 4.3)	1.19 (0.52, 2.7)	1.51 (0.56, 4.02)	1.69 (0.57, 5.01)	3.09 (0.65, 14.66)	1.5 (0.67, 3.36)	1.6 (0.67, 3.81)	0.21 (0.01, 4.02)	1.5 (0.06, 39.18)	1.35 (0.45, 4.06)	1.18 (0.57, 2.43)	24 per 1000 (11 to 49)
2473 (5)	1.76 (0.73, 4.28)	BIME	0.57 (0.25, 1.31)	0.76 (0.33, 1.71)	0.49 (0.23, 1.07)	0.42 (0.07, 2.44)	0.49 (0.2, 1.18)	0.58 (0.26, 1.29)	0.54 (0.25, 1.16)	0.66 (0.23, 1.91)	0.52 (0.24, 1.11)	0.66 (0.25, 1.78)	0.74 (0.25, 2.22)	1.36 (0.29, 6.4)	0.66 (0.29, 1.5)	0.7 (0.29, 1.69)	0.09 (0.0, 1.77)	0.66 (0.03, 17.24)	0.59 (0.2, 1.8)	0.52 (0.25, 1.08)	10 per 1000 (5 to 22)
5875 (8)	1.8 (0.74, 4.36)	1.02 (0.92, 1.13)	IXE	1.32 (0.75, 2.32)	0.86 (0.54, 1.37)	0.73 (0.14, 3.8)	0.85 (0.45, 1.62)	1.01 (0.64, 1.58)	0.94 (0.58, 1.54)	1.14 (0.49, 2.67)	0.91 (0.53, 1.55)	1.15 (0.53, 2.5)	1.29 (0.52, 3.19)	2.36 (0.56, 9.89)	1.14 (0.71, 1.83)	1.22 (0.65, 2.28)	0.16 (0.01, 2.89)	1.14 (0.05, 28.33)	1.03 (0.41, 2.6)	0.9 (0.6, 1.35)	18 per 1000 (12 to 27)
3078 (10)	1.88 (0.77, 4.56)	1.06 (0.96, 1.18)	1.05 (0.94, 1.17)	RISAN	0.65 (0.4, 1.05)	0.56 (0.11, 2.9)	0.65 (0.34, 1.24)	0.76 (0.45, 1.3)	0.72 (0.45, 1.13)	0.87 (0.36, 2.1)	0.69 (0.41, 1.15)	0.88 (0.4, 1.93)	0.98 (0.39, 2.46)	1.79 (0.46, 7.03)	0.87 (0.49, 1.53)	0.93 (0.49, 1.77)	0.12 (0.01, 2.21)	0.87 (0.03, 21.59)	0.78 (0.31, 2.0)	0.68 (0.45, 1.05)	14 per 1000 (9 to 21)
9202(21)	2.04 (0.84, 4.94)	1.15 (1.08, 1.23)	1.13 (1.04, 1.23)	1.08 (0.99, 1.19)	SECU	0.85 (0.17, 4.3)	1.0 (0.55, 1.79)	1.17 (0.82, 1.69)	1.1 (0.75, 1.62)	1.33 (0.58, 3.07)	1.06 (0.66, 1.69)	1.34 (0.64, 2.81)	1.51 (0.63, 3.61)	2.75 (0.68, 11.21)	1.33 (0.83, 2.15)	1.42 (0.8, 2.55)	0.19 (0.01, 3.34)	1.33 (0.05, 32.75)	1.2 (0.49, 2.94)	1.05 (0.76, 1.45)	21 per 1000 (15 to 29)
313 (1)	2.1 (0.84, 5.24)	1.19 (0.94, 1.51)	1.17 (0.92, 1.49)	1.12 (0.88, 1.43)	1.03 (0.82, 1.29)	SONELO	1.17 (0.22, 6.25)	1.37 (0.27, 7.06)	1.29 (0.25, 6.59)	1.56 (0.26, 9.24)	1.24 (0.24, 6.42)	1.57 (0.28, 8.9)	1.76 (0.29, 10.62)	3.23 (0.39, 26.62)	1.56 (0.3, 8.1)	1.67 (0.31, 8.88)	0.22 (0.01, 5.82)	1.56 (0.04, 55.13)	1.41 (0.23, 8.55)	1.23 (0.25, 6.1)	25 per 1000 (5 to 122)
4722 (5)	2.22 (0.91, 5.4)	1.26 (1.12, 1.41)	1.23 (1.09, 1.4)	1.18 (1.04, 1.34)	1.09 (0.98, 1.21)	1.05 (0.82, 1.35)	BRODA	1.18 (0.63, 2.2)	1.11 (0.63, 1.93)	1.33 (0.53, 3.38)	1.06 (0.56, 2.01)	1.35 (0.58, 3.11)	1.51 (0.58, 3.95)	2.76 (0.64, 11.97)	1.34 (0.71, 2.53)	1.43 (0.71, 2.89)	0.19 (0.01, 3.44)	1.34 (0.05, 33.65)	1.21 (0.45, 3.2)	1.05 (0.63, 1.75)	21 per 1000 (13 to 35)
4467 (7)	2.22 (0.92, 5.38)	1.26 (1.16, 1.37)	1.23 (1.15, 1.33)	1.18 (1.07, 1.3)	1.09 (1.02, 1.16)	1.05 (0.84, 1.33)	1.0 (0.89, 1.12)	GUSEL	0.94 (0.59, 1.49)	1.13 (0.48, 2.67)	0.9 (0.56, 1.45)	1.15 (0.53, 2.46)	1.28 (0.52, 3.15)	2.35 (0.57, 9.72)	1.14 (0.68, 1.9)	1.21 (0.66, 2.25)	0.16 (0.01, 2.87)	1.14 (0.05, 28.09)	1.02 (0.41, 2.56)	0.9 (0.61, 1.31)	18 per 1000 (12 to 26)
11063 (16)	2.84 (1.17, 6.87)	1.61 (1.49, 1.74)	1.58 (1.45, 1.72)	1.51 (1.38, 1.66)	1.39 (1.31, 1.47)	1.35 (1.07, 1.7)	1.28 (1.17, 1.4)	1.28 (1.18, 1.38)	USK	1.21 (0.52, 2.79)	0.96 (0.59, 1.56)	1.22 (0.58, 2.57)	1.37 (0.57, 3.29)	2.5 (0.62, 10.14)	1.21 (0.75, 1.96)	1.29 (0.72, 2.33)	0.17 (0.01, 3.03)	1.21 (0.05, 29.74)	1.09 (0.44, 2.68)	0.95 (0.68, 1.34)	19 per 1000 (14 to 27)
2217 (3)	2.89 (1.16, 7.2)	1.64 (1.27, 2.11)	1.61 (1.26, 2.06)	1.54 (1.19, 2.0)	1.42 (1.11, 1.82)	1.37 (0.98, 1.92)	1.3 (1.0, 1.7)	1.3 (1.02, 1.67)	1.02 (0.8, 1.31)	TILDRA	0.8 (0.33, 1.9)	1.01 (0.36, 2.81)	1.13 (0.37, 3.48)	2.07 (0.42, 10.09)	1.0 (0.46, 2.19)	1.07 (0.43, 2.67)	0.14 (0.01, 2.74)	1.0 (0.04, 26.61)	0.9 (0.29, 2.83)	0.79 (0.36, 1.73)	16 per 1000 (7 to 35)
5476 (11)	3.05 (1.26, 7.4)	1.73 (1.58, 1.89)	1.7 (1.54, 1.87)	1.62 (1.47, 1.79)	1.5 (1.38, 1.62)	1.45 (1.14, 1.84)	1.37 (1.21, 1.56)	1.37 (1.28, 1.48)	1.07 (0.98, 1.18)	1.05 (0.82, 1.36)	ADA	1.27 (0.59, 2.75)	1.42 (0.58, 3.52)	2.6 (0.63, 10.75)	1.26 (0.73, 2.18)	1.35 (0.72, 2.52)	0.18 (0.01, 3.19)	1.26 (0.05, 31.2)	1.14 (0.45, 2.86)	0.99 (0.67, 1.47)	20 per 1000 (13 to 29)
2173 (4)	3.52 (1.4, 8.87)	2.0 (1.46, 2.73)	1.96 (1.44, 2.67)	1.87 (1.37, 2.57)	1.73 (1.27, 2.35)	1.67 (1.14, 2.45)	1.59 (1.15, 2.18)	1.59 (1.16, 2.16)	1.24 (0.91, 1.69)	1.22 (0.84, 1.77)	1.16 (0.85, 1.58)	DEUCRAVA	1.12 (0.39, 3.2)	2.05 (0.44, 9.48)	0.99 (0.46, 2.14)	1.06 (0.5, 2.25)	0.14 (0.01, 2.63)	0.99 (0.04, 25.68)	0.89 (0.31, 2.6)	0.78 (0.4, 1.52)	16 per 1000 (8 to 30)
1323 (5)	4.04 (1.6, 10.19)	2.29 (1.7, 3.09)	2.25 (1.68, 3.02)	2.15 (1.59, 2.92)	1.98 (1.48, 2.66)	1.92 (1.33, 2.78)	1.82 (1.34, 2.48)	1.82 (1.35, 2.45)	1.43 (1.06, 1.91)	1.4 (0.98, 1.99)	1.33 (0.98, 1.79)	1.15 (0.77, 1.72)	CERTO	1.83 (0.37, 9.08)	0.89 (0.36, 2.16)	0.95 (0.37, 2.44)	0.12 (0.01, 2.44)	0.89 (0.03, 23.71)	0.8 (0.25, 2.56)	0.7 (0.31, 1.58)	14 per 1000 (6 to 32)
486 (6)	5.03 (1.96, 12.9)	2.85 (2.03, 4.0)	2.8 (1.99, 3.93)	2.68 (1.92, 3.72)	2.47 (1.76, 3.45)	2.39 (1.6, 3.58)	2.27 (1.6, 3.21)	2.27 (1.62, 3.18)	1.77 (1.27, 2.48)	1.74 (1.16, 2.61)	1.65 (1.18, 2.32)	1.43 (0.93, 2.19)	1.24 (0.8, 1.93)	MTX	0.48 (0.12, 2.03)	0.52 (0.12, 2.23)	0.07 (0.0, 1.63)	0.48 (0.02, 15.57)	0.44 (0.09, 2.19)	0.38 (0.1, 1.52)	8 per 1000 (2 to 30)
10021 (18)	5.09 (2.1, 12.33)	2.88 (2.55, 3.26)	2.83 (2.54, 3.15)	2.71 (2.37, 3.09)	2.5 (2.23, 2.79)	2.42 (1.88, 3.11)	2.29 (1.99, 2.64)	2.29 (2.04, 2.57)	1.79 (1.6, 2.01)	1.76 (1.4, 2.2)	1.67 (1.47, 1.89)	1.44 (1.07, 1.95)	1.26 (0.95, 1.66)	1.01 (0.72, 1.42)	ETA	1.07 (0.58, 1.95)	0.14 (0.01, 2.53)	1.0 (0.04, 24.73)	0.9 (0.36, 2.26)	0.79 (0.53, 1.17)	16 per 1000 (11 to 23)
3949 (8)	5.41 (2.18, 13.44)	3.06 (2.36, 3.98)	3.01 (2.32, 3.89)	2.88 (2.21, 3.75)	2.65 (2.05, 3.43)	2.57 (1.83, 3.61)	2.44 (1.86, 3.19)	2.44 (1.88, 3.15)	1.91 (1.47, 2.47)	1.87 (1.34, 2.6)	1.77 (1.36, 2.31)	1.54 (1.24, 1.9)	1.34 (0.93, 1.93)	1.07 (0.73, 1.58)	1.06 (0.83, 1.36)	APRE	0.13 (0.01, 2.4)	0.94 (0.04, 23.46)	0.84 (0.32, 2.21)	0.74 (0.45, 1.2)	15 per 1000 (9 to 24)
322 (3)	5.8 (2.29, 14.7)	3.29 (2.39, 4.51)	3.22 (2.36, 4.41)	3.09 (2.25, 4.23)	2.84 (2.08, 3.89)	2.75 (1.87, 4.05)	2.61 (1.89, 3.61)	2.61 (1.91, 3.57)	2.04 (1.49, 2.79)	2.0 (1.37, 2.92)	1.9 (1.39, 2.61)	1.65 (1.15, 2.37)	1.43 (0.95, 2.16)	1.15 (0.8, 1.66)	1.14 (0.84, 1.54)	1.07 (0.79, 1.46)	CICLO	7.19 (0.1, 523.33)	6.47 (0.33, 128.8)	5.66 (0.32, 100.06)	113 per 1000 (6 to 1000)
333 (2)	10.95 (3.4, 35.27)	6.21 (2.81, 13.73)	6.09 (2.76, 13.47)	5.83 (2.63, 12.9)	5.37 (2.43, 11.86)	5.2 (2.28, 11.85)	4.94 (2.23, 10.94)	4.93 (2.23, 10.9)	3.86 (1.75, 8.53)	3.79 (1.66, 8.62)	3.59 (1.63, 7.95)	3.11 (1.35, 7.17)	2.71 (1.17, 6.26)	2.18 (0.93, 5.12)	2.15 (0.97, 4.77)	2.03 (0.89, 4.6)	1.89 (0.81, 4.39)	NETA	0.9 (0.03, 24.19)	0.79 (0.03, 19.01)	16 per 1000 (1 to 380)
1190 (3)	12.81 (4.55, 36.09)	7.26 (4.08, 12.93)	7.13 (4.0, 12.68)	6.82 (3.82, 12.15)	6.28 (3.54, 11.17)	6.09 (3.28, 11.28)	5.77 (3.23, 10.32)	5.77 (3.24, 10.26)	4.52 (2.54, 8.03)	4.43 (2.39, 8.2)	4.2 (2.36, 7.48)	3.64 (1.93, 6.85)	3.17 (1.68, 5.99)	2.55 (1.33, 4.87)	2.52 (1.41, 4.49)	2.37 (1.28, 4.37)	2.21 (1.16, 4.19)	1.17 (0.45, 3.03)	FUM	0.87 (0.38, 2.01)	17 per 1000 (8 to 40)
-	49.16 (20.49, 117.96)	27.86 (23.56, 32.94)	27.35 (23.16, 32.29)	26.16 (22.03, 31.07)	24.12 (20.57, 28.28)	23.36 (17.74, 30.75)	22.16 (18.54, 26.48)	22.14 (18.83, 26.05)	17.33 (14.76, 20.35)	16.99 (12.92, 22.35)	16.13 (13.65, 19.06)	13.96 (10.26, 19.0)	12.16 (8.87, 16.68)	9.77 (6.83, 13.99)	9.66 (8.14, 11.48)	9.09 (6.97, 11.86)	8.48 (6.09, 11.8)	4.49 (2.07, 9.75)	3.84 (2.2, 6.68)	PBO	20 per 1000
	934 per 1000 (389 to 1000)	529 per 1000 (448 to 626)	520 per 1000 (440 to 614)	497 per 1000 (419 to 590)	458 per 1000 (391 to 537)	444 per 1000 (337 to 584)	421 per 1000 (352 to 503)	421 per 1000 (358 to 495)	329 per 1000 (280 to 387)	323 per 1000 (245 to 425)	306 per 1000 (259 to 362)	265 per 1000 (195 to 361)	231 per 1000 (169 to 317)	186 per 1000 (130 to 266)	184 per 1000 (155 to 218)	173 per 1000 (132 to 225)	161 per 1000 (116 to 224)	85 per 1000 (39 to 185)	73 per 1000 (42 to 127)	19 per 1000	Anticipated absolute effects

ACI = acitretin; ADA = adalimumab; APRE = apremilast; BIME = bimekizumab; BRODA = brodalumab; CERTO = certolizumab; CICLO = ciclosporin; DEUCRAVA = deucravacitinib; ETA = etanercept; FUM = fumaric acid; IFX = infliximab; IXE = ixekizumab; GUSEL = guselkumab; MTX = methotrexate; NETA = netakimab; PASI = psoriasis Area and Severity Index; PBO = placebo; RISAN = risankizumab; SAE = serious adverse event; SECU = secukinumab; SONELO = sonelokimab; TILDRA = tildrakizumab; USK = ustekinumab.

Note: All outcomes were measured at the induction phase (assessment from 8 to 24 weeks after randomization).

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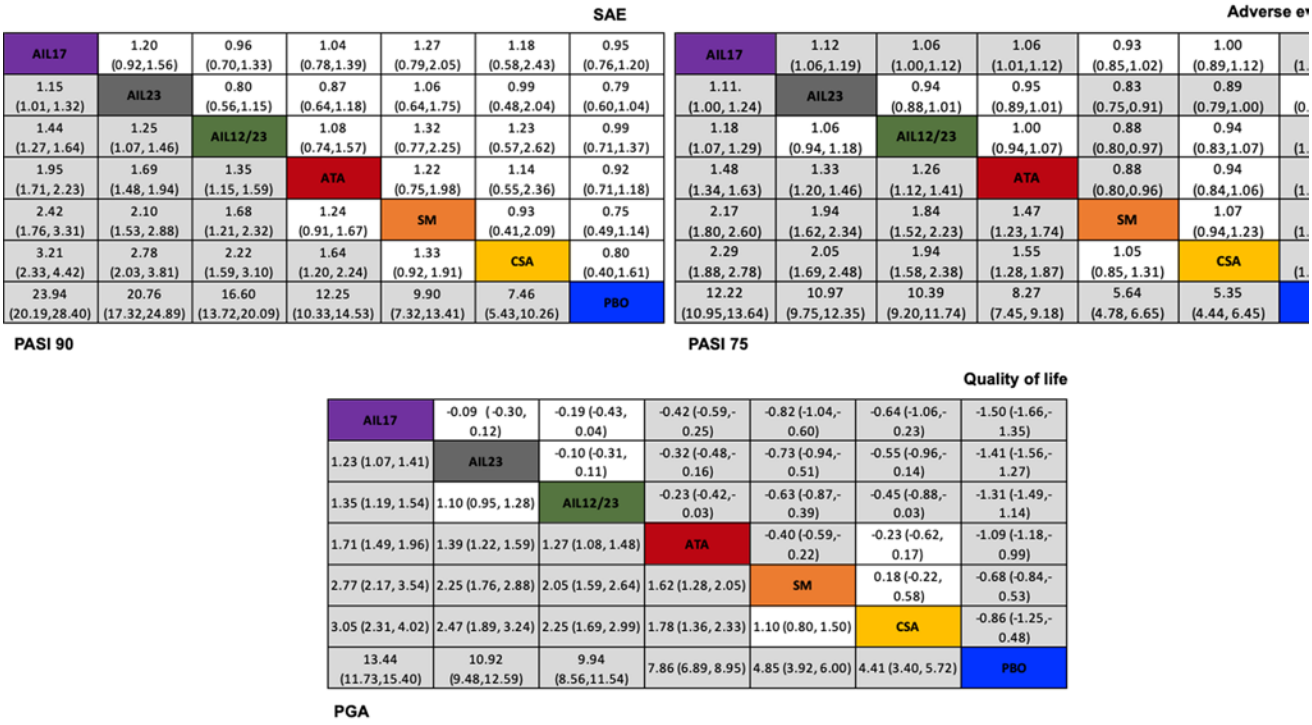
Figure 6: Relative Effects of the Class-Level Intervention as Estimated From the Network Meta-Analysis Model



Note: All outcomes were measured at the induction phase (assessment from 8 to 24 weeks after randomization). Drugs are reported in order of primary benefit ranking. Each cell contains the risk ratio (RR) (for dichotomous outcomes: PASI 90, serious adverse events, PASI 75, PGA 0/1, adverse events) or the standardized mean difference (SMD) (for the quality of life outcome), plus the 95% confidence interval, of the class level in the respective column versus the class level in the respective row. RRs larger than 1 for the lower triangle and smaller than 1 (or SMDs smaller than zero) for the upper triangle favour the treatment on the left. Significant results are highlighted in grey.

SAE without worsening of psoriasis correspond to SAE after exclusion of flares of psoriasis.

AE = adverse events; PASI = Psoriasis Area and Severity Index; PGA = Physician's Global Assessment; QoL = quality of life; SAE = serious adverse events; AIL12/23 = anti-IL12/23; AIL17 = anti-IL17; AIL23 = anti-IL23, ATA = anti-TNF alpha; CSA = non-biological conventional systemic agents; PBO = placebo; SM = small molecules.

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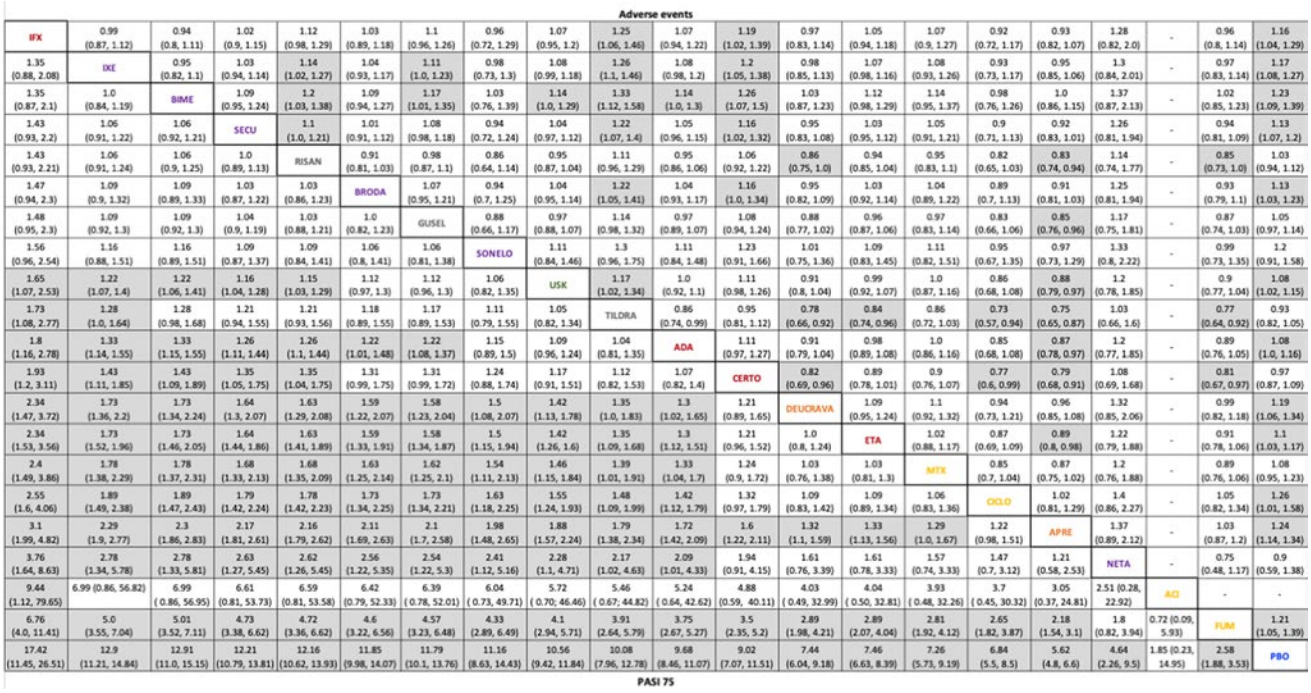
Figure 7: Relative Effects of the Intervention as Estimated From the Network Meta-Analysis Model for PASI 75 and AEs



Note: All outcomes were measured at the induction phase (assessment from 8 to 24 weeks after randomization). Each cell contains the risk ratio (RR) and 95% confidence interval for the two secondary outcomes (PASI 75 and AEs) of the intervention in the respective column versus the comparator in the respective row. RRs larger than 1 for the lower triangle and smaller than 1 for the upper triangle favour the treatment on the left. Significant results are highlighted in grey.

ACI = acitretin; ADA = adalimumab; AE = adverse events; APRE = apremilast; BIME = bimekizumab; BRODA = brodalumab; CERTO = certolizumab; CICLO = ciclosporin; DEUCRAVA = deucravacitinib; ETA = etanercept; FUM = fumaric acid; IFX = infliximab; IXE = ixekizumab; GUSEL = guselkumab; MTX = methotrexate; NETA = netakimab; PBO = placebo; PASI = Psoriasis Area and Severity Index; RISAN = risankizumab; SECU = secukinumab; SONELO = sonelokimab; TILDRA = tildrakizumab; USK = ustekinumab.

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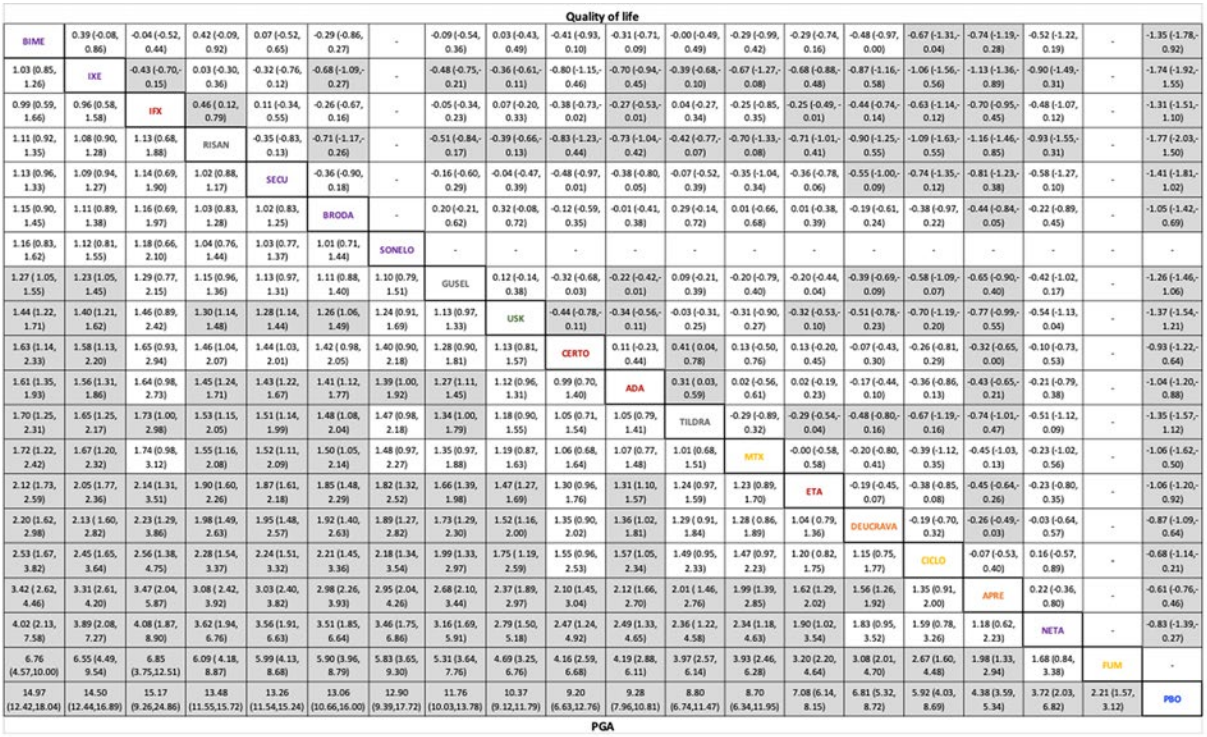
Figure 8: Relative Effects of the Intervention as Estimated From the Network Meta-Analysis Model for Physician Global Assessment and Quality of Life



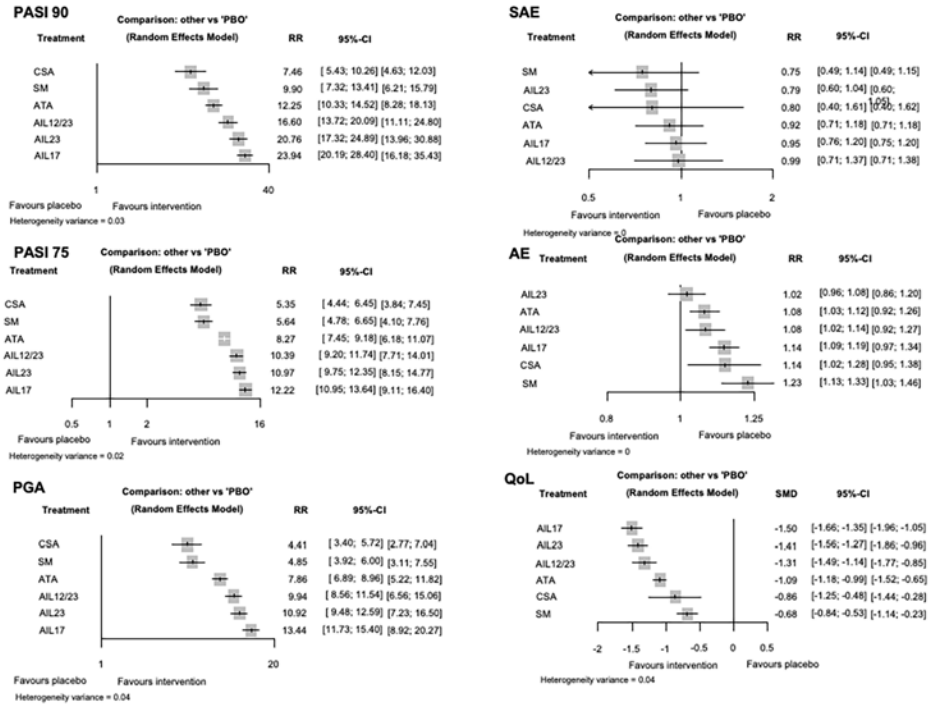
Quality of life																		
BIME	0.39 (-0.08, 0.86)	-0.04 (-0.52, 0.44)	0.42 (-0.09, 0.92)	0.07 (-0.52, 0.65)	-0.29 (-0.86, 0.27)	-	-0.09 (-0.54, 0.36)	0.03 (-0.43, 0.49)	-0.41 (-0.93, 0.10)	-0.31 (-0.71, 0.09)	-0.00 (-0.49, 0.49)	-0.29 (-0.99, 0.42)	-0.29 (-0.74, 0.16)	-0.48 (-0.97, 0.00)	-0.67 (-1.31,-0.04)	-0.74 (-1.19,-0.28)	-0.52 (-1.22, 0.19)	-	-1.35 (-1.78,-0.92)
1.03 (0.85, 1.26)	IXE	-0.43 (-0.70,-0.15)	0.03 (-0.30, 0.36)	-0.32 (-0.76, 0.12)	-0.68 (-1.09,-0.27)	-	-0.48 (-0.75,-0.21)	-0.36 (-0.61,-0.11)	-0.80 (-1.15,-0.46)	-0.70 (-0.94,-0.45)	-0.39 (-0.68,-0.10)	-0.67 (-1.27,-0.08)	-0.68 (-0.88,-0.48)	-0.87 (-1.16,-0.58)	-1.06 (-1.56,-0.56)	-1.13 (-1.36,-0.89)	-0.90 (-1.49,-0.31)	-	-1.74 (-1.92,-1.55)
0.99 (0.59, 1.66)	0.96 (0.58, 1.58)	IFX	0.46 (0.12, 0.79)	0.11 (-0.34, 0.55)	-0.26 (-0.67, 0.16)	-	-0.05 (-0.34, 0.23)	0.07 (-0.20, 0.33)	-0.38 (-0.73,-0.02)	-0.27 (-0.53,-0.01)	0.04 (-0.27, 0.34)	-0.25 (-0.85, 0.35)	-0.25 (-0.49,-0.01)	-0.44 (-0.74,-0.14)	-0.63 (-1.14,-0.12)	-0.70 (-0.95,-0.45)	-0.48 (-1.07, 0.12)	-	-1.31 (-1.51,-1.10)
1.11 (0.92, 1.35)	1.08 (0.90, 1.28)	1.13 (0.68, 1.88)	RISAN	-0.35 (-0.83, 0.13)	-0.71 (-1.17,-0.26)	-	-0.51 (-0.84,-0.17)	-0.39 (-0.66,-0.13)	-0.83 (-1.23,-0.44)	-0.73 (-1.04,-0.42)	-0.42 (-0.77,-0.07)	-0.70 (-1.33,-0.08)	-0.71 (-1.01,-0.41)	-0.90 (-1.25,-0.55)	-1.09 (-1.63,-0.55)	-1.16 (-1.46,-0.85)	-0.93 (-1.55,-0.31)	-	-1.77 (-2.03,-1.50)
1.13 (0.96, 1.33)	1.09 (0.94, 1.27)	1.14 (0.69, 1.90)	1.02 (0.88, 1.17)	SECU	-0.36 (-0.90, 0.18)	-	-0.16 (-0.60, 0.29)	-0.04 (-0.47, 0.39)	-0.48 (-0.97, 0.01)	-0.38 (-0.80, 0.05)	-0.07 (-0.52, 0.39)	-0.35 (-1.04, 0.34)	-0.36 (-0.78, 0.06)	-0.55 (-1.00,-0.09)	-0.74 (-1.35,-0.12)	-0.81 (-1.23,-0.38)	-0.58 (-1.27, 0.10)	-	-1.41 (-1.81,-1.02)
1.15 (0.90, 1.45)	1.11 (0.89, 1.38)	1.16 (0.69, 1.97)	1.03 (0.83, 1.28)	1.02 (0.83, 1.25)	BRODA	-	0.20 (-0.21, 0.62)	0.32 (-0.08, 0.72)	-0.12 (-0.59, 0.35)	-0.01 (-0.41, 0.38)	0.29 (-0.14, 0.72)	0.01 (-0.66, 0.68)	0.01 (-0.38, 0.39)	-0.19 (-0.61, 0.24)	-0.38 (-0.97, 0.22)	-0.44 (-0.84,-0.05)	-0.22 (-0.89, 0.45)	-	-1.05 (-1.42,-0.69)
1.16 (0.83, 1.62)	1.12 (0.81, 1.55)	1.18 (0.66, 2.10)	1.04 (0.76, 1.44)	1.03 (0.77, 1.37)	1.01 (0.71, 1.44)	SONELO	-	-	-	-	-	-	-	-	-	-	-	-	-
1.27 (1.05, 1.55)	1.23 (1.05, 1.45)	1.29 (0.77, 2.15)	1.15 (0.96, 1.36)	1.13 (0.97, 1.31)	1.11 (0.88, 1.40)	1.10 (0.79, 1.51)	GUSEL	0.12 (-0.14, 0.38)	-0.32 (-0.68, 0.03)	-0.22 (-0.42,-0.01)	0.09 (-0.21, 0.39)	-0.20 (-0.79, 0.40)	-0.20 (-0.44, 0.04)	-0.39 (-0.69,-0.09)	-0.58 (-1.09,-0.07)	-0.65 (-0.90,-0.40)	-0.42 (-1.02, 0.17)	-	-1.26 (-1.46,-1.06)
1.44 (1.22, 1.71)	1.40 (1.21, 1.62)	1.46 (0.89, 2.42)	1.30 (1.14, 1.48)	1.28 (1.14, 1.44)	1.26 (1.06, 1.49)	1.24 (0.91, 1.69)	1.13 (0.97, 1.33)	USK	-0.44 (-0.78,-0.11)	-0.34 (-0.56,-0.11)	-0.03 (-0.31, 0.25)	-0.31 (-0.90, 0.27)	-0.32 (-0.53,-0.10)	-0.51 (-0.78,-0.23)	-0.70 (-1.19,-0.20)	-0.77 (-0.99,-0.55)	-0.54 (-1.13, 0.04)	-	-1.37 (-1.54,-1.21)
1.63 (1.14, 2.33)	1.58 (1.13, 2.20)	1.65 (0.93, 2.94)	1.46 (1.04, 2.07)	1.44 (1.03, 2.01)	1.42 (0.98, 2.05)	1.40 (0.90, 2.18)	1.28 (0.90, 1.81)	1.13 (0.81, 1.57)	CERTO	0.11 (-0.23, 0.44)	0.41 (0.04, 0.78)	0.13 (-0.50, 0.76)	0.13 (-0.20, 0.45)	-0.07 (-0.43, 0.30)	-0.26 (-0.81, 0.29)	-0.32 (-0.65, 0.00)	-0.10 (-0.73, 0.53)	-	-0.93 (-1.22,-0.64)
1.61 (1.35, 1.93)	1.56 (1.31, 1.86)	1.64 (0.98, 2.73)	1.45 (1.24, 1.71)	1.43 (1.22, 1.67)	1.41 (1.12, 1.77)	1.39 (1.00, 1.92)	1.27 (1.11, 1.45)	1.12 (0.96, 1.31)	0.99 (0.70, 1.40)	ADA	0.31 (0.03, 0.59)	0.02 (-0.56, 0.61)	0.02 (-0.19, 0.23)	-0.17 (-0.44, 0.10)	-0.36 (-0.86, 0.13)	-0.43 (-0.65,-0.21)	-0.21 (-0.79, 0.38)	-	-1.04 (-1.20,-0.88)
1.70 (1.25, 2.31)	1.65 (1.25, 2.17)	1.73 (1.00, 2.98)	1.53 (1.15, 2.05)	1.51 (1.14, 1.99)	1.48 (1.08, 2.04)	1.47 (0.98, 2.18)	1.34 (1.00, 1.79)	1.18 (0.90, 1.55)	1.05 (0.71, 1.54)	1.05 (0.79, 1.41)	TILDRA	-0.29 (-0.89, 0.32)	-0.29 (-0.54,-0.04)	-0.48 (-0.80,-0.16)	-0.67 (-1.19,-0.16)	-0.74 (-1.01,-0.47)	-0.51 (-1.12, 0.09)	-	-1.35 (-1.57,-1.12)
1.72 (1.22, 2.42)	1.67 (1.20, 2.32)	1.74 (0.98, 3.12)	1.55 (1.16, 2.08)	1.52 (1.11, 2.09)	1.50 (1.05, 2.14)	1.48 (0.97, 2.27)	1.35 (0.97, 1.88)	1.19 (0.87, 1.63)	1.06 (0.68, 1.64)	1.07 (0.77, 1.48)	1.01 (0.68, 1.51)	MTX	-0.00 (-0.58, 0.58)	-0.20 (-0.80, 0.41)	-0.39 (-1.12, 0.35)	-0.45 (-1.03, 0.13)	-0.23 (-1.02, 0.56)	-	-1.06 (-1.62,-0.50)
2.12 (1.73, 2.59)	2.05 (1.77, 2.36)	2.14 (1.31, 3.51)	1.90 (1.60, 2.26)	1.87 (1.61, 2.18)	1.85 (1.48, 2.29)	1.82 (1.32, 2.52)	1.66 (1.39, 1.98)	1.47 (1.27, 1.69)	1.30 (0.96, 1.76)	1.31 (1.10, 1.57)	1.24 (0.97, 1.59)	1.23 (0.89, 1.70)	ETA	-0.19 (-0.45, 0.07)	-0.38 (-0.85, 0.08)	-0.45 (-0.64,-0.26)	-0.23 (-0.80, 0.35)	-	-1.06 (-1.20,-0.92)
2.20 (1.62, 2.98)	2.13 (1.60, 2.82)	2.23 (1.29, 3.86)	1.98 (1.49, 2.63)	1.95 (1.48, 2.57)	1.92 (1.40, 2.63)	1.89 (1.27, 2.82)	1.73 (1.29, 2.30)	1.52 (1.16, 2.00)	1.35 (0.90, 2.02)	1.36 (1.02, 1.81)	1.29 (0.91, 1.84)	1.28 (0.86, 1.89)	1.04 (0.79, 1.36)	DEUCRAVA	-0.19 (-0.70, 0.32)	-0.26 (-0.49,-0.03)	-0.03 (-0.64, 0.57)	-	-0.87 (-1.09,-0.64)
2.53 (1.67, 3.82)	2.45 (1.65, 3.64)	2.56 (1.38, 4.75)	2.28 (1.54, 3.37)	2.24 (1.51, 3.32)	2.21 (1.45, 3.36)	2.18 (1.34, 3.54)	1.99 (1.33, 2.97)	1.75 (1.19, 2.59)	1.55 (0.96, 2.53)	1.57 (1.05, 2.34)	1.49 (0.95, 2.33)	1.47 (0.97, 2.23)	1.20 (0.82, 1.75)	1.15 (0.75, 1.77)	CICLO	-0.07 (-0.53, 0.40)	0.16 (-0.57, 0.89)	-	-0.68 (-1.14,-0.21)
3.42 (2.62, 4.46)	3.31 (2.61, 4.20)	3.47 (2.04, 5.87)	3.08 (2.42, 3.92)	3.03 (2.40, 3.82)	2.98 (2.26, 3.93)	2.95 (2.04, 4.26)	2.68 (2.10, 3.44)	2.37 (1.89, 2.97)	2.10 (1.45, 3.04)	2.12 (1.66, 2.70)	2.01 (1.46, 2.76)	1.99 (1.39, 2.85)	1.62 (1.29, 2.02)	1.56 (1.26, 1.92)	1.35 (0.91, 2.00)	APRE	0.22 (-0.36, 0.80)	-	-0.61 (-0.76,-0.46)
4.02 (2.13, 7.58)	3.89 (2.08, 7.27)	4.08 (1.87, 8.90)	3.62 (1.94, 6.76)	3.56 (1.91, 6.63)	3.51 (1.85, 6.64)	3.46 (1.75, 6.86)	3.16 (1.69, 5.91)	2.79 (1.50, 5.18)	2.47 (1.24, 4.92)	2.49 (1.33, 4.65)	2.36 (1.22, 4.58)	2.34 (1.18, 4.63)	1.90 (1.02, 3.54)	1.83 (0.95, 3.52)	1.59 (0.78, 3.26)	1.18 (0.62, 2.23)	NETA	-	-0.83 (-1.39,-0.27)
6.76 (4.57,10.00)	6.55 (4.49, 9.54)	6.85 (3.75,12.51)	6.09 (4.18, 8.87)	5.99 (4.13, 8.68)	5.90 (3.96, 8.79)	5.83 (3.65, 9.30)	5.31 (3.64, 7.76)	4.69 (3.25, 6.76)	4.16 (2.59, 6.68)	4.19 (2.88, 6.11)	3.97 (2.57, 6.14)	3.93 (2.46, 6.28)	3.20 (2.20, 4.64)	3.08 (2.01, 4.70)	2.67 (1.60, 4.48)	1.98 (1.33, 2.94)	1.68 (0.84, 3.38)	FUM	-
14.97 (12.42,18.04)	14.50 (12.44,16.89)	15.17 (9.26,24.86)	13.48 (11.55,15.72)	13.26 (11.54,15.24)	13.06 (10.66,16.00)	12.90 (9.39,17.72)	11.76 (10.03,13.78)	10.37 (9.12,11.79)	9.20 (6.63,12.76)	9.28 (7.96,10.81)	8.80 (6.74,11.47)	8.70 (6.34,11.95)	7.08 (6.14, 8.15)	6.81 (5.32, 8.72)	5.92 (4.03, 8.69)	4.38 (3.59, 5.34)	3.72 (2.03, 6.82)	2.21 (1.57, 3.12)	PBO
PGA																			

Note: All outcomes were measured at the induction phase (assessment from 8 to 24 weeks after randomization). Each cell contains the risk ratio (RR) and 95% confidence interval (PGA 0/1) or standardized mean difference (quality of life) of the intervention in the respective column versus the comparator in the respective row. RRs larger than 1 for the lower triangle and smaller than 1 (or SMD smaller than zero) for the upper triangle favour the treatment on the left. Significant results are highlighted in grey.

ACI = acitretin; ADA = adalimumab; APRE = apremilast; BIME = bimekizumab; BRODA = brodalumab; CERTO = certolizumab; CICLO = ciclosporin; DEUCRAVA = deucravacitinib; ETA = etanercept; FUM = fumaric acid; IFX = infliximab; IXE = ixekizumab; GUSEL = guselkumab; MTX = methotrexate; NETA = netakimab; PBO = placebo; PGA = Physician Global Assessment; RISAN = risankizumab; SECU = secukinumab; SONELO = sonelokimab; TILDRA = tildrakizumab; USK = ustekinumab.

Source: Sbidian E, Chaimani A, Guelimi R, et al. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. Cochrane Database Syst Rev. 2023. Copyright © 2023 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd. Reprinted with permission from John Wiley & Sons, Ltd.[37]

Figure 9: Interval Plot — Network Meta-Analysis Estimates of Class-Level Versus Placebo for All Outcomes



Note: All outcomes were measured at the induction phase (assessment from 8 to 24 weeks after randomization).

AE = adverse events; AIL12/23 = anti-IL12/23; AIL17 = anti-IL17; AIL23 = anti-IL23, ATA = anti-TNF alpha; CI = confidence interval; CSA = non-biological conventional systemic agents; PGA = Physician Global Assessment; PrI = predictive interval; PBO = placebo; QoL = specific quality of life scale; RR = risk ratio; SAE = serious adverse events; SM = small molecules; SMD = standardised mean difference.

Source: Sbidian E, Chaimani A, Guelimi R, et al. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. Cochrane Database Syst Rev. 2023. Copyright © 2023 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd. Reprinted with permission from John Wiley & Sons, Ltd.[37]

Appendix 5: Critical Appraisal

Note that this appendix has not been copy-edited.

Table 17: AMSTAR 2 — A Critical Appraisal Tool for Systematic Reviews That Include Randomized or Nonrandomized Studies of Health Care Interventions, or Both (Shea, 2017)

AMSTAR 2: A Critical Appraisal Tool for Systematic Reviews That Include Randomized or Nonrandomized Studies of Health care Interventions, or Both (Shea 2017)		
Did the research questions and inclusion criteria for the review include the components of PICO?		
For Yes: • Population • Intervention • Comparator group • Outcome **Reason: PICO components were reported (p. 9 to 11)**	Optional (recommended): • Time frame for follow-up	**Yes** No
Did the report of the review contain an explicit statement that the review methods were established before the conduct of the review and did the report justify any significant deviations from the protocol?		
For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following: • review question(s) • a search strategy • inclusion/exclusion criteria • a risk of bias assessment	For Yes: As for partial yes, plus the protocol should be registered and should also have specified: • a meta-analysis/synthesis plan, if appropriate, and • a plan for investigating causes of heterogeneity • justification for any deviations from the protocol **Reason: Data synthesis (p. 13)**	**Yes** Partial Yes No
Did the review authors explain their selection of the study designs for inclusion in the review?		
For Yes, the review should satisfy ONE of the following: • Explanation for including only RCTs • OR explanation for including only NRSI OR explanation for including only RCTs and NRSI **Reason: RCTs are the appropriate study design for this study.**		**Yes** No
Did the review authors use a comprehensive literature search strategy?		
• searched at least 2 databases (relevant to research question) • provided key word and/or search strategy • justified publication restrictions (e.g., language)	For Yes, should also have (all the following): • searched the reference lists / bibliographies of included studies • searched trial/study registries • included/consulted content experts in the field • where relevant, searched for grey literature • conducted search within 24 months of completion of the review	**Yes** Partial Yes No

AMSTAR 2: A Critical Appraisal Tool for Systematic Reviews That Include Randomized or Nonrandomized Studies of Health care Interventions, or Both (Shea 2017)		
	Reason: Details of search methods for identification of studies was detailed (p. 10 to 11)	
Did the review authors perform study selection in duplicate?		
For Yes, either ONE of the following: • at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include • OR two reviewers selected a sample of eligible studies **and** achieved good agreement (at least 80 percent), with the remainder selected by one reviewer. **Reason: The selection process was conducted through Covidence, a web tool allowing dual screening of search results based on titles and abstracts, and then full text by independent review authors (p. 11).**		**Yes** No
Did the review authors perform data extraction in duplicate?		
For Yes, either ONE of the following: • at least two reviewers achieved consensus on which data to extract from included studies • OR two reviewers extracted data from a sample of eligible studies **and** achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer. **Reason: Two review authors extracted the data from published and unpublished reports independently, using a standardized form (p. 11).**		**Yes** No
Did the review authors provide a list of excluded studies and justify the exclusions?		
For Partial Yes: • provided a list of all potentially relevant studies that were read in full-text form but excluded from the review	For Yes, must also have: • Justified the exclusion from the review of each potentially relevant study **Reason: Excluded studies and reasons for exclusion were reported (p. 525).**	**Yes** Partial Yes No
Did the review authors describe the included studies in adequate detail?		
For Partial Yes (ALL the following): • described populations • described interventions • described comparators • described outcomes • described research designs	For Yes, should also have ALL the following: • described population in detail • described intervention in detail (including doses where relevant) • described comparator in detail (including doses where relevant) • described study's setting • time frame for follow-up **Reason: Characteristics of all included studies were reported in detail (p. 126 to 524).**	**Yes** Partial Yes No
The review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?		
RCTs For Partial Yes, must have assessed RoB from: • unconcealed allocation, and • lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)	For Yes, must also have assessed RoB from: • allocation sequence that was not truly random, and • selection of the reported result from among multiple measurements or analyses of a specified outcome	**Yes** Partial Yes No Includes only NRSI

AMSTAR 2: A Critical Appraisal Tool for Systematic Reviews That Include Randomized or Nonrandomized Studies of Health care Interventions, or Both (Shea 2017)		
	Reason: Cochrane Risk of Bias (RoB) tool was used to assess risk of bias of included studies (p. 11).	
NRSI For Partial Yes, must have assessed RoB: • from confounding, and • from selection bias	For Yes, must also have assessed RoB: • methods used to ascertain exposures and outcomes, and • selection of the reported result from among multiple measurements or analyses of a specified outcome	Yes Partial Yes No Includes only RCTs
Did the review authors report on the sources of funding for the studies included in the review?		
For Yes: • Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information, but it was not reported by study authors also qualifies **Reason: Characteristics of all included studies including funding source were reported in detail (p. 126 to 524).**		**Yes** No
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?		

RCTs
For Yes:
• The authors justified combining the data in a meta-analysis
  ◦ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present.
  ◦ AND investigated the causes of any heterogeneity
Reason: Data synthesis methods including assessment of heterogeneity were reported (p. 13).
		Yes
		No
		No meta-analysis conducted

For NRSI
For Yes:
• The authors justified combining the data in a meta-analysis
  ◦ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present
  ◦ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available
  ◦ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review
		Yes
		No
		No meta-analysis conducted

If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?		
For Yes: • included only low risk of bias RCTs • OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect. **Reason: Sensitivity analyses were conducted excluding trials at high risk of bias (p.13).**		**Yes** No No meta-analysis conducted

AMSTAR 2: A Critical Appraisal Tool for Systematic Reviews That Include Randomized or Nonrandomized Studies of Health care Interventions, or Both (Shea 2017)	
Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	
For Yes: • included only low risk of bias RCTs OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results **Reason: the percentage of studies with RoB rated as high, low, or unclear was reported and discussed when interpreting results.**	**Yes** No
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	
For Yes: • There was no significant heterogeneity in the results • OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review **Reason: The authors performed a thorough assessment of heterogeneity and took steps to restrict the risk of important heterogeneity. There was no important heterogeneity in the results (p.13).**	**Yes** No
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	
For Yes: • performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias **Reason: risk of publication bias was assessed using comparison-adjusted funnel plots that test the presence of small study effects in the network (p. 15).**	**Yes** No No meta-analysis conducted
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	
For Yes: • The authors reported no competing interests OR • The authors described their funding sources and how they managed potential conflicts of interest **Reasons: Declarations of interest were reported for all authors of the review (p. 805).**	**Yes** No

Table 18: Network Meta-Analysis

Indirect Treatment Comparison – ISPOR Checklist (Jansen, 2014)
Relevance: The extent to which the results of the NMA apply to the setting of interest to the decision maker. Assess this first. If deemed relevant, move forward with credibility.
Is the population relevant? Yes. The population matches the population of interest to the decision maker. Selection criteria are thoroughly outlined.
Are any relevant interventions missing? No. All biologic interventions of interest are included.
Are any relevant outcomes missing? No. All main outcomes commonly used in RCTs of interventions for psoriasis (PASI 90, 100, 75) are included.

Indirect Treatment Comparison – ISPOR Checklist (Jansen, 2014)
Is the context (settings and circumstances) applicable? Potentially yes. Clinical trial setting is often not entirely generalizable to the real world setting but no major exclusions of patient groups were evident in the included trials.
Credibility: The extent to which the NMA or ITC accurately or validly answers the question it is designed to answer. Encompasses internal validity, reporting quality, transparency, interpretation, conflicts of interest.
Were the outcomes for the NMA pre-specified (e.g., in a protocol or registry)? Yes
Did the researchers attempt to identify and include all relevant RCTs? Yes. A systematic search was conducted and reasons for excluding studies was provided.
Do the trials for the interventions of interest form one connected network of RCTs? Yes
Is it apparent that poor quality studies were included, thereby leading to bias? No
Is it likely that bias was induced by selective reporting of outcomes in the studies? No
Are there systematic differences in treatment effect modifiers (i.e., baseline patient or study characteristics that have an impact on the treatment effects) across the different treatment comparisons in the network? No
If there are systematic differences in treatment effect modifiers, were these imbalances in effect modifiers across the different treatment comparisons identified before comparing individual study results? N/A
Analysis
Were statistical methods used that preserve within-study randomization? (No naïve comparisons) Yes
Were the selected grouping variants of an intervention (i.e., nodes) adequately justified? Yes, nodes being individual drugs or classes of drugs.
If both direct and indirect comparisons are available for pairwise contrasts (i.e., closed loops), was agreement in treatment effects (i.e., consistency) evaluated or discussed? Yes
In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the NMA? Yes
With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis? N/A
Was a valid rationale provided for the use of random-effects or fixed-effect models? Yes (random-effects model was appropriately selected)
If a random-effects model was used, were assumptions about heterogeneity explored or discussed? Yes

Indirect Treatment Comparison – ISPOR Checklist (Jansen, 2014)
If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with prespecified covariates performed? Yes
Reporting Quality and Transparency
Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison? Yes
Are the individual study results reported? Yes
Are the results of direct comparisons reported separately from results of the indirect comparisons or NMA? Yes
Are all pairwise contrasts between interventions as obtained with the NMA reported along with measures of uncertainty? Yes
Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome? Yes
Is the effect of important patient characteristics on treatment effects reported? No (NA)
Interpretation
Are the conclusions fair and balanced? Yes
Conflict of Interest
Were there any potential conflicts of interest? No
If yes, were steps taken to address these? N/A

Appendix 6: Additional Information on Biologics for Plaque Psoriasis

Note that this appendix has not been copy-edited.

Table 19: Key Characteristics of Biologics for Plaque Psoriasis Approved in Canada

Drug	Indication	Recommended dose and administration
Anti-IL17		
Bimekizumab	Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy	320 mg SC every 4 weeks for the first 16 weeks, then 320 mg SC every 8 weeks thereafter Note: For patients with a body weight ≥ 120 kg who did not achieve a complete skin response, a dose of 320 mg every 4 weeks after week 16 may be considered
Brodalumab	Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy	210 mg SC at weeks 0, 1, and 2, followed by 210 mg SC every 2 weeks
Secukinumab	Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy Treatment of severe plaque psoriasis in pediatric patients 12 to under 18 years of age who are candidates for systemic therapy or phototherapy and have a body weight ≥ 50 kg	300 mg SC at weeks 0, 1, 2, 3, and 4, followed by monthly maintenance administration
Ixekizumab	Treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy Treatment of pediatric patients from 6 to less than 18 years of age with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy	160 mg SC at week 0, followed by 80 mg SC at weeks 2, 4, 6, 8, 10, and 12, then 80 mg SC every 4 weeks
Anti-IL23		
Tildrakizumab	Treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy	100 mg administered by SC injection at weeks 0 and 4, and every 12 weeks thereafter
Risankizumab	Treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy	150 mg administered by SC injection at weeks 0 and 4, and every 12 weeks thereafter
Guselkumab	Treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy	100 mg administered SC at weeks 0 and 4, followed by maintenance administration every 8 weeks thereafter
Anti-IL12/23		
Ustekinumab	Treatment of adult patients with chronic moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy	45 mg SC at weeks 0 and 4, then every 12 weeks thereafter. Alternatively, 90 mg SC may be used in patients

Drug	Indication	Recommended dose and administration
	Treatment of chronic moderate to severe plaque psoriasis in adolescent patients from 12 to 17 years of age, whose psoriasis is inadequately controlled by, or who are intolerant to, other systemic therapies or phototherapies	with a body weight > 100 kg. For patients who respond inadequately to administration every 12 weeks, consideration may be given to treating as often as every 8 weeks Dose of 0.75 mg/kg is recommended in pediatric patients weighing < 60 kg
Anti-TNF alpha		
Adalimumab	Treatment of adult patients with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy; for patients with chronic moderate plaque psoriasis, adalimumab should be used after phototherapy has been shown to be ineffective or inappropriate	Initial dose of 80 mg SC followed by 40 mg SC every other week starting 1 week after the initial dose Continued therapy beyond 16 weeks should be carefully reconsidered in a patient not responding within this time period
Certolizumab pegol	Treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy	400 mg SC every 2 weeks A dose of 400 mg SC initially (week 0) and at weeks 2 and 4 followed by 200 mg every 2 weeks may be considered
Etanercept	Treatment of adult patients with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy Treatment of pediatric patients ages 4 to 17 years with chronic severe psoriasis who are candidates for systemic therapy or phototherapy	Starting dose of 50 mg SC given twice weekly (administered 3 or 4 days apart) for 3 months, followed by a reduction to a maintenance dosage of 50 mg SC per week. A maintenance dosage of 50 mg SC given twice weekly has also been shown to be efficacious
Infliximab	Treatment of adult patients with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy; for patients with chronic moderate plaque psoriasis, infliximab should be used after phototherapy has been shown to be ineffective or inappropriate	5 mg/kg IV followed by additional 5 mg/kg IV doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. If a patient does not show an adequate response at week 14, no additional treatment with infliximab should be given

IL = interleukin; SC = subcutaneous

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