CADTH

**CADTH RAPID RESPONSE REPORT:**
**SUMMARY WITH CRITICAL APPRAISAL**

# Adalimumab for Adult Patients with Plaque Psoriasis: A Review of Clinical Effectiveness


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## Abbreviations

| | |
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| AE | Adverse event |
| AMSTAR | A Measurement Tool to Assess Systematic Reviews |
| CDR | Common Drug Review |
| CI | Confidence interval |
| CrI | Credible interval |
| DLQI | Dermatology life quality index |
| GRADE | Grading of Recommendations Assessment, Development and Evaluation |
| IL | Interleukin |
| ISPOR | International Society for Pharmacoeconomics and Outcomes Research |
| MD | Mean |
| NIHR | National Institute for Health Research |
| NMA | Network meta-analysis |
| PASI | Psoriasis Area Severity Index |
| PASI 100 | 100% improvement in PASI score |
| PASI 75 | ≥75% improvement in PASI score |
| PASI 90 | ≥90% PASI score |
| PGA | Physician's global assessment |
| RCT | Randomized controlled trials |
| RR | Risk ratio |
| SAE | Serious adverse event |
| SD | Standard deviation |
| SR | Systematic review |
| WDAE | Withdrawal due to adverse event |

## Context and Policy Issues

Psoriasis is an autoimmune and inflammatory disease with genetic predispositions that generally occurs before age 35.[1] The development of the disease is driven by multiple pathways of immune mediators, including tumor necrosis factor-α (TNF-α), interleukin (IL)-23 and IL-17 cytokines. Psoriasis affects about 3% of the population and is associated with systemic diseases including inflammatory bowel disease, metabolic syndrome, and cardiovascular disease.[1] Plaque psoriasis is the most common form of the disease,

accounting for about 70% to 90% of all patients with psoriasis.[1,2] It is characterized by itchy, red, scaly, raised lesions on the skin, especially on the scalp, elbows, knees, scalp, and back extensor extremities and trunk.[1] Psoriasis significantly impairs patients' quality of life.[3]

Most patients with plaque psoriasis have mild disease that is adequately managed with topical application of corticosteroids, emollients, vitamin D analogs, coal tar products, retinoids and calcineurin inhibitors, or phototherapy.[1] Moderate-to-severe chronic plaque psoriasis symptoms are generally treated with systemic therapies.[2,4] They have a significant negative impact on patient quality of life.[1,2] and are associated with a considerable economic burden.[4,5] Treatment options include conventional agents such as methotrexate and cyclosporine, and relatively newer biologic agents. Biologics approved for patients with moderate-to-severe plaque psoriasis include of TNF-α inhibitors (e.g., as adalimumab and infliximab), IL-17 inhibitors (e.g., ixekizumab, and secukinumab) and IL-23 inhibitors (e.g., risankizumab).[3,4,6-9] Unlike the non-specific conventional immunomodulators, biologic treatments for psoriasis are less likely to cause systematic adverse events because of their specificity for immune targets.[3,10]

Adalimumab was among the earlier biologic agents that received approval from Health Canada for the treatment of severe plaque psoriasis.[11] Others with similar approved indications include infliximab, ixekizumab, risankizumab, and secukinumab.[11] The variety of biologic agents currently available for the treatment of moderate-to-severe plaque psoriatic presents a challenge to clinicians in making choices that optimize patients' outcomes. It also creates the need for decision-makers to determine suitable places in therapy for the available treatment options, using evidence-based information. In 2008, CADTH conducted a Common Drug Review (CDR) of adalimumab in patients with plaque psoriasis.[12] However, that review[12] did not cover the comparative effectiveness of adalimumab to other biologics for that indication.

The aim of this Rapid Response review is to compare and summarize evidence about the clinical effectiveness of adalimumab versus other biologic drugs indicated for the treatment of in adult patients with plaque psoriasis.

## Research Question

What is the clinical effectiveness of adalimumab versus other biologic drugs in adult patients with plaque psoriasis?

## Key Findings

Evidence from five systematic reviews (four with network meta-analysis and one with traditional meta-analysis) and one randomized controlled trial suggested that adalimumab was less effective than infliximab, ixekizumab, risankizumab, and secukinumab in achieving skin clearance and improvements in health-related quality of life in patients diagnosed with moderate-to-severe plaque psoriasis. Apart from the randomized controlled trial comparing adalimumab to risankizumab, separate data from direct comparison were not available for effectiveness and safety. There was not enough evidence to draw a firm conclusion about the comparative safety of adalimumab versus the other biologics of interest.

Substantial overlap of primary studies across the systematic reviews showed that the pooled estimates from the separate reviews contain some data from the same primary studies. An assessment of the methodological quality of the included studies did not find issues that present significant uncertainty about the findings in four systematic reviews and

the randomized controlled trial. The quality of one systematic review was limited due to inadequate reporting. However, the results from that study were consistent with the others. Thus, they did not appear likely to impact the overall evidence reported here. The consistency could be due to the overlap of the primary studies included in the systematic reviews.

## Methods

### Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were psoriasis and adalimumab and other biologics. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, and meta analyses, and randomized controlled trials. The search was also limited to English language documents published between January 1, 2010 and April 21, 2020.

### Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

**Table 1: Selection Criteria**

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| **Population** | Adults patients with plaque psoriasis |
| **Intervention** | Adalimumab |
| **Comparator** | Infliximab, secukinumab, risankizumab, ixekizumab |
| **Outcomes** | Clinical effectiveness:<br>• Health-related quality of life (measuring instruments such as DLQI, SF-36, EQ-5D);<br>• Clinical or therapeutic response (e.g., Skin clearance/ psoriasis score [i.e., PASI response, global assessment])<br>• Disease recurrence<br>• Morbidity (e.g., disability)<br>• Patient-reported symptoms (e.g., PSI)<br>Adverse events (e.g., Infections, injection-site reactions, inflammatory bowel disease, serious hypersensitivity reactions, malignancy, cardiovascular and cerebrovascular events, suicidal ideation, mortality, discontinuation or failure rate of therapy) |
| **Study Designs** | Health Technology Assessments, Systematic Reviews, Randomized Controlled Trials |

DLQI = dermatology life quality index; EQ-5D = EuroQol five-dimension scale; PASI = Psoriasis Area Severity Index; PSI = psoriasis symptom inventory; SF-36 = Short Form 36.

### Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2015. Systematic reviews (SRs) in

which all relevant studies were captured in other more recent or more comprehensive systematic reviews were excluded. Primary studies retrieved by the search were excluded if they were captured in one or more included SRs.

### Critical Appraisal of Individual Studies

The included publications were critically appraised by one reviewer using the following tools as a guide: A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)[13] for SRs, the "Questionnaire to assess the relevance and credibility of a network meta-analysis"[14] for network meta-analyses (NMAs), the Downs and Black checklist[15] for the randomized controlled trial (RCT). Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

## Summary of Evidence

### Quantity of Research Available

A total of 464 citations were identified in the literature search. Following screening of titles and abstracts, 442 citations were excluded and 22 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search for full-text review. Of 23 potentially relevant articles, 17 publications were excluded for various reasons, and six publications met the inclusion criteria and were included in this report. These comprised five SRs,[3,4,7-9] and one RCT.[6] Appendix 1 presents the PRISMA[16] flowchart of the study selection.

### Summary of Study Characteristics

Overall, the six studies[3,4,6-9] included in this report assessed the effectiveness of 13 biologics in patients with moderate-to-severe psoriasis. They were adalimumab, briakinumab, brodalumab, certolizumab pegol, etanercept, guselkumab, infliximab, itolizumab, ixekizumab, risankizumab, secukinumab, tildrakizumab, and ustekinumab. However, only data and comparisons needed to answer the research question of this Rapid Response report will be discussed further. The citation matrix in Appendix 5 shows the degree of overlap of primary studies across the SRs.

Additional details regarding the characteristics of included publications are provided in Appendix 2.

#### *Study Design*

Five SRs[3,4,7-9] and one RCT[6] were included in this report. The SRs were published from 2015 to 2020 and their included studies were published from 2001 to 2019. Four SRs conducted NMA,[3,4,7,8] whereas one performed a traditional meta-analysis.[9] Details about the study arms of the RCTs included the SRs[3,4,7-9] were not enough to determine the number of studies that directly compared adalimumab to any of the other biologics agents of interest to this report (i.e., infliximab, ixekizumab, risankizumab and secukinumab).

The SR by Warren et al.[3] included 33 RCTs. They were identified by systematic literature review of databases, books and journals offered by the Medical Library at Health First (i.e., the OvidSP platform) for literature published from 1 January 1990 to 12 December 2018. Eighteen of the RCTs evaluated biologics agents of interest to this report and were included in NMA.[3]

Sawyer et al.[4] included 98 publications covering 67 RCTs, including 17 trials that were involved in NMA. Of the 17 trials, nine RCTs investigated biologics agents of interest to this report. The studies were identified from a systematic search of multiple databases from 2000 to 31st August 2016.[4]

The SR by Xu et al.[7] included 54 RCTs, including 27 trials that assessed biologics agents of interest to this report. They were identified by systematic search conducted in multiple databases from inception to 8th August 2018 and supplemented with manual searches of related bibliographies.

The SR by Jabbar-Lopez et al.[8] was based on 45 articles presenting data from 41 RCT including 16 RCTs that evaluated the biologics of interest to this report. The studies were identified through a systematic literature search conducted in multiple databases from inception to 17th October, 2016.[8]

The SR by Nast et al.[9] included 31 publications based on 25 RCTs, including nine RCTs that investigated biologics agents of interest to this report . The investigators conducted systematic literature searches of the OvidSP platform for relevant studies from inception to 5th January 2015.

The RCT by Reich et al.[6] was published in 2019. It was randomized, double-blind, active-comparator-controlled trial conducted at 66 clinics. The RCT had two parts. In the first section (Part A), patients were randomly assigned 1:1 to either of the two treatment groups (risankizumab or adalimumab) for a 16-week double-blind treatment period. In the second phase (Part B), adalimumab intermediate responders were re-randomized 1:1 to continue receiving adalimumab or switch to risankizumab for weeks 16 to 44. It is worth noting that this RCT was one of four studies that were included a CADTH CDR published in June 2019.[17]

### *Country of Origin*

Lead authors of the three SRs with NMA[3,4,8] were from the United Kingdom and the authors other of another SR with NMA[7] were from China. The SR with traditional MA was conducted by reviewers in Germany.[9] The RCT[6] was a global study with sites in Canada, seven European countries (Czech Republic, Finland, France, Germany, Poland, Portugal, and Sweden), Mexico, Taiwan, and the United States of America.

### *Patient Population*

Four SRs[3,4,7,9] included RCTs involving adult patients (≥ 18 years of age) with moderate-to-severe psoriasis. One other SR[8] included RCTs that enrolled all people with psoriasis of any severity being treated primarily for their skin disease. However, the included studies of relevance to this report involved adult patients with moderate-to-severe psoriasis. There was not enough information in the SR by Warren et al.[3] about the specific number of patients treated with the biologics of interest to provide in this Rapid Response report. For the remaining SRs by Sawyer et al.,[4] Xu et al.,[7] Jabbar-Lopez et al.[8] and Nast et al.,[9] the total number of patients per SR treated with biologics agents of interest to this report ranged from 2,447 to 9,530. Note that for NMAs, all included patients (not just those from trials relevant to this report) contribute to the indirect treatment comparisons. The RCT by Reich et al.[6] involved a total of 605 adult patients (mean age 46 ± 13 years) with moderate-to-severe chronic plaque psoriasis.

### *Interventions and Comparators*

Overall, the six studies[3,4,6-9] included in this report assessed the effectiveness of 13 biologics (adalimumab, briakinumab, brodalumab, certolizumab pegol, etanercept, guselkumab, infliximab, itolizumab, ixekizumab, risankizumab, secukinumab, tildrakizumab, and ustekinumab) in patients with moderate-to-severe psoriasis. However, only data and comparisons needed to answer the research question of this Rapid Response report will be discussed further. The treatment protocols of the biologics in the primary studies of the included SRs[3,4,7-9] were not uniformly reported. In the included RCT by Reich et al.,[6] patients were randomly assigned to receive 150 mg risankizumab at weeks 0 and 4 or 80 mg adalimumab at randomization, then 40 mg at weeks 1, 3, 5, and every other week after that during a 16-week double-blind treatment period (Part A). In Part B of the trial (weeks 16 to 44), patients who had intermediate responses to adalimumab were re-randomized to either continue 40 mg adalimumab or switch to 150 mg risankizumab. An intermediate response was defined as Psoriasis Area and Severity Index (PASI) scores ≥50 to PASI <90. Each treatment was administered subcutaneously.

### *Outcomes*

Four of the included SRs[3,4,7,9] and the RCT[6] used the Psoriasis Area and Severity Index (PASI) scores. The PASI is a validated measure widely used in clinical trials to assess symptomatic changes in thickness, scale, and erythema in psoriasis patients, usually performed following 12 weeks of therapy.[10] Treatment success is determined by the percentage improvement in PASI score from baseline, with PASI 75, PASI 90, or PASI 100 denoting ≥ 75%, ≥ 90%, or 100% improvement, respectively.

Four of the included SRs[3,7-9] and the RCT[6] investigated Dermatology Life Quality Index (DLQI) response rates. The DLQI is a well-established tool widely used to measure the quality of life related to skin disease in psoriasis trials.[10] The DLQI scores range from 0 (not affected at all) to 3 (very much affected) for each of 10 questions, with a total scores range from 0 to 30, where lower scores mean better quality of life.

Three of the included SRs[7-9] and the RCT[6] reported Physician's Global Assessment (PGA) outcomes. The PGA is a 5- to 7-point scale ranging from "clear" to "very severe psoriasis," which is used in trials for clinical assessment.[10] Treatment success on PGA is generally defined as achieving clear or almost clear disease.[10] These four included studies[6-9] also reported safety outcomes, such as adverse events (AEs), serious (SAEs) and withdrawal (or discontinuation) due to adverse events (WDAEs).

## Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

**Included Systematic Reviews**

The authors of each the included SRs[3,4,7-9] provided well-defined study objectives and inclusion criteria that identified the population, interventions, comparators and outcomes of their respective research questions. One SR[8] established the study protocol and registered with the International prospective register of systematic reviews (PROSPERO) before conducting the review. It was unclear if any of the remaining SRs[3,4,7,9] established a protocol ahead of conducting the studies. Each SR was based on RCTs retrieved through a systematic literature search in multiple databases. The reporting of one SR[3] was poor, with

no information about many quality parameters such as methods for abstract screening, study selection and data extraction, characteristics of the included studies, the number of excluded studies and reasons for exclusion, and evaluation of the risk of bias of primary RCTs. In four of the SRs,[4,7-9] the characteristics of the individual included studies were provided, and abstracts screening, study selection, and data extractions were performed in duplicate, resolving any disputes by consensus or through a third reviewer. The four SRs,[4,7-9] assessed the risk of bias of included primary studies and considered the limitations in the individual studies in discussing the results of the reviews. Three SRs[7-9] investigated publication bias, whereas two others[3,4] did not. Two SRs[8,9] assessed heterogeneity with one using visual inspection of the forest plots,[8] while the other used the $I^2$ test.[9] Methodological limitations in the SRs included absence of information on the number and lists of excluded studies,[3,4] and reasons for exclusion,[3] lack of clarity on the method of abstract screening,[3] study selection[3] and data extraction,[3,4] as well as inadequate information about the characteristic of the included studies[3] and evaluation of the risk of bias in the primary RCTs.[3] Other limitations were uncertainty about appropriate assessment of heterogeneity[3,7] and publication bias.[3,4]

All the included SRs[3,4,7-9] used appropriate methods for statistical analyses and reported results along with measures of uncertainty. All the NMAs used the more robust random effects models and there were no naïve comparisons. The NMAs in three SRs,[3,4,7] were based on Bayesian analysis, whereas one SR[8] used the frequentist approach for NMA. Although the reported study selection criteria indicated that the populations of RCTs included in the SRs.[3,4,7-9] were applicable to the population of interest of this Rapid Response report, there was not enough information to assess the relevance of the setting for the included RCTs. Also, there was not enough information to evaluate if systematic differences in treatment effect modifiers existed across the different treatment comparisons in the networks. One SR[7] did not receive any funding for the study and one SR[8] was funded by the British Association of Dermatologists to inform the next update to the clinical guidelines for biologic therapy for psoriasis, and another SR was funded by the European Dermatology Forum to update of the European psoriasis guidelines. In all three SRs,[7-9] no conflicts were reported that could potentially impact the conduct and reporting of the studies. Two SRs[3,4] were funded by pharmaceutical companies, and all the authors were involved with the pharmaceutical industry in various capacities, such as areas advisory board member, consultant and/or speaker, employee, investigator, and shareholder. There was no apparent issue with the methodological quality of four SRs[4,7-9] that presented a significant uncertainty about their findings. The quality of one SR[3] was limited due inadequate reporting.

**Included Primary Clinical Study**

The included RCT[6] was a phase 3 randomized, double-blind, double-dummy, active-comparator trial done at 66 sites in 11 countries, including Canada. Thus, the study design minimizes the risk of bias, and the multiple countries and sites suggest a good generalizability. The objectives of the study and patients' characteristics were well-defined and the interventions (risankizumab and adalimumab) were described with details about doses, route of administration, and periods of follow-up. The investigators performed sample size calculations to determine that the study was adequately powered to identify clinically meaningful differences in treatment effects between the risankizumab and the adalimumab groups. The outcomes were measured with validated scales that are commonly used in clinical research, and the results were analyzed using appropriate statistical methods. The primary analysis was based on the intention-to-treat population and

estimates for the main findings were reported along with corresponding 95% confidence intervals and P values. Patients enrolled in Part B of the RCT had achieved intermediate response to adalimumab during the first phase of the trial which lasted 16 weeks. Thus, the re-randomization of these patients to continue treatment with adalimumab or switch to receive risankizumab could have resulted in selection bias in favour of risankizumab. The number of missing data from each study arm was low (two or fewer patients missing per arm) and similar across groups for the entire study period. Missing efficacy data were handled using non-responder imputation for categorical variables and last observation carried forward for continuous variables. A per-protocol analysis produced consistent results with the intention-to-treat analyses, suggesting robustness of the findings. Adverse events were assessed and reported for the two arms of the study. However, the study duration was not enough for long-term safety and effectiveness. The article, which was the source of evidence from the RCT,[6] for this report, did not provide information about patients' adherence to the allocated treatment. However, a previous CADTH CDR[17] that included this RCT[6] and three others in assessing the effectiveness of risankizumab for psoriasis, reported that "adherence was generally high throughout each study and well balanced across treatment groups; it was therefore unlikely to create bias in favour of any treatment." In general, the CDR process accesses a wider scope of information, including unpublished materials; however, the critical appraisal provided in this Rapid Response report is in agreement with the main appraisal points of that CDR report.[17] The study was sponsored by a pharmaceutical company that contributed to study design and participated in data collection, data analysis and interpretation, as well as the writing, review, and approval of the manuscript.

## Summary of Findings

Appendix 4 presents the main study findings and authors' conclusions.

### *Clinical Effectiveness of adalimumab versus other biologic drugs in adult patients with plaque psoriasis*

Five SRs[3,4,7-9] and one RCT[6] reported findings on the comparative effectiveness of adalimumab versus infliximab,[3,4,7-9] ixekizumab,[3,7,8] risankizumab,[3,6] and secukinumab in adult patients diagnosed with moderate-to-severe psoriasis.[3,4,7-9] Evidence of effectiveness was evaluated using PASI and PGA for skin clearance and DLQI for patients' health-related quality of life. The statistical approaches used to handle data and the units of outcome reporting were different for each of the included SRs[3,4,7-9] and RCT.[6] However, all the included studies were consistent in showing that adalimumab was less effective than the comparator biologic agents for skin clearance and improvements in the quality of life for patients with moderate- to-severe psoriasis in the short-term (12 weeks),[3,7] medium-term (16 to 24 weeks),[7,9] extended follow-up of 40 to 60 weeks,[4] or up to three years.[8] It should be noted that in Part B of the included RCT,[6] the re-randomization of patients from Part A who achieved intermediate response to adalimumab to either continue treatment with adalimumab or switch to risankizumab may have introduced selection bias in favour of risankizumab. That may explain the bigger differences in outcomes between the two drugs in Part B compared to Part A (Table 8).

**Skin clearance**

Psoriasis Area and Severity Index

Four SRs[3,7-9] and one RCT[6] provided PASI findings. Warren et al.[3] found that for PASI 75, the relative treatment effect was 0.63 (95% credible interval [CrI], 0.604, 0.662) for

adalimumab and 0.85 (95 CrI, 0.825, 0.866), 0.80 (95 CrI, 0.752, 0.839), 0.76 (95 CrI, 0.740, 0.789), and 0.75 (95 CrI, 0.715, 0.793) for ixekizumab, risankizumab, secukinumab, and infliximab, respectively. The comparisons in the SRs by Sawyer et al.,[4] Xu et al.,[7] and Nast et al. showed a similar trend,[9] which was repeated for PASI 90 and PASI 100 scores. In the RCT by Reich et al.,[6] 72% of patients treated with risankizumab achieved the co-primary endpoint at PASI 90 at the week-16 follow-up assessment compared with 47% of those who were treated with adalimumab. The difference was statistically significant with an adjusted absolute difference of 24.9% (95% CI, 17.5 to 32.4; p<0.0001). Risankizumab also showed superior PASI 75 and PASI 100 scores than adalimumab. The difference was statistically significant (p<0.0001) in all comparisons. Similar trends were observed at week 44 assessment among patients who had intermediate response (defined as PASI ≥50 to PASI <90) after 16 weeks of adalimumab treatment who were re-randomized to receive risankizumab or to continue treatment with adalimumab.

Physician's global assessment

Three SRs[6-8] reported skin clearance findings as evaluated with the PGA score of clear or nearly clear (0, 1). Jabbar-Lopez et al.[8] compare the PGA (0, 1) of infliximab, ixekizumab and secukinumab to adalimumab and reported pairwise odds ratios (OR) of 4.08 (95% confidence interval [CI] 1.69, 9.88), 2.86 (95% CI, 1.30, 6.27), and 0.98 (95% CI, 0.43, 2.26), respectively. Xu et al.[7] found that the odds ratio (OR) for PGA was 11 (95% CrI, 6.2, 17) for adalimumab, 87 (95% CrI, 52, 140) for ixekizumab, and 40 (95% CrI, 9.1, 180) for and infliximab. Pooled risk ratios (RR) for PGA in the SR by Nast et al.[9] were consistent with these findings showing that adalimumab was the least effective compared with infliximab and secukinumab for skin clearance, as indicated by the PGA (0, 1) score. In the RCT by Reich et al.,[6] 84% patients treated with risankizumab achieved PGA (0, 1) score compared with 60% patients given adalimumab. The difference was statistically significant with an adjusted absolute difference of 23.3% (95% CI, 16.6 to 30.1; p<0.0001).

**Quality of Life**

Four SRs[3,7-9] and one RCT[6] reported psoriasis-related quality of life outcomes as measured by the DLQI. Warren et al.[3] found that the relative treatment effect of achieving scores of 0 or 1 (i.e., no effect on the patient's life) was 0.18 (95% Cr, 0.101, 0.260) for adalimumab, 0.53 (95% Cr, 0.497, 0.567) for secukinumab, and 0.57 (95% Cr, 0.533, 0.612) for ixekizumab. DLQI scores of 0 or 1 results from Xu et al.,[7] Jabbar-Lopez et al.,[8] and Nast et al.[9] were consistent with this finding in showing that treatment adalimumab was associated with a lower improvements in health-related quality of life for patients with moderate-to-severe psoriasis compared with infliximab, ixekizumab, and secukinumab. In the RCT by Reich et al.,[6] 66% of patients treated with risankizumab achieved DLQI scores of 0 or 1 compared with 49% who were treated with adalimumab. The difference was statistically significant (p<0.0001); however, the adjusted absolute difference was not reported for this outcome.

**Safety**

Adverse event (AE) findings were reported by three SRs[7-9] and one RCT.[6] Xu et al.,[7] assessed the occurrence of headache and infection, as well as AEs leading to withdrawal from treatment or discontinuation of study drug. They reported that infliximab and ixekizumab had a higher risk than placebo for the occurrence of headache, whereas adalimumab and ixekizumab had a higher risk than placebo for the occurrence of infection. The odds of withdrawal or discontinuation was also higher with ixekizumab versus placebo. The SR by Nast et al.[9] found that the relative risk of AEs, serious AEs, and AEs leading to

withdrawal or discontinuation of treatment drug was higher in infliximab versus placebo than adalimumab versus placebo. Two SRs[7,9] did not report data comparing the safety of adalimumab to the other biologics of interest. Rather, they provided results of comparing each biologic to placebo. Thus, it was unclear if a significant difference in safety parameters existed between adalimumab and infliximab, ixekizumab, or secukinumab. Jabbar-Lopez et al.,[8] reported that the odds of AEs leading to withdrawal was statistically significantly lower with adalimumab compared with infliximab or ixekizumab, but not statistically significantly different compared to secukinumab. Based on higher occurrence of AEs leading to discontinuation, they suggested that ixekizumab and infliximab had poorer tolerability than adalimumab and secukinumab, which were considered to have comparable tolerability.

In the RCT by Reich et al.,[6] the frequencies of AEs were low for both risankizumab and adalimumab, and there were no statistically significant differences in AEs between the two study groups.

### Limitations

Considerable overlap occurred in the primary studies that were included in the SRs.[3,4,7-9] Thus, the pooled estimates from the separate reviews contain some of the same data. The citation matrix in Appendix 5 shows the degree of overlap of primary studies across the SRs.

Apart from one RCT[6] comparing adalimumab directly to risankizumab, there was no other study identified that compared adalimumab directly to any of the biologic agents of interest to this report. Thus, the results from the five SRs[3,4,7-9] were derived from indirect treatment comparisons, which require additional assumptions (e.g., homogeneity of included studies) for valid conclusions relative to a head-to-head evaluation of interventions in a high-quality RCT. However, the results of all the five SRs[3,4,7-9] and the one RCT[6] included in this report consistently showed that adalimumab was less effective than the infliximab, ixekizumab, risankizumab and secukinumab agents for skin clearance and improvements in the psoriasis-related quality of life for patients with moderate- to-severe psoriasis, suggesting that a similar finding is likely from further studies. There was not enough information about the long-term safety and effectiveness of the reviewed biologic treatments.

## Conclusions and Implications for Decision or Policy Making

Five SRs[3,4,7-9] and one RCT[6] provided the information in this report. The comparative skin clearing effectiveness of adalimumab versus infliximab, ixekizumab, risankizumab, and secukinumab in patients with moderate- to-severe psoriasis was assessed using the PASI and the PGA (0, 1) tools. Evidence from the SRs[3,4,7-9] and the RCT[6] indicated that adalimumab was the least effective for skin clearance among the five compared biologic agents based on PASI[3,4,6,7,9] or PGA[3,6-9] results.

The comparative effectiveness of adalimumab for improving the psoriasis-related quality of life was compared to that of infliximab, ixekizumab, risankizumab, and secukinumab in using DLQI scores of 0 or 1 (i.e., no effect on the patient's life). Evidence from four SRs[3,7-9] and the RCT[6] indicated that adalimumab was the least effective among the five compared biologic agents for improving the health-related quality of life in patients with moderate-to-severe psoriasis among the five compared biologic agents.

On safety, the three SRs[7-9] generally did not indicate a clear difference in safety parameters assessed between adalimumab and infliximab, ixekizumab, or secukinumab, with one

exception; in one SR[8] ixekizumab and infliximab were shown to be associated with higher odds of withdrawal due to adverse events compared with adalimumab, whereas the odds of withdrawal were comparable between adalimumab and secukinumab. The other two SRs[7,9] did not report data comparing the safety of adalimumab to any other biologics. Rather, results of comparing each biologic to placebo was provided. Overall, there was not enough evidence to draw a firm conclusion about the comparative safety of adalimumab versus the other biologics of interest. The evidence from the included RCT[6] suggested that the frequencies of AEs with risankizumab was not statistically significantly different from that of adalimumab in the short-term (up to 44 weeks). There were no long-term data on safety or efficacy.

Overall, there was consistent evidence from the studies[3,4,6-9] included in this report indicating that adalimumab was less effective than infliximab, ixekizumab, risankizumab, and secukinumab in achieving skin clearance and improvements in health-related quality of life in patients diagnosed with moderate-to-severe psoriasis. However, there was a substantial overlap of the primary studies across the SRs.[3,4,7-9] Thus, the pooled estimates from the separate SRs[3,4,7-9] contain some data from the same primary studies.

The assessment of the methodological quality of four SRs[4,7-9] and the RCT[6] did not find issues that present significant uncertainty about the finding they reported. The quality of one SR[3] was limited due poor reporting. However, the results from that SR[3] were consistent with the other included studies and did not appear likely to impact the reported evidence, which may be due to the substantial overlap of primary studies across the SRs.[3,4,7-9]

These findings, in combination with other factors such as cost-effectiveness and patients' preferences, may help decision-makers develop policies on the place in therapy of biologic agents, including the use of a tiering approach to optimize treatment outcomes for patients with moderate-to-severe plaque psoriasis.

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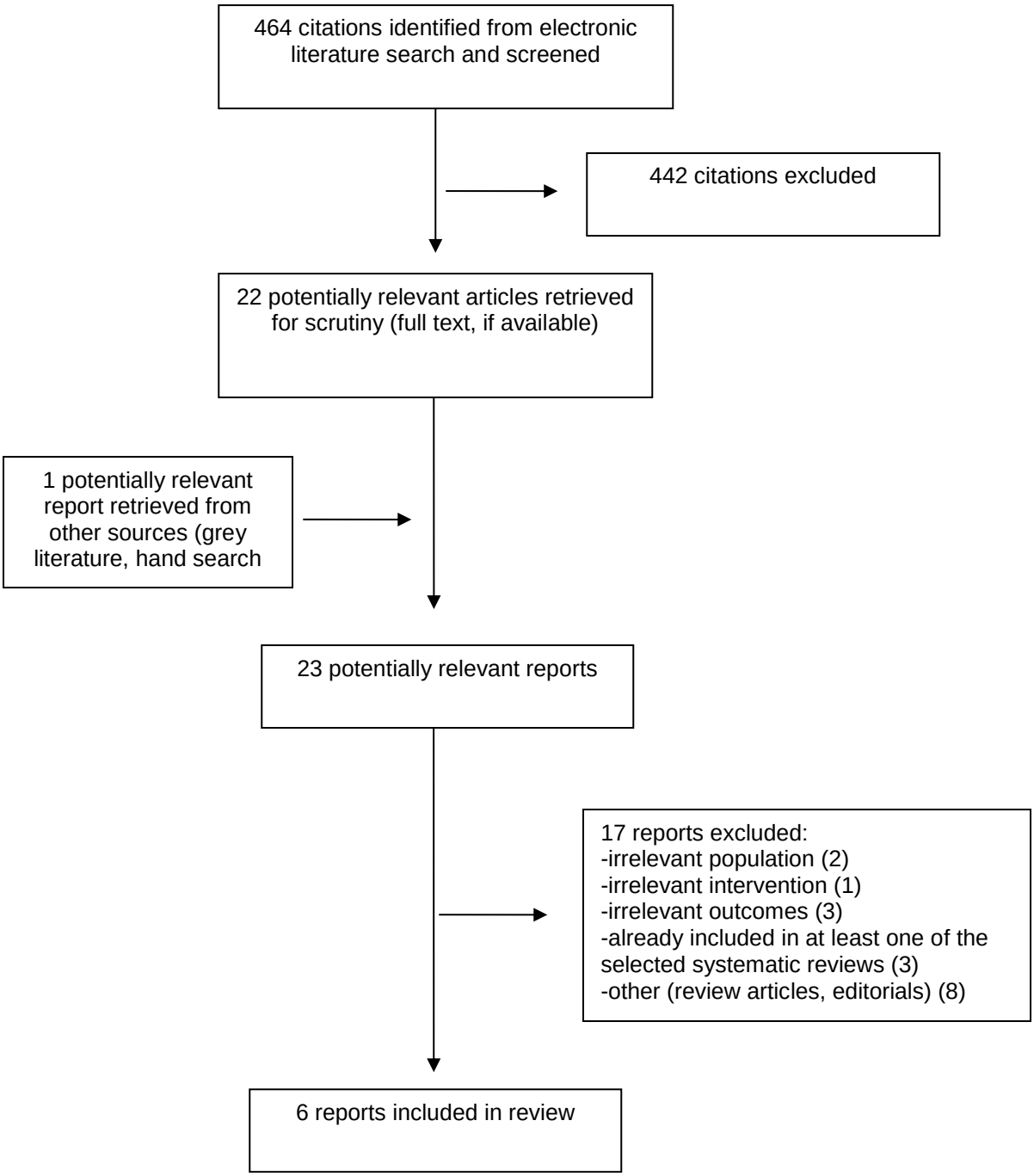
## Appendix 1: Selection of Included Studies



# Appendix 2: Characteristics of Included Publications

## Table 2: Characteristics of Included Systematic Reviews and Network Meta-Analyses

| Study citation, country, funding source | Study designs and numbers of primary studies included | Population characteristics | Intervention and comparator(s) [a] | Clinical outcomes, length of follow-up |
|---|---|---|---|---|
| **Warren et al., 2020**[3]<br><br>**United Kingdom,**<br><br>**Funded by Eli Lilly and Company.** | A systematic review of 32 RCTs with NMA. 20 RCTs evaluated the biologics of interest to this report. | Adult patients with moderate-to-severe psoriasis. The number of patients involved in studies that evaluated treatment of interest to this report was unclear. | • Adalimumab,<br>• Infliximab<br>• Ixekizumab<br>• Risankizumab<br>• Secukinumab | *Efficacy – Follow-up at weeks 12*<br>• PASI 75<br>• PASI 90<br>• DLQI |
| **Sawyer et al., 2019**[4]<br><br>**United Kingdom**<br><br>**Funded by LEO Pharma A/S.** | A systematic review of 24 RCTs, with NMA of 17, including nine RCTs of interest to this report. | A total of 2,447 adult patients with moderate-to-severe plaque psoriasis were involved in studies that evaluated treatment of interest to this report | • Adalimumab<br>• Infliximab<br>• Ixekizumab<br>• Secukinumab | *Efficacy – Follow-up at 40 to 64 weeks*<br>• PASI 75<br>• PASI 90<br>• PASI 100 |
| **Xu et al., 2019**[7]<br><br>**China**<br><br>**Funding – None** | A systematic review of 54 RCTs with NMA. Nine RCTs evaluated biologics of interest to this report | A total of 9,530 adult patients diagnosed with moderate to severe psoriasis were involved in studies that evaluated treatment of interest to this report. | • Adalimumab<br>• Infliximab<br>• Ixekizumab<br>• Secukinumab | *Efficacy – Follow-up 12 to 16 weeks;*<br>• PASI 75<br>• PASI 90<br>• PASI 100<br>*Safety*<br>headache, infection and discontinuation |
| **Jabbar-Lopez et al., 2017**[8]<br><br>**United Kingdom**<br><br>**Funded by an NIHR doctoral research fellowship** | A systematic review of 41 RCTs, with NMA, including 16 RCTs that evaluated the biologics of interest to this report. | A total of 9,023 adult patients with moderate-to-severe psoriasis were involved in studies that evaluated treatment of interest to this report | • Adalimumab<br>• Infliximab<br>• Ixekizumab<br>• Secukinumab | *Efficacy – Follow-up at 3 to 4 months, I year, and 3 years*<br>• PGA "clear or almost clear"<br>• DLQI<br>*Safety*<br>• Tolerability, as assessed by WDAEs |
| **Nast et al., 2015**[9]<br><br>**Germany**<br><br>**There was no funding for the work on this manuscript** | Systematic review of 25 RCTs, with meta-analysis.<br><br>Nine of the RCTs evaluated the biologics of interest to this report.[18] | Data from a total of 11,279 patients with moderate-to-severe psoriasis were involved in the SR.<br><br>The number of patients involved in studies that evaluated treatment of interest | • Adalimumab<br>• Infliximab<br>• Ixekizumab<br>• Secukinumab | *Efficacy – Follow-up at least 24 weeks.*<br>• PASI 75,<br>• PASI 90,<br>• PGA "clear or almost clear",<br>• DLQI<br>*Safety*<br>• AEs,<br>• SAEs,<br>• WDAEs |

| Study citation, country, funding source | Study designs and numbers of primary studies included | Population characteristics | Intervention and comparator(s) [a] | Clinical outcomes, length of follow-up |
|---|---|---|---|---|
| | | to this report was unclear. | | |

[a] All the systematic reviews evaluated more treatments than specified in the inclusion criterial for this Rapid Response report. Only the interventions of interest to this report are listed in this table

AE = adverse events; DLQI = dermatology life quality index; NIHR = National Institute for Health Research; NMA = network meta-analysis; PGA = physician's global assessment; PASI = Psoriasis Area Severity Index; PASI 75 = ≥75% improvement in Psoriasis Area and Severity Index; PASI 90 = ≥90% improvement in Psoriasis Area and Severity Index; PASI 100 = 100% improvement in Psoriasis Area and Severity Index; RCT = randomized controlled trials.

## Table 3: Characteristics of the Included Primary Clinical Study

| Study citation, country, funding source | Study design | Population characteristics | Intervention and comparator(s) | Clinical outcomes, length of follow-up |
|---|---|---|---|---|
| **Reich et al., 2019**[6]<br><br>Canada<br><br>**Funded by AbbVie and Boehringer Ingelheim** | A phase 3, randomized, double-blind, active-comparator-controlled trial completed at 66 clinics in 11 countries (including Canada). | • 605 adult patients with stable (for ≥6 months) moderate-to-severe chronic plaque psoriasis involving at least 10% of the BSA, with a PASI of 12 or higher, and an PGA score of 3 or higher.<br>• The mean age with standard deviation (SD) was 45·3 (13·8) years in the risankizumab group and 47·0 (13·1) years in the adalimumab group. | <u>Part A (16-week double-blind)</u><br>150 mg risankizumab sc. at weeks 0 and 4 versus adalimumab sc. 80 mg at randomization, then 40 mg at weeks 1, 3, and every other week thereafter.<br><u>Part B (week 16 to 44)</u><br>Adalimumab intermediate responders were re-randomized 1:1 to continue 40 mg adalimumab or switch to 150 mg risankizumab. | <u>Part A – week 16 follow-up</u><br><br>*Efficacy*<br>• Co-primary endpoints of PASI 90 and PGA score of 0 or 1<br>• PASI 100<br>• PASI 75<br>• DLQI<br>*Safety*<br>• AEs<br>• SAEs<br>• WDAEs<br><br><u>Part B – week 44 follow-up of re-randomized patients</u><br><br>*Efficacy*<br>• PASI 90<br>• PASI 100<br>• PASI 75<br>• DLQI<br>*Safety*<br>• AEs<br>• SAEs<br>• WDAEs |

AE = adverse events; BSA = body surface area; DLQI = dermatology life quality index; PGA = physician's global assessment; PASI = Psoriasis Area Severity Index; PASI 75 = ≥75% improvement in Psoriasis Area and Severity Index; PASI 90 = ≥90% improvement in Psoriasis Area and Severity Index; PASI 100 = 100% improvement in Psoriasis Area and Severity Index; SD = standard deviation; WDAEs = withdrawal due to adverse events.

# Appendix 3: Critical Appraisal of Included Publications

## Table 4: Strengths and Limitations of Included Systematic Reviews [a] Using AMSTAR 2[13]

| Strengths | Limitations |
|---|---|
| Warren et al., 2020[3] | |
| • A well-defined objective was specified, and the elements of the research question were present.<br>• A systematic search of the OvidSP platform for literature published from 1st January 1990 to 12th December 2018.<br>• The included studies were listed in the references.<br>• Bayesian NMA was used in analysis, applying a random-effect, normal independent model. A fixed-treatment effect NMA was conducted as sensitivity analysis to test the robustness of the findings | • The study protocol was not registered before the review was conducted, and it was unknown if the protocol was established prior to conduct of the review.<br>• The description of the characteristics of the included studies was inadequate.<br>• A list of excluded studies and the reasons for exclusion were not provided.<br>• No information was provided about methods for abstract screening, study selection, and data extraction. Thus, it was unknown whether steps were taken to minimize selection bias and ensure data integrity.<br>• The RoB in individual studies that were included in the review was not assessed.<br>• Heterogeneity and potential for publication bias were not investigated<br>• The potential impact of RoB in individual studies on the results of the NMA was not assessed or accounted for in interpreting the results of the review.<br>• There were no direct active comparisons between the biologics of interest (adalimumab, infliximab, ixekizumab, risankizumab, and secukinumab) to the research question of this Rapid Response report.<br>• The study was sponsored by a pharmaceutical company. All the authors were involved with the pharmaceutical industry in at least two of the following areas: advisory board member, consultant and/or speaker, employee, investigator, and shareholder. |
| Sawyer et al., 2019[4] | |
| • The authors provided a well-defined study objective.<br>• The inclusion criteria and the PICO elements of the research question were clear.<br>• A systematic search was conducted in multiple databases to identify relevant articles published in English from 2000 to 31st August 2016. Database searches were supplemented with searching bibliography review, congress abstract searching and hand searching.<br>• The screening of potentially relevant publications was performed independently in duplicate, with a third reviewer resolving any differences as to eligibility<br>• The characteristics of the individual included studies were provided in tabular form. | • It was unknown if the study protocol was established and registered with an independent research office before conducting the review.<br>• A list of excluded studies was not provided.<br>• It was unclear if data extraction was done in duplicate or extracted data were independently verified.<br>• It was unclear if potential for publication bias in the included studies was investigated, though a study was excluded for having a small sample size.<br>• There were no direct active comparisons between the biologics of interest (adalimumab, infliximab, ixekizumab, risankizumab, and secukinumab) to the research question of this Rapid Response report. |

| Strengths | Limitations |
|---|---|
| • The methodological quality of included studies was assessed using the Cochrane Risk of Bias Tool.<br>• The included studies were assessed for heterogeneity<br>• The authors used appropriate methods **(**Bayesian NMA using both fixed- and random-effects models) for statistical analyses of the results.<br>• The limitations in the individual studies and the methods used to adjust for them were considered in interpreting the results of the review. | • The study was sponsored by a pharmaceutical company. All the authors had been associated with the pharmaceutical industry in at least one of the following areas: consultant, employee, honoraria and/or grant recipient, and investigator. |
| Xu et al., 2019[7] | |
| • The authors provided a well-defined study objective.<br>• The inclusion criteria and the PICO elements of the research question were clear.<br>• A systematic search was conducted in multiple databases from inception to 8th August 2018, and supplemented with manual searches of related bibliographies<br>• Two reviewers independently screened abstracts and selected relevant studies to include in the review. Disputes regarding study eligibility were resolved by consensus or through a third reviewer.<br>• All information and data were extracted independently by two reviewers. Disputes were resolved by consensus or through a third reviewer.<br>• The characteristics of the individual included studies were provided in tabular form.<br>• Cochrane Collaboration's tool was used to assess the risk of bias of eligible studies.<br>• Publication bias was evaluated with the aid of comparison-adjusted funnel plots.<br>• The authors used appropriate methods for statistical analyses of the results (NMA was based on Bayesian framework using a random-effects model).<br>• The limitations in the individual studies and the methods used to adjust for them were considered in discussing the results of the review.<br>• The authors had no conflict of interest to declare and the study received no external funding. | • It was unclear if the study protocol was established and registered with an independent research office conducting the review.<br>• The authors stated that no heterogeneity was observed between the comparisons. However, there was no information about how heterogeneity was assessed.<br>• There were no direct active comparisons between the biologics of interest (adalimumab, infliximab, ixekizumab, risankizumab, and secukinumab) to the research question of this Rapid Response report. |
| Jabbar-Lopez et al., 2017[8] | |
| • The authors provided a well-defined study objective.<br>• The inclusion criteria and the PICO elements of the research question were clear.<br>• The study protocol was established and registered with PROSPERO before conducting the review.<br>• A systematic search was conducted in multiple databases from inception to 17th October 2016.[8]<br>• Two reviewers independently screened abstracts and selected relevant studies to include in the review. Disputes regarding study eligibility were resolved through a third reviewer. | • There were no direct active comparisons between the biologics of interest (adalimumab, infliximab, ixekizumab, risankizumab, and secukinumab) to the research question of this Rapid Response report.<br>• Three of the13 authors were associated with the pharmaceutical industry in at least one of the following areas: consultant, speaker, recipient of research grant. The remaining 10 authors had no conflicts of interest to declare. |

| Strengths | Limitations |
|---|---|
| • The co-authors extracted data using a standardized data extraction tool and the extractions were checked by another.<br>• The characteristics of the individual included studies were provided in tabular form.<br>• A list of excluded studies with the reasons for exclusion were provided.[8]<br>• The methodological quality of included studies was assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[19]<br>• Heterogeneity was assessed using visual inspection of the forest plots.<br>• Publication bias was evaluated with the aid of comparison-adjusted funnel plots.<br>• The authors used appropriate methods (random-effects model within a frequentist approach) for statistical analyses of the results.<br>• The limitations in the individual studies and the methods used to adjust for them were considered in discussing the results of the review.<br>• The systematic review and NMA were supported by the British Association of Dermatologists to inform the next update to the clinical guidelines for biologic therapy for psoriasis. | |
| Nast et al., 2015[9] | |
| • The authors provided a well-defined study objective and the PICO elements of the research question were clear.<br>• A systematic search was conducted in multiple databases from inception to 5th January 2015. The databases searches were supplemented by screening the reference lists of relevant reviews and included studies.<br>• Study selection, data extraction, and quality assessment were performed independently by two assessors, with differences solved by consensus.<br>• A list of excluded studies with the reasons for exclusion were provided.[18]<br>• The methodological quality of included studies was assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[19] Also, the quality of the available evidence was summarized for the outcome in each comparison using the GRADE approach.[20]<br>• Heterogeneity was assessed and inconsistencies among estimates were quantified using the $I^2$ test.<br>• The authors graded the likelihood of publication bias for each outcome, however, the method used was not specified.<br>• The statistical analysis used appropriate methods, applying a random-effects model to pool estimates of the individual studies in the meta-analysis. | • It was unknown if the study protocol was established and registered with an independent research office before conducting the review.<br>• There were no direct active comparisons between the biologics of interest (adalimumab, infliximab, ixekizumab, risankizumab, and secukinumab) to the research question of this Rapid Response report.<br>• One of the four authors received honoraria for continuous medical education certified educational talks that received direct or indirect sponsoring pharmaceutical industry. This was unlikely to have any impact on the study. The remaining three authors had no conflicts of interest to declare. |

| Strengths | Limitations |
|---|---|
| • The limitations in the individual studies and the methods used to adjust for them were considered in discussing the results of the review. | |

[a] The network meta-analyses portions of systematic reviews were critically appraised separately in the next table.

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2; GRADE = Grading of Recommendations Assessment, Development and Evaluation; RoB = risk of bias.

## Table 5: Strengths and Limitations of Included Network Meta-Analyses Using the ISPOR Questionnaire[14,21]

| Item | Authors of Network Meta-Analyses | | | |
|---|---|---|---|---|
| | Warren et al., 2020[3] | Sawyer et al., 2019[4] | Xu et al., 2019[7] | Jabbar-Lopez et al., 2017[8] |
| Relevance | | | | |
| 1. Is the population relevant? | Yes | Yes | Yes | Yes |
| 2. Are any critical interventions missing? | No | Yes (no RIS) | Yes (no RIS) | Yes (no RIS) |
| 3. Are any relevant outcomes missing? | Yes (no AE data) | Yes (no AE and QoL data) | No | No |
| 4. Is the context (e.g., settings and circumstances) applicable to your population? | Can't answer, NR | Can't answer, NR | Can't answer, NR | Can't answer, NR |
| Credibility | | | | |
| 5. Did the researchers attempt to identify and include all relevant randomized controlled trials? | Yes | Yes | Yes | Yes |
| 6. Do the trials for the interventions of interest form one connected network of randomized controlled trials? | Yes | Yes | Yes | Yes |
| 7. Is it apparent that poor quality studies were included thereby leading to bias? | No | No | No | No |
| 8. Is it likely that bias was induced by selective reporting of outcomes in the studies? | No | No | No | No |
| 9. Are there systematic differences in treatment effect modifiers (i.e. baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network? | Can't answer, NR | Can't answer, insufficient information | Can't answer, NR | Can't answer, NR |
| 10. If yes (i.e. there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results? | Not applicable | Not applicable | Not applicable | Not applicable |

| Item | Authors of Network Meta-Analyses | | | |
|---|---|---|---|---|
| | Warren et al., 2020[3] | Sawyer et al., 2019[4] | Xu et al., 2019[7] | Jabbar-Lopez et al., 2017[8] |
| Analysis | | | | |
| 11. Were statistical methods used that preserve within-study randomization? (No naïve comparisons) | Yes | Yes | Yes | Yes |
| 12. 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? | No | Yes | Yes | Yes |
| 13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis? | Can't answer, NR | Yes | Yes | Yes |
| 14. 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? | Can't answer, NR | Not applicable | Not applicable | Not applicable |
| 15. Was a valid rationale provided for the use of random effects or fixed effect models? | No | Yes | No | No |
| 16. If a random effects model was used, were assumptions about heterogeneity explored or discussed? | No | Yes | Can't answer, insufficient information | Yes |
| 17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed? | Not applicable | No (rather, some studies were excluded) | Not applicable | Yes |
| 18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison? | Yes | Yes | Yes | Yes |
| 19. Are the individual study results reported? | No | Yes | Yes | Yes |
| 20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis? | No | Yes | No | Yes |
| 21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty? | Yes | Yes | Yes | Yes |
| 22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome? | Yes | Yes | Yes | Yes |
| 23. Is the impact of important patient characteristics on treatment effects reported? | Yes | No | No | Yes |
| Interpretation | | | | |
| 24. Are the conclusions fair and balanced? | Yes | Yes | Yes | Yes |

| Item | Authors of Network Meta-Analyses | | | |
|---|---|---|---|---|
| | Warren et al., 2020[3] | Sawyer et al., 2019[4] | Xu et al., 2019[7] | Jabbar-Lopez et al., 2017[8] |
| Conflict of Interest | | | | |
| 25. Were there any potential conflicts of interest? | Yes | Yes | No | Yes |
| 26. If yes, were steps taken to address these? | No | No | Not applicable | No |

AE = adverse event; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; QoL = quality of life; RCT = randomized controlled trial; RIS = risankizumab.

## Table 6: Strengths and Limitations of Included Primary Clinical Study Using the Downs and Black Checklist[15]

| Strengths | Limitations |
|---|---|
| Reich et al., 2019[6] | |
| • A phase 3 randomized, double-blind, double-dummy, active-comparator trial done at 66 sites in 12 countries, including Canada. Thus, the study design minimizes risk of bias and the multiple countries and sites of study suggest a good generalizability.<br>• The objectives of the study and patients' characteristics were well-defined.<br>• The interventions of interest (risankizumab and adalimumab) were described, providing details about route of administration, doses given, and periods of follow-up.<br>• The main outcomes to be measured and the findings of the study were described.<br>• The outcome measures (PASI 75, PASI 90, PGA, and DLQI) are validated and widely used in clinical research.<br>• The statistical tests used to assess the main outcomes was appropriate<br>• Calculations were performed to determine that the sample sizes had 90% power, assuming 70% of patients in the risankizumab and 50% of patients in the adalimumab groups would achieve the primary end point of PASI 90.<br>• The estimates for the main outcomes were reported along with corresponding random variability data, and actual probability values were reported<br>• Adverse events were assessed and reported for the two arms of the study.<br>• The number of patients lost to follow-up in each arm of the study was low (≤2 in in both part A and part B) and similar across the study groups.<br>• Missing efficacy data were handled using non-responder imputation for categorical variables and last observation carried forward for continuous variables. | • No information was provided about compliance with the allocated treatment. However, a previous CADTH CDR[17] that included this RCT[6] and three others in assessing the effectiveness of risankizumab for psoriasis, reported that "adherence was generally high throughout each study and well balanced across treatment groups; it was therefore unlikely to create bias in favour of any treatment."<br>• Patients enrolled in part B of the study had achieved intermediate response to adalimumab during the first phase of the trial which lasted 16 weeks. Thus, the re-randomization of these patients to either adalimumab or risankizumab could have resulted in selection bias in favour of risankizumab concerning the week-44 results.<br>• The study duration was not enough for long-term safety and effectiveness.<br>• The study was sponsored by a pharmaceutical company that contributed to study design and participated in data collection, data analysis and interpretation, as well as the writing, review, and approval of the manuscript. |

CDR = Common Drug Review; DLQI = Dermatology Life Quality Index; PASI = Psoriasis Area and Severity Index; PGA = static Physician's Global Assessment.

# Appendix 4: Main Study Findings and Authors' Conclusions

## Table 7: Summary of Findings Included Systematic Reviews and Network Meta-Analyses

| Main study findings | Authors' conclusion |
|---|---|
| **Warren et al., 2020[3]** | |
| 1. For PASI scores, the placebo-anchored Bayesian NMA showed the following relative treatment effects at 12 weeks for the different biologic agents in patients with moderate-to-severe psoriasis.<br><br>**PASI 75**<br>Biologic agent — RTE (95% CrI)<br>IXE — 0.85 (0.825, 0.866)<br>RIS — 0.80 (0.752, 0.839)<br>SEC — 0.76 (0.740, 0.789)<br>INF — 0.75 (0.715, 0.793)<br>ADA — 0.63 (0.604, 0.662)<br><br>**PASI 90**<br>Biologic agent — RTE (95% CrI)<br>IXE — 0.70 (0.671, 0.720)<br>RIS — 0.62 (0.577, 0.665)<br>SEC — 0.59 (0.558, 0.615)<br>INF — 0.57 (0.511, 0.634)<br>ADA — 0.37 (0.343, 0.399)<br><br>**PASI 100**<br>Biologic agent — RTE (95% CrI)<br>IXE — 0.38 (0.359, 0.408)<br>RIS — 0.31 (0.267, 0.344)<br>SEC — 0.29 (0.262, 0.316)<br>INF — NR<br>ADA — 0.13 (0.114, 0.152)<br><br>2. For DLQI (0,1), the placebo-anchored BNMA showed the following relative treatment effects at 12 weeks for the different biologic agents in patients with moderate-to-severe psoriasis:<br><br>**DLQI (0,1)**<br>Biologic agent — RTE (95% CrI)<br>IXE — 0.57 (0.533, 0.612)<br>RIS — NR<br>SEC — 0.53 (0.497, 0.567)<br>INF — NR<br>ADA — 0.18 (0.101, 0.260) | Overall, the NMA results show that among the biologic agents of interest to this report, ixekizumab was the most effective for skin clearance and quality of life improvement for patients with moderate- to-severe psoriasis within 12 weeks, whereas adalimumab was the least effective in all the comparisons. No data were reported for both infliximab and risankizumab in the DLQI (0,1) and for infliximab alone in the PASI 100 comparisons. |
| **Sawyer et al., 2019[4]** | |
| 1. The median RR (95% CrI) for PASI scores from induction phase placebo control NMA of 52-week RCTs indirectly comparing biologic agents in patients with moderate-to-severe psoriasis was as follows: | Analysis based on PASI scores demonstrated that ixekizumab was the most efficacious to treat moderate-to-severe psoriasis followed by secukinumab, infliximab, and adalimumab in that order. |

| Main study findings | Authors' conclusion |
|---|---|
| **PASI 75**<br>ITC — Median RR (95% CrI)<br>ADA vs. INF — 0.96 (0.57 to 1.39)<br>IXE vs. ADA — 1.22 (0.96 to 2.38)<br>SEC vs. ADA — 1.19 (0.95 to 2.26)<br><br>**PASI 90**<br>ITC — Median RR (95% CrI)<br>ADA vs. INF — 0.93 (0.46 to 1.6)<br>IXE vs. ADA — 1.38 (0.94 to 3.28)<br>SEC vs. ADA — 1.32 (0.91 to 3.05)<br><br>**PASI 100**<br>ITC — Median RR (95% CrI)<br>ADA vs. INF — 0.90 (0.34 to 1.98)<br>IXE vs. ADA — 1.67 (0.9 to 5.1)<br>SEC vs. ADA — 1.56 (0.86 to 4.58) | |

Xu et al., 2019[7]

**Efficacy**

1. **From the NMA, results of achieving PASI at the various limits are as follows**

| ITC vs. PBO | ORs (95% CrI) | | |
|---|---|---|---|
| | **PASI 75** | **PASI 90** | **PASI100** |
| ADA | 28 (21, 35) | 30 (22, 43) | 24 (14, 42) |
| INF | 250 (66, 1200) | 190 (26, 4200) | 22 (1.5, 1100) |
| IXE | 100 (78, 140) | 120 (89, 180) | 71 (42, 120) |
| SEC | 92 (69, 130) | 100 (69, 150) | 64 (40. 110) |

2. **From the NMA, results for PGA and DLQI are as follows**

| ITC vs. PBO | ORs (95% CrI) | |
|---|---|---|
| | **PGA** | **DLQI** |
| ADA | 11 (6.2 to 17) | 16 (9.0, 30) |
| INF | 40 (9.1 to 180 | NR |
| IXE | 87 (52 to 140) | 22 (14, 36) |
| SEC | NR | 49 (24, 100) |

**Safety**

The odds of getting an infection, a headache, or AEs leading to withdrawal of study agent or discontinuation of the study drug are shown below:

The PASI, PGA and DLQI scores from the NMA show that compared to infliximab, ixekizumab, or secukinumab, adalimumab has lower effectiveness in treating patients with moderate-to-severe psoriasis. Overall, ixekizumab was the most effective for skin clearance, whereas secukinumab was the most effective for quality of life improvement. The risk of headache, infections, and AEs leading to withdrawal of study agent or discontinuation of the study drug were lowest with adalimumab, Infliximab, and secukinumab, respectively.

| Main study findings | Authors' conclusion |
|---|---|

| ITC vs. PBO | ORs (95% CrI) | | |
|---|---|---|---|
| | **Infection** | **Headache** | **Discontinuation** |
| ADA | 1.3 (1.10, 1.5) | 1.20 (0.71, 1.9) | 0.87 (0.48, 1.6) |
| INF | 1.10 (0.71, 1.6) | 2.60 (1.20, 6.1) | NR |
| IXE | 1.40 (1.10, 1.9) | 1.60 (1.00, 2.5) | 1.60 (0.70, 3.6) |
| SEC | 1.30 (0.68, 1.8) | 1.40 (0.68, 2.8) | 0.62 (0.14, 2.5) |

**Jabbar-Lopez et al., 2017[8]**

At 12 to 16 weeks the NMA results were:

1. **PGA (0 or 1)**

| ITC | OR (95% CI) |
|---|---|
| INF vs. ADA | 4.08 (1.69, 9.88) |
| IXE vs. ADA | 2.86 (1.30, 6.27) |
| SEC vs. ADA | 0.98 (0.43, 2.26) |

2. **Mean change in DLQI**

| ITC | OR (95% CI) |
|---|---|
| INF vs. ADA | –1.13 (–3.15, 0.90) |
| IXE vs. ADA | –0.76 (–2.98, 1.46) |
| SEC vs. ADA | –1.30 (–3.28, 0.69) |

3. **Withdrawal due to adverse events**

| ITC | OR (95% CI) |
|---|---|
| INF vs. ADA | 4.08 (1.69, 9.88) |
| IXE vs. ADA | 2.86 (1.30, 6.27) |
| SEC vs. ADA | 0.98 (0.43, 2.26) |

- Overall, the results of the analyses demonstrated that ixekizumab had the most efficacy for the treatments for skin psoriasis followed in order by secukinumab, infliximab, and adalimumab.
- "Ixekizumab, while the most efficacious treatment in terms of clear/nearly clear, was relatively less well tolerated than placebo, adalimumab, or secukinumab."[8] (*p1651*)

**Nast et al., 2015[9]**

The pooled RR (95% CI) for PASI and PGA 'clear/almost clear'. scores at weeks 24 to 28 from the meta-analysis of studies on biologic agents in patients with moderate-to-severe psoriasis was as follows:

1. **PASI 75**

| Biologic agent | RR (95% CI) | Number of studies ($I^2$) | Quality of evidence |
|---|---|---|---|
| INF | 13.07(8.60, 19.87), | 6 (0%) | Low |
| SEC | 11.97 (8.83, 16.23) | 1 (0%) | Low |
| ADA | 8.92 (6.33, 12.57) | 3 (8%) | Low |

2. **PASI 90**

| Biologic agent | RR (95% CI) | Number of studies ($I^2$) | Quality of evidence |
|---|---|---|---|

The analysis showed that infliximab and secukinumab, were more efficacious than adalimumab for long-term treatments in patients with moderate-to-severe psoriasis. No significant differences were observed in safety parameters between adalimumab or infliximab versus placebo. Safety data were not reported for secukinumab.

| Main study findings | Authors' conclusion |
|---|---|

| | | | |
|---|---|---|---|
| INF | 31.00 (13.45, 71.46) | 6 (0%) | Low |
| SEC | 40.15 (20.97, 76.89) | 1 (0%) | Low |
| ADA | 23.17 (12.51, 42.91) | 3 (0%) | Low |

**3. PGA 'clear/almost clear'**

| Biologic agent | RR (95% CI) | Number of studies ($I^2$) | Quality of evidence |
|---|---|---|---|
| INF | 13.13 (8.45, 20.38), | 5 (0%) | Low |
| SEC | 9.84 (7.25, 13.36) | 1 (0%) | Low |
| ADA | 8.06 (5.89, 11.04) | 3 (0%) | Low |

4. **DLQI**

| Biologic agent | MD (95% CI) | Number of studies | Quality of evidence |
|---|---|---|---|
| INF | 9.80 (8.19, 11.41), | 2 | High |
| ADA | 4.20 (1.54, 6.86) | 1 | Low |

**Safety**

The number of patients with at least one AE, or one SAE, or WDAE was not different between adalimumab and placebo or infliximab and placebo as shown below:

| | RR (95% CI) | Number of studies, | Quality of evidence |
|---|---|---|---|
| **1. Patients with ≥1 AEs** | | | |
| ADA vs. PBO | 1.04 (0.93, 1.16), | 1 | Moderate |
| INF vs. PBO | 1.15 (0.99, 1.34) | 2 | Moderate |
| **2. Patients with ≥1 SAE** | | | |
| ADA vs. PBO | 0.75 (95% CI: 0.14, 3.95), | 1 | Low |
| INF vs. PBO | 2.16 (0.65, 7.17) | 3 | Moderate |
| **3. ≥1 WDAE** | | | |
| ADA vs. PBO | 0.87 (0.24, 3.23) | 1 | Low |
| INF vs. PBO | 1.38 (0.55, 3.46) | 2 | Moderate |

ADA = adalimumab; AE = adverse event; CI = confidence interval; CrI = credible interval; DLQI (0,1) = Dermatology Life Quality Index (no effect/no impact on patient's life); ES = effect estimate; INF = infliximab; ITC = indirect treatment comparison; IXE ixekizumab; NA = not applicable; NMA = network meta-analysis; NR = not reported; NS = non-significant; PASI = psoriasis area and severity index; PASI 100 = 100% improvement in PASI score; PASI 90 = 90% improvement in PASI score; PASI 75 = 75% improvement in PASI score; PBO = placebo; PGA = physician's global assessment; PGA (0 or 1) = PGA (clear or nearly clear); RIS = risankizumab; RTE = relative treatment effect; RR = risk ratio; SAE = serious adverse event; SEC = secukinumab; vs. = versus; SUCRA = Surface under cumulative ranking curve; WDAE = withdrawal due to adverse event.

## Table 8: Summary of Findings of the Included Primary Clinical Study

| Main study findings | Authors' conclusion |
|---|---|
| Reich et al., 2019[6] | |
| The re-randomization of patients with intermediate response to adalimumab in Part A to either continue adalimumab or risankizumab in Part B may have introduced selection bias in favour of risankizumab, which may explain the bigger differences in outcomes between drugs in Part B compared to Part A.<br><br>Part A – results at week 16 after initial randomization<br><br>1. Skin clearance as measured by PASI and PGA (0, 1) scores<br><br>**a.** PASI 90 and PGA<br>• 72% of patients in the RIS group achieved PASI 90 versus 47% in the ADA group.<br>  ○ The adjusted absolute difference 24.9% (95% CI, 17.5 to 32.4; p<0.0001)<br>• 84% of patients in the RIS group achieved PGA scores of 0 or 1 (i.e., clear or almost clear) versus 60% in the ADA group<br>  ○ The adjusted absolute difference was 23.3% (95% CI, 16.6 to 30.1; p<0.0001).<br><br>**b.** PASI100 and PGA<br>• 40% of patients in the RIS group achieved PASI 100 versus 23% in the ADA group.<br>  ○ The adjusted absolute difference was 16.7% (95% CI, 9.5 to 29.3; p<0·0001).<br>• 41% of patients in the RIS group achieved PGA clear or almost clear versus 23% in the ADA group.<br>  ○ The adjusted absolute difference was 17.7% (95% CI, 10.4 to 24.9; p<0.0001).<br><br>**c.** PASI 75 and PGA<br>• 91% of patients in the RIS group achieved PASI 75 versus 72% in the ADA group.<br>  ○ The adjusted absolute difference was 18.9% (95% CI, 13.0 to 24.9; p<0.0001)<br>• A corresponding PGA scores of 0 or 1 were not reported.<br><br>2. Psoriasis-related quality of life improvement outcomes at 16 weeks as measured by DLQI scores of 0 or 1 (i.e., no effect on the patient's life)<br>• 66% of patients in the RIS group achieved PASI 100 versus 49% in the ADA group. The difference was statistically significant (p<0.0001).<br>3. Safety<br>• The number of patients with any AE was similar in both RIS and ADA groups (168 [56%] vs. 173 [57%], respectively). | • The PASI and DLQI scores demonstrated that treatment with risankizumab resulted in significantly greater efficacy in skin clearance and improvement in quality of life over adalimumab in patients with moderate-to-severe chronic plaque psoriasis. The frequencies of adverse events were low for both risankizumab and adalimumab, and not statistically different between the two groups.<br>• "Treatment decisions are complex and individualized, and these data are not intended to suggest that patients should be switched from adalimumab to risankizumab if physicians are satisfied with results achieved for patients while they are on adalimumab. For patients who do not respond adequately to adalimumab, however, these data support that patients can be switched to risankizumab after 16 weeks without undergoing a washout period and that this switch might result in improved efficacy with no additional safety risk."[6] (*p585*) |

| Main study findings | Authors' conclusion |
|---|---|
| • The most frequently reported AE was infection, occurring in 88 (29%) patients treated with RIS and 74 (24%) patients treated with ADA.<br>• The number of patients with SAE was similar with RIS as with ADA (10 [3%] vs. 9 [3%], respectively).<br>• Adverse event leading to drug discontinuation was similar in both RIS and ADA groups (4 [1%] vs. 6 [2%], respectively)<br><br>Part B (results at week 44 among patients with intermediate response (defined as PASI ≥50 to PASI <90) after 16 weeks of adalimumab treatment who were rerandomized were as follows:<br>1. Skin clearance as measured by PASI and PGA (0, 1) scores<br><br>**a.** PASI 90 and PGA<br>• 66% of patients rerandomized to RIS achieved PASI 90 versus 21% rerandomized to continue ADA.<br>  ○ The adjusted absolute difference 45.0% (95% CI, 28.9 to 61.1; p<0.0001).<br>• 74% of patients in the RIS group achieved PGA clear or almost clear versus 34% in the ADA group<br>  ○ The adjusted absolute difference was 38.9% (95% CI, 22.0 to 55.8; p<0.0001).<br><br>**b.** PASI 100 and PGA<br>• 40% of patients in the RIS group achieved PASI 100 versus 7% of in the ADA group.<br>  ○ The adjusted absolute difference was 32.8% (95% CI, 18.8 to 46.9; p<0·0001).<br>• 40% of patients in the RIS group achieved PGA clear or almost clear versus 7% in the ADA group.<br>  ○ The adjusted absolute difference was 32.8% (95% CI, 18.8 to 46.9; p<0.0001).<br><br>**c.** PASI 75 and PGA<br>• 91% of patients in the RIS group achieved PASI 75 versus 46% of in the ADA group.<br>  ○ The adjusted absolute difference was 18.9% (95% CI, 29.2 to 59.2; p<0.0001)<br>• A corresponding PGA scores of 0 or 1 were not reported.<br><br>2. DLQI scores of 0 or 1 (i.e., no effect on the patient's life)<br>• 66% of patients in the RIS group achieved PASI 100 versus 29% in the ADA group. The difference was statistically significant (p<0.0001)<br><br>3. Safety<br>• The percentage of re-randomized patients with any AE from week 16 up until week 44 was nominally | |

| Main study findings | Authors' conclusion |
|---|---|
| higher in RIS group (75%) than the ADA groups (66%).<br>• However, the percentage of patient with AE at week 44 as accessed by the initial treatment assignment was similar between the RIS and ADA groups (64% vs. 66%, respectively).<br>• The most frequently reported AE was infection, occurring in 25 (47%) patients re-randomized to receive RIS and 18 (32%) patients re-randomized to continue ADA.<br>• The percentage of patient with SAE at week 44 as accessed by the initial treatment assignment was the same for the RIS and ADA groups (4% in each group)<br>• The number of patients with SAE was similar with RIS as with ADA (3 [6%] vs. 2 [4%], respectively).<br>• Among the patients re-randomized to receive RIS b, there was no drug discontinuation due to AEs. Three patients (5%) re-randomized to continue ADA experienced AEs leading to drug discontinuation. | |

ADA = adalimumab; AE = adverse event; CI = confidence interval; DLQI (0,1) = Dermatology Life Quality Index (no effect/no impact on patient's life); OR = odds ratio; PASI = psoriasis area and severity index; PASI 100 = 100% improvement in PASI score; PASI 90 = 90% improvement in PASI score; PASI 75 = 75% improvement in PASI score; PGA = physician's global assessment; PGA (0 or 1) = PGA (clear or nearly clear); RIS = risankizumab; SAE = serious adverse event; vs. = versus; WDAE = withdrawal due to adverse event.

# Appendix 5: Overlap between Included Systematic Reviews

## Table 9: Overlap in Relevant Primary Studies between Included Systematic Reviews

| Primary study citation | Systematic review citation | | | | |
|---|---|---|---|---|---|
| | Warren et al., 2020[3] | Sawyer et al., 2019[4] | Xu et al 2019 | Jabbar-Lopez et al., 2017[8] | Nast et al., 2015[9] |
| Paul et al., 2019[22] | X | | | | |
| Bagel et al., 2018[23] | X | | | | |
| Gordon et al., 2018[24] | X | | | | |
| Langley et al., 2018[25] | X | | | | |
| Blauvelt et al., 2017[26] | X | | X | | |
| Cai et al., 2017[27] | X | | X | X | |
| Lacour et al, 2017[28] | | X | | | |
| Reich et al., 2017[29] | X | | X | | |
| Reich et al., 2017[30] | X | | | | |
| Augustin et al., 2016[31] | | | X | | |
| Blauvelt et al. 2016[32] | | | X | | |
| Gordon et al., 2016[33] | X | X | X | X | |
| Gottlieb et al. 2016[34] | | X | | X | |
| Mease et al., 2016[35] | | | X | | |
| Blauvelt et al., 2015[36] | X | X | X | X | |
| Gordon et al., 2015[37] | | X | X | X | |
| Griffiths et al., 2015[38] | X | X | X | | |
| Paul et al., 2015[39] | X | X | X | X | |
| Thaçi et al., 2015[40] | X | X | X | | |
| Langley et al., 2014[41] | X | X | X | X | X |
| Ohtsuki et al., 2014[42] | | | X | X | |
| Papp et al., 2013[43] | | | X | | |
| Rich et al. 2013[44] | | | X | X | |
| Leonardi et al., 2012[45] | | | X | X | |
| Yang et al., 2012[46] | | | | X | X |
| Asahina et al, 2010[47] | | | X | X | X |
| Torii et al 2010[48] | | X | X | | X |
| Feldman et al 2008[49] | | | X | | |
| Menter et al., 2008[50] | X | | X | X | X |
| Saurat et al., 2008[51] | X | | | X | |
| Menter et al., 2007[52] | X | X | X | X | X |

| Primary study citation | Systematic review citation | | | | |
|---|---|---|---|---|---|
| | Warren et al., 2020[3] | Sawyer et al., 2019[4] | Xu et al 2019 | Jabbar-Lopez et al., 2017[8] | Nast et al., 2015[9] |
| Revicki et al., 2007[53] | | | X | | |
| Shikiar et al., 2007[54] | | | | | |
| Gordon et al., 2006[55] | | X | X | X | X |
| Reich et al., 2006[56] | | X | | | X |
| Feldman et al. 2005[57] | | | X | | |
| Reich et al., 2005[58] | X | X | X | X | X |
| Chaudhari et al 2001[59] | | | X | | |