An update report on Janus kinase-inhibitors and monoclonal antibodies for the treatment of moderate to severe atopic eczema for Universitätsklinikum Schleswig-Holstein/Campus Kiel

Kleijnen Systematic Reviews Ltd

April 2022

Kleijnen Systematic Reviews Ltd
Unit 6, Escrick Business Park
Riccall Road
Escrick
York
YO19 6FD
United Kingdom
Telephone: +44 (0)1904 727980
Fax: +44 (0)1904 720429
Email: robert@systematic-reviews.com
Website: www.systematic-reviews.com

Pawel Posadzki
Jennifer Freyman
Steven Duffy
Jos Kleijnen
Robert Wolff

CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AE	Adverse events
CDSR	Cochrane Database of Systematic Reviews
CI	Confidence interval
CrI	Credible interval
CRD	Centre for Reviews and Dissemination
DARE	Database of Abstracts of Reviews of Effects
DLQI	Dermatology Life Quality Index
EQ-5D	EuroQol 5-dimension questionnaire
FAQ	Frequently asked question
IQWiG	Institute for Quality and Efficiency in Health Care
JAK	Janus kinase(s)
KSR	Kleijnen Systematic Reviews
MA	Meta-analysis
MAB	Monoclonal antibodies
MD	Mean difference
N/A	Not applicable
NMA	Network meta-analysis
NR	Not reported
OR	Odds ratio
PICOS	Participants, intervention, comparators, outcomes, and study design
POEM	Patient Oriented Eczema Measure
PRISMA	Preferred Reporting of Systematic Reviews and Meta-Analyses
QOL	Quality of life
RCT	Randomised controlled trial
RD	Risk difference
RR	Risk ratio
SDM	Shared decision making
SD	Standard deviation
SAE	Serious adverse events
SMD	Standardised mean difference
SR	Systematic review
TRAE	Treatment-related adverse events
UKSH	Universitätsklinikum Schleswig-Holstein

1. PROJECT OBJECTIVES

A key aim of the research project "Making SDM a reality" is to inform patients as part of shared decision making (SDM).

Kleijnen Systematic Reviews (KSR) Ltd has prepared an evidence report with a synthesis of the evidence of the treatment options for moderate to severe atopic eczema/neurodermatitis (ND) herein reported interchangeably.

2. METHODS

2.1 INCLUSION CRITERIA

The frequently asked questions (FAQs) underpinning the literature searches were developed in collaboration with clinicians at the Universitätsklinikum Schleswig-Holstein (UKSH)/Campus Kiel. Randomised controlled trials evaluated herein will aim to inform patients, clinicians, researchers, and health policy makers on relevant evidence relating to the treatment options for ND. Table 1 refers to the relevant characteristics of participants, interventions, comparators, outcomes, and study designs (PICOS) that underpins FAQ outlined below.

Table 1: Inclusion and exclusion criteria

	Included	Excluded
Population	Adult patients with moderate-to-severe atopic eczema (atopic dermatitis)*	Adolescents or children as the primary participants. Studies including mixed population of different dermatologic conditions without a separate analysis limited to adults with moderate to severe atopic eczema.
Intervention	Baricitinib, Upadacitinib Abrocitinib Tralokinumab	Treatments other than the listed
Comparator	Placebo	N/A
Outcomes	• Patient-reported outcome measures • Clinician-assessed outcome measures • Quality of life • Adverse-effects**	N/A
Study design	Systematic reviews, clinical practice guidelines	Randomised trials, narrative reviews, expert opinions, letters, overviews of reviews

N/A = not applicable.
* = There is no established definition of moderate-to-severe AD, so studies will be eligible if the population is limited to ''patients with moderate-to-severe AD,'' ''patients with non-adequately controlled AD despite the use of topical anti-inflammatory therapy,'' or patients with moderate-to-severe AD according to severity criteria, such as Rajka and Langeland score > 4.52, SCORAD score > 20%, total body surface area > 10%, Pruritus numerical rating scale score ≥ 4, Physician's global assessment score ≥ 3, or Dermatology Life Quality Index score ≥ 10 (Roekevisch 2014, Lynde 2018). ** = The list is not exhaustive

2.2 FREQUENTLY ASKED QUESTIONS

The following FAQs were identified:

1. What does the treatment involve?
2. Will my skin and symptoms improve?
3. Will my quality of life improve?

4. What are the risks or side effects?
5. What if I am pregnant or want to get pregnant?

2.3 LITERATURE SEARCHES

Literature searches were conducted to identify systematic reviews and evidence-based guidelines about baricitinib, upadacitinib, abrocitinib and tralokinumab for neurodermatitis/atopic eczema.

The search strategies were developed specifically for each database and the keywords adapted according to the configuration of each database. Searches were not limited by date, language or publication status.

2.4 SEARCH SOURCES

2.4.1 Systematic reviews and guidelines

The following systematic review and health technology assessment specific databases were searched:

- Cochrane Database of Systematic Reviews (CDSR) (Wiley): issue 2 of 12, February 2022
- KSR Evidence (Internet) (https://ksrevidence.com/): up to 22 February 2022
- Epistemonikos (Internet) (https://www.epistemonikos.org/): up to 22 February 2022
- International HTA Database (INAHTA) (https://database.inahta.org/): up to 22 February 2022

The following guidelines resources were searched:

- Guidelines International Network (GIN) (Internet) (https://www.g-i-n.net/home): up to 22 February 2022
- NICE Evidence (Internet) (www.evidence.nhs.uk/): up to 22 February 2022
- NICE Guidance (Internet) (https://www.nice.org.uk/guidance): up to 22 February 2022
- ECRI Guidelines Trust (Internet) (https://guidelines.ecri.org/): up to 22 February 2022
- Trip Database (https://www.tripdatabase.com/): up to 22 February 2022
- Canadian Agency for Drugs and Technologies in Health (CADTH) (www.cadth.ca): up to 22 February 2022

Full details of all search strategies are presented in Appendix 1.

2.4.2 Handling of citations

References identified from the searches were downloaded into EndNote bibliographic management software for further assessment and handling.

2.4.3 Supplementary searches

The bibliographies of included studies and review articles were also checked for additional relevant articles.

UPDATE – Concluding Assessment by SHARE TO CARE Evidence Team (18/08/22)

Due to new drugs that have been approved for neurodermatitis, we carried out an update search, presented in this report (KSR Ltd in April 2022). The decision aid has been revised accordingly, i.e., we incorporated the additional information on tralokinumab and the group of JAK-inhibitors, whereas the drugs already included in the current decision aid (immunosuppressants, dupilumab, systemic corticosteroids) were not updated because the corresponding systematic search was conducted less than 18 months ago.

The update report is based on systematic reviews and guidelines, therefore single RCTs are not included. But as the follow-up-time in systematic reviews for tralokinumab was only up to 16 weeks, we added data on responses at week 52 from Wollenberg *et al.* 2021, as well as recent comparative data for JAK-inhibitors from Bieber *et al.* 2021 and Blauvelt *et al.* 2021 (time to symptom improvement from baseline). These studies will be fully considered as part of the next update of the evidence report.

Wollenberg, A., Blauvelt, A., Guttman-Yassky, E., Worm, M., Lynde, C., Lacour, J. P., et al. ECZTRA 1 and ECZTRA 2 study investigators. Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2). The British journal of dermatology 2021;184(3), 437–449. https://doi.org/10.1111/bjd.19574

Bieber, T., Simpson, E. L., Silverberg, J. I., Thaçi, D., Paul, C., Pink, A. E., et al. Abrocitinib versus Placebo or Dupilumab for Atopic Dermatitis. The New England journal of medicine 2021;384(12), 1101–1112. https://doi.org/10.1056/NEJMoa2019380

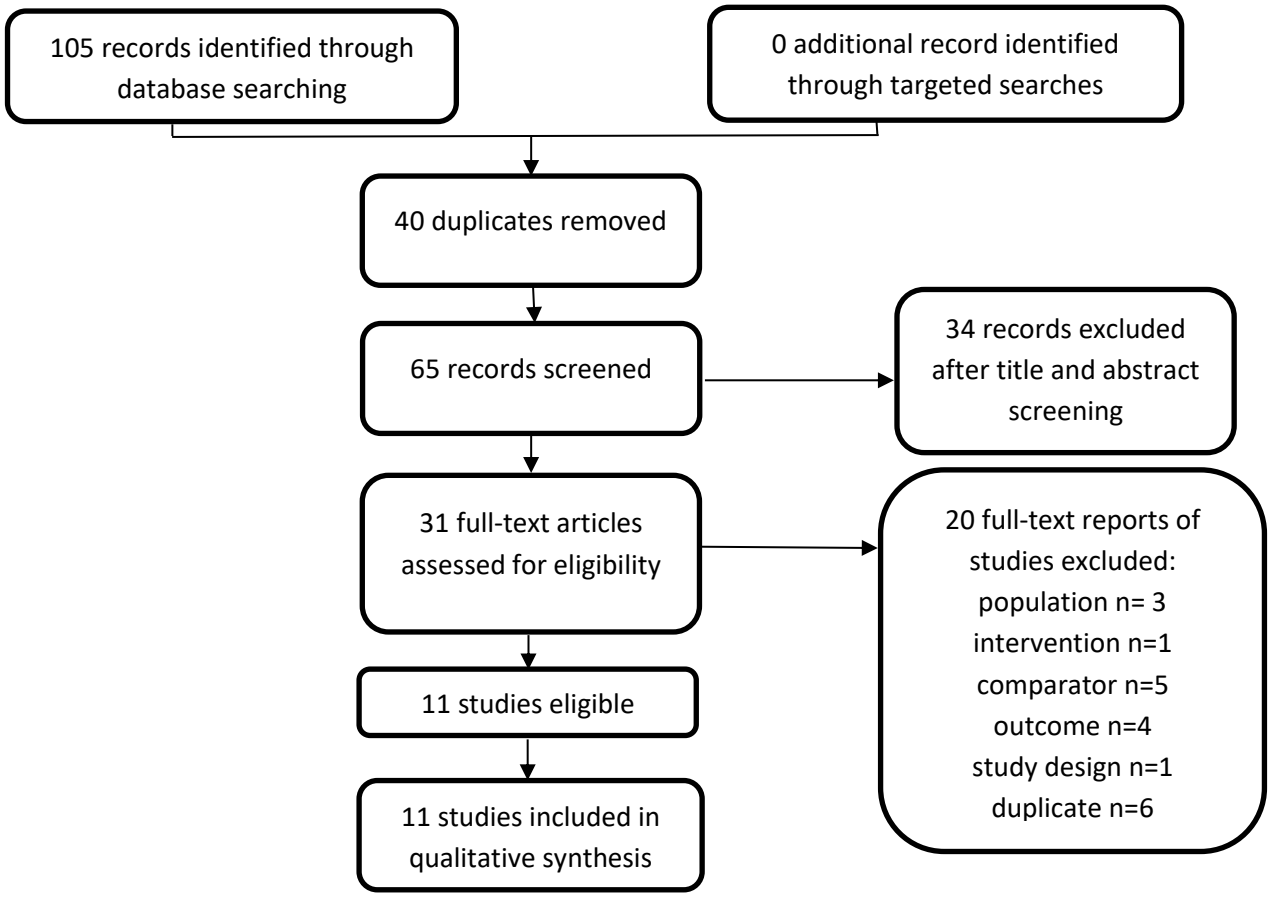
Blauvelt, A., Teixeira, H. D., Simpson, E. L., Costanzo, A., De Bruin-Weller, M., Barbarot, S. et al. Efficacy and Safety of Upadacitinib vs Dupilumab in Adults With Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial. JAMA dermatology 2021;157(9), 1047–1055. https://doi.org/10.1001/jamadermatol.2021.3023

3. RESULTS

3.1 LITERATURE SEARCHES AND INCLUSION ASSESSMENT

The original EBSCO searches were conducted between 14th of April 2020 to identify all relevant studies. Additional searches were conducted in February 2022 to identify systematic reviews (SRs) and clinical practice guidelines (CPG) of Janus kinase-inhibitors and monoclonal antibodies. A total of 105 records were retrieved from the literature searches. After removal of duplicate records, 65 titles and abstracts were screened by two reviewers. After screening of 31 full-text papers, 11 met the inclusion criteria.[1-11] A summary of the study selection process according to modified PRISMA reporting guidelines is reported in Figure 1.[12, 13]

Figure 1: Study selection process



3.2 OVERVIEW OF INCLUDED STUDIES

Table 2 summarises the sources of evidence used to answer the six FAQs. Only SRs and CPGs published anytime (no date restrictions) were included. Quantitative evidence from direct comparisons evaluating monoclonal antibodies i.e., tralokinumab or Janus kinase (JAK) inhibitors i.e., baricitinib, upadacitinib, abrocitinib against placebo was evaluated.

Table 2: Evidence sources

Study/year reference	Evidence source	Primary studies	Intervention(s)	FAQ1: What does the treatment involve?	FAQ2: Will my skin and symptoms improve?	FAQ3: Will my quality of life improve?	FAQ4: What are the risks or side effects?	FAQ5: What if I am pregnant or want to get pregnant?
Sawangjit 2020[1]	SR/NMA	RCT	Abrocitinib	✓	✓		✓	
			Baricitinib					
			Tralokinumab					
Snast 2018[2]	SR	RCT, OS	Tralokinumab	✓	✓		✓	
Siegels 2021[3]	SR	RCTs, SRs, CPG	Baricitinib	✓			✓	
			Upadacitinib	✓	✓			
Kerschbaumer 2020[4]	SR	RCT	Baricitinib	✓				
			Upadacitinib	✓	✓			
Zhou 2021[5]	SR	RCT	Abrocitinib	✓	✓	✓	✓	
Silverberg 2021[6]	SR	RCT	Abrocitinib	✓		✓		
Silverberg 2021a[7]	SR/NMA	RCT	Abrocitinib	✓	✓	✓	✓	
			Baricitinib	✓	✓	✓	✓	
			Tralokinumab	✓	✓	✓	✓	
			Upadacitinib	✓	✓	✓	✓	
Fadlalmola 2021[8]	SR	RCT	Abrocitinib	✓	✓	✓	✓	
Pereyra-Rodriguez 2021[9]	SR/NMA	RCT	Abrocitinib	✓	✓	✓	✓	
			Baricitinib					
			Tralokinumab					
			Upadacitinib					
Mostafa 2021[11]	SR/NMA	RCT	Abrocitinib	✓		✓		
			Baricitinib	✓		✓		
			Tralokinumab	✓		✓		
			Upadacitinib	✓				
Meher 2021[10]	SR	RCT	Abrocitinib	✓	✓		✓	

CPG = clinical practice guideline; NMA = network meta-analysis; OS = observational study; RCT = randomised controlled trial; SR = systematic review.

3.3 FAQ 1: What does the treatment involve?

This section covers two main treatment options for neurodermatitis i.e., monoclonal antibodies and JAK inhibitors. Both treatment options alongside the purported mechanisms of action are described in Table 3 (below). This is relatively new and fast developing field of research.

Table 3: Description of treatments

Monoclonal antibodies
Monoclonal antibodies (MAB) e.g., tralokinumab are targeted biological medications made by cloning cells of a living organisms that is then modified to bind to specific target molecules in humans.[2] MAB are used for the diagnosis and treatment of various diseases including neurodermatitis.[14] It has been suggested that tralokinumab neutralises interleukin-13, which is a key cytokine (a small protein released by cells and having a specific effect on the interactions and communications between cells) responsible for driving peripheral inflammation in the condition, thereby reducing the symptoms of the condition.[1] There are other MAB currently being investigated for the treatment of neurodermatitis. For instance, lebrikizumab is still being investigated including dosing regimens, time of treatment, long-term use as maintenance therapy and their use as monotherapy or as part of a treatments' combination. Other MAB e.g., dupilumab has been recently approved by the U.S. Food and Drug Administration for the use in the treatment of atopic dermatitis.
Janus kinase (JAK) inhibitors
JAK inhibitors are used for the treatment of various chronic inflammatory disorders including neurodermatitis.[15] JAK inhibitors (e.g., baricitinib, upadacitinib, abrocitinib) are classes of medications that block the action of enzymes known as Janus kinases thereby playing a key role in reducing the processes of inflammation.[7] JAK inhibitors act intracellularly and modulate the response of multiple cytokines (described above) implicated in the pathogenesis of neurodermatitis.[6]

3.4 FAQ 2: Will it help my symptoms?

This section explains whether the two classes of medications reduce some of the common symptoms of the disease including erythema, infiltration/papulation, excoriations, and lichenification (itchy, dry, cracked and sore skin). The included trials typically measured symptoms with Eczema Area and Severity Index (EASI) or Investigator's Global Assessment Scale (IGA). The most commonly reported outcomes were EASI 75 and EASI-50 (we did not extract data on EASI-90 less commonly reported). Nine studies provided quantitative data pertaining to these outcomes with mixed findings.[1-5, 7-10] The certainty of the evidence ranged from moderate to low for this FAQ due to inconsistency, indirectness, imprecision, study limitations (see Table 4).

3.4.1 Eczema Area and Severity Index (EASI-75)

Monoclonal antibodies

Tralokinumab

In their SR and network meta-analysis (NMA), Sawangjit 2020[1] aimed to assess the comparative efficacy and safety of different types of systemic immunosuppressive treatments for moderate to severe eczema. They authors reported that there was a greater proportion of participants who achieved at least 75% improvement in the Eczema Area and Severity Index (EASI-75) following tralokinumab compared with placebo at short-term (≤16 weeks) follow-up (39.8% versus 15.6%).

There were no data at long-term follow-up >16 weeks. The certainty of the evidence was low for this outcome due to imprecision and study limitations.

Silverberg 2021[7] aimed to provide an up-to-date analysis of the comparative efficacy and safety of systemic treatments for moderate-to-severe AD as monotherapy and in combination with topical therapies. The authors searched MEDLINE, EMBASE, Cochrane Controlled Register of Trials, HTA and DARE from inception until October 2019; and included 17 trials with a total of 5,532 participants. They found that there was a greater proportion of participants who achieved EASI-75 following tralokinumab 300 mg (combination therapy) compared with placebo at 12 weeks follow-up. The certainty of the evidence was low for this outcome due to imprecision and indirectness.

Pereyra-Rodriguez 2021[9] aimed to evaluate the efficacy and safety of biological agents and small molecules in AD. They searched MEDLINE, EMBASE, and the Cochrane Central between January 2000 and 19 December 2020; and included 30 trials. They found that there was a greater proportion of participants who achieved EASI-75 following tralokinumab 300 mg (monotherapy) compared with placebo at 12 weeks follow-up. The certainty of the evidence was low for this outcome due to imprecision and indirectness.

All three studies found greater reduction of symptoms (measured with EASI-75) in tralokinumab compared with placebo at short-term follow-up (up to 16 weeks).

For monoclonal antibodies, the reduction of symptoms (measured with EASI-75) was 39.8% at short-term follow-up (up to 16 weeks) in one study[1]. In comparison, this number for placebo was 15.6%[1]. Absolute numbers were unavailable in the remaining two studies.[7, 9]

Janus kinase (JAK) inhibitors

Abrocitinib

Meta-analysis of three trials[16-18] (identified in Zhou 2021[5]) found that there was a greater proportion of participants who achieved at least 75% improvement in EASI following abrocitinib 100 mg and 200 mg compared with placebo at 12 weeks follow-up (41.9% and 62.2% versus 12.1% respectively). The certainty of the evidence was moderate for this outcome due to imprecision (see Table 4).

Silverberg 2021[7] found that there was a greater proportion of participants who achieved EASI-75 following abrocitinib 100 mg or abrocitinib 200 mg compared with placebo at 12 weeks follow-up. The certainty of the evidence was low for this outcome due to imprecision and indirectness.

Fadlalmola 2021[8] aimed to assess the efficacy and safety of abrocitinib for moderate-to-severe AD. The authors searched PubMed, Cochrane, Web of Science, Scopus, and EczemATrials until Feb 2021; and included 4 trials with 1,882 patients. The authors reported there was a greater proportion of participants who achieved EASI-75 following abrocitinib 100 mg and 200 mg compared with placebo at 12 weeks follow-up (48.5% and 65.3% versus 17.9% respectively). The certainty of the evidence was low for this outcome due to inconsistency and study limitations (see Table 4).

Pereyra-Rodriguez 2021[9] reported that there was a greater proportion of participants who achieved EASI-75 following abrocitinib 100 mg and 200 mg compared with placebo at 12 weeks follow-up. The certainty of the evidence was low for this outcome due to imprecision and indirectness.

Meher et al. 2021[10] aimed to assess the overall efficacy and safety of abrocitinib in moderate to severe AD. The authors searched PubMed, Cochrane Central, and the International Clinical Trials Registry

Platform and included four trials of low risk of bias. The authors reported there was a greater proportion of participants who achieved EASI-75 following abrocitinib 100 mg and 200 mg compared with placebo at 12 weeks follow-up (48.5% and 65.3% versus 17.9% respectively). The certainty of the evidence was low for this outcome due to inconsistency (see Table 4).

Baricitinib

Siegels 2021[3] aimed to systematically review and critically appraise the evidence on systemic treatments in children, adolescents and adults with moderate-to-severe AD. The authors searched MEDLINE, EMBASE, Cochrane Controlled Register of Trials and Global Resource of Eczema Trials up to February 2020; and included 50 trials with a total of 6,681 participants. They authors reported that there was a greater proportion of participants who achieved at least 75% improvement in EASI-75 following baricitinib (4 mg daily) compared with placebo at 16 weeks follow-up (Risk Difference (RD) = 0.16; 95% CI 0.10 to 0.23). The certainty of the evidence was low for this outcome due to imprecision, indirectness and study limitations.

Silverberg 2021[7] found that there was a greater proportion of participants who achieved EASI-75 following baricitinib 2 mg or 4 mg compared with placebo at 12 weeks follow-up. The certainty of the evidence was low for this outcome due to imprecision and indirectness.

Pereyra-Rodriguez 2021[9] reported that there was a greater proportion of participants who achieved EASI-75 following baricitinib 2 mg or 4 mg compared with placebo at 12 weeks follow-up. The certainty of the evidence was low for this outcome due to imprecision and indirectness.

Upadacitinib

Silverberg 2021[7] found that there was a greater proportion of participants who achieving EASI-75 following upadacitinib 15 mg or 30 mg compared with placebo at 12 weeks follow-up. The certainty of the evidence was low for this outcome due to imprecision and indirectness.

Pereyra-Rodriguez 2021[9] reported that there was a greater proportion of participants who achieved EASI-75 following upadacitinib 15 mg or 30 mg compared with placebo at 12 weeks follow-up. The certainty of the evidence was low for this outcome due to imprecision and indirectness.

For JAK inhibitors, the reduction of symptoms (measured with EASI-75) ranged from 35.9% to 65.3% at short-term follow-up (up to 16 weeks). In comparison, these numbers for placebo ranged from 12.1% to 19.5%.

3.4.2 Eczema Area and Severity Index (EASI-50)

Monoclonal antibodies

Tralokinumab

Snast 2018[2] aimed to evaluate the efficacy and safety of biologic agents in atopic dermatitis. The authors searched Medline (via PubMed), Global Resource for Eczema Trials and clinicaltrials.gov from inception until May 2017; and included 13 RCTs and 10 observational studies of nine biologics. They reported that there were no between-group differences in improving EASI-50 following tralokinumab compared with placebo at 12 weeks follow-up. The certainty of the evidence was low for this outcome due to imprecision and study limitations (see Table 4).

Janus kinase (JAK) inhibitors

Baricitinib

Kerschbaumer 2020[4] aimed to review the efficacy and safety of JAK inhibitors in immune-mediated inflammatory diseases. The authors searched MEDLINE, EMBASE and the Cochrane Library for RCTs published until March 2019; and included a total of 85 studies. They authors reported that there was a greater proportion of participants who achieved at least 50% reduction in EASI score (EASI-50) following baricitinib (2 mg and 4 mg daily) compared with placebo at 16 weeks follow-up (56.7% and 60.5% versus 36.7% respectively). The certainty of the evidence was low for this outcome due to imprecision and study limitations (see Table 4).

3.4.3 Investigators' Global Assessment (IGA)

Monoclonal antibodies

Tralokinumab

Sawangjit 2020[1] reported that there were no between-group differences in reducing Investigators' Global Assessment (IGA) score following tralokinumab compared with placebo at short-term (≤16 weeks) follow-up (18.9% versus 11.7%). The certainty of the evidence was low for these two comparisons and this outcome due to imprecision and study limitations.

Snast 2018[2] reported that there were no between-group differences in IGA scores following tralokinumab (all doses combined) compared with placebo at 12 weeks follow-up (19% versus 12%). The certainty of the evidence was low for these two comparisons and this outcome due to imprecision and study limitations.

Silverberg 2021[7] found that there were no between-group differences in IGA scores following tralokinumab 300 mg (combination therapy) compared with placebo at 12 weeks follow-up (OR = 2.58; 95% CI 0.80 to 9.63). The certainty of the evidence was low for these two comparisons and this outcome due to imprecision and indirectness.

Pereyra-Rodriguez 2021[9] found that there was a greater proportion of participants who improved in IGA scores following tralokinumab 300 mg (monotherapy) compared with placebo at 12 weeks follow-up. The certainty of the evidence was low for this outcome due to imprecision and indirectness.

For monoclonal antibodies, the reduction of symptoms (measured with Investigators' Global Assessment) ranged from 18.9% to 19% at 12 weeks follow-up. In comparison, these numbers for placebo ranged from 11.7% to 12%.

Janus kinase (JAK) inhibitors

Abrocitinib

Sawangjit 2020 [1] reported that patients in the abrocitinib had greater IGA scores when compared with placebo at short-term (≤16 weeks) follow-up (23.6% versus 7.1%). The certainty of the evidence was low for these two comparisons and this outcome due to imprecision and study limitations.

Meta-analysis of three trials [16-18] (identified in Zhou 2021[5]) found that there was a greater improvement in IGA scores following abrocitinib 100 mg and 200 mg compared with placebo at 12 weeks follow-up (26.5% and 41.2% versus 7.8% respectively). The certainty of the evidence was moderate for this outcome due to imprecision (see Table 4).

Silverberg 2021[7] reported that there was a greater improvement in IGA scores following abrocitinib (100 mg and 200 mg) compared with placebo at 12 weeks follow-up (OR = 5.11; 95% CI 3.89 to 6.57 and OR = 9.96; 95% CI 7.77 to 12.59 respectively). The certainty of the evidence was low for this outcome due to imprecision and indirectness (see Table 4).

Fadlalmola 2021[8] reported that there was a greater improvement in IGA scores following abrocitinib 100 mg and 200 mg compared with placebo at 12 weeks follow-up (29.7% and 43.6% versus 9.7% respectively). The certainty of the evidence was low for this outcome due to imprecision and study limitations (see Table 4).

Pereyra-Rodriguez 2021[9] reported that there was a greater improvement in IGA scores following abrocitinib 100 mg and 200 mg compared with placebo at 12 weeks follow-up. The certainty of the evidence was low for these two comparisons and this outcome due to imprecision and indirectness.

Meher et al. 2021[10] reported that there was a greater improvement in IGA scores following abrocitinib 100 mg and 200 mg compared with placebo at 12 weeks follow-up (30.5% and 44% versus 10.1% respectively). The certainty of the evidence was low for this outcome due to imprecision (see Table 4).

Baricitinib

Silverberg 2021[7] reported that there was a greater improvement in IGA scores following baricitinib (2 mg and 4 mg daily) compared with placebo at 12 weeks follow-up (OR = 1.81; 95% CI 1.16 to 2.75 and OR = 2.69; 95% CI 1.84 to 3.91 respectively). The certainty of the evidence was low for this outcome due to imprecision and indirectness (see Table 4).

Pereyra-Rodriguez 2021[9] reported that there was a greater improvement in IGA scores following baricitinib 2 mg or 4 mg compared with placebo at 12 weeks follow-up (OR = 2.52; 95% CI 1.41 to 4.50 and OR = 3.70; 95% CI 2.15 to 6.37). The certainty of the evidence was low for these two comparisons and this outcome due to imprecision and indirectness.

Upadacitinib

Pereyra-Rodriguez 2021[9] reported that there was a greater improvement in IGA scores following upadacitinib 15 mg or 30 mg compared with placebo at 12 weeks follow-up (OR = 10.95; 95% CI 7.52 to 15.94 and OR = 19.13; 95% CI 13.14 to 27.85). The certainty of the evidence was low for these two comparisons and this outcome due to imprecision and indirectness.

For JAK inhibitors, the reduction of symptoms measured with Investigators' Global Assessment ranged from 23.6% to 44% at short-term follow-up (up to 16 weeks). In comparison, these numbers for placebo ranged from 7.1% to 10.1%.

Table 4: FAQ 2 – Evidence synthesis

First author year	Type of study	Follow-up time	Intervention	Comparator/placebo (unless otherwise specified)	Effect estimate with 95% CIs, e.g., risk ratio, odds ratio, risk difference	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate n/N (%) or mean/median (SD)				
EASI-75 (Monoclonal antibodies)							
Sawangjit 2020[1]	SR/NMA	Short-term (≤16 weeks)	61/153 (39.8) tralokinumab	8/51 (15.6)	RR = 2.54 [1.31,4.94]*	Low (imprecision, study limitations)	Difference in favour of tralokinumab; but imprecise data at a high risk of bias⇗
Silverberg 2021[7]	SR/NMA	12 weeks	Median (CrI) = 0.52 (0.36–0.68) tralokinumab 300 mg**^^$	Median (CrI) = 0.10 (0.09–0.11)**$	Not estimable	Low (imprecision, indirectness)	Difference in favour of tralokinumab 300 mg; but imprecise and indirect data⇗
Pereyra-Rodriguez 2021[9]	SR/NMA	12 weeks	Not estimable tralokinumab 300 mg	Not estimable	OR = 2.95 [2.13, 4.09]**	Low (imprecision, indirectness)	Difference in favour of tralokinumab 300 mg; but imprecise and indirect data⇗
EASI-75 (JAK inhibitors)							
Siegels 2021[3]	SR	16 weeks	102/284 (35.9) baricitinib	105/537 (19.5)	RD = 0.16 [0.10, 0.23]	Low (indirectness, imprecision, study limitations)	Difference in favour of baricitinib; but imprecise data at a high risk of bias⇗
Zhou 2021[5]	SR	12 weeks	153/365 (41.9) abrocitinib 100 mg	25/205 (12.1)	RR = 0.66 [0.60, 0.73]*	Moderate (imprecision)	Difference in favour of abrocitinib 100 mg; but imprecise data⇗

First author year	Type of study	Follow-up time	Intervention	Comparator/placebo (unless otherwise specified)	Effect estimate with 95% CIs, e.g., risk ratio, odds ratio, risk difference	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate n/N (%) or mean/median (SD)				
Zhou 2021[5]	SR	12 weeks	221/355 (62.2) abrocitinib 200 mg	25/205 (12.1)	RR = 0.43 [0.37, 0.49]*	Moderate (imprecision)	Difference in favour of abrocitinib 200 mg; but imprecise data⇗
Silverberg 2021[7]	SR/NMA	12 weeks	Median (CrI) = 0.23 (0.15–0.32) baricitinib 2 mg**$	Median (CrI) = 0.10 (0.09–0.11)**$	Not estimable	Low (imprecision, indirectness)	Difference in favour of baricitinib 2 mg; but imprecise and indirect data⇗
Silverberg 2021[7]	SR/NMA	12 weeks	Median (CrI) = 0.28 (0.20–0.38) baricitinib 4 mg**$	Median (CrI) = 0.10 (0.09–0.11)**$	Not estimable	Low (imprecision, indirectness)	Difference in favour of baricitinib 4 mg; but imprecise and indirect data⇗
Silverberg 2021[7]	SR/NMA	12 weeks	Median (CrI) = 0.53 (0.28–0.78) upadacitinib 15 mg**$	Median (CrI) = 0.10 (0.09–0.11)**$	Not estimable	Low (imprecision, indirectness)	Difference in favour of upadacitinib 15 mg; but imprecise and indirect data⇗
Silverberg 2021[7]	SR/NMA	12 weeks	Median (CrI) = 0.70 (0.43–0.89) upadacitinib 30 mg**$	Median (CrI) = 0.10 (0.09–0.11)**$	Not estimable	Low (imprecision, indirectness)	Difference in favour of upadacitinib 30 mg; but imprecise and indirect data⇗
Silverberg 2021[7]	SR/NMA	12 weeks	Median (CrI) = 0.39 (0.29–0.48)	Median (CrI) = 0.10 (0.09–0.11)**$	Not estimable	Low (imprecision, indirectness)	Difference in favour of abrocitinib 100 mg; but imprecise and indirect

First author year	Type of study	Follow-up time	Intervention	Comparator/placebo (unless otherwise specified)	Effect estimate with 95% CIs, e.g., risk ratio, odds ratio, risk difference	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate n/N (%) or mean/median (SD)				
			abrocitinib 100 mg**$				data⇗
Silverberg 2021[7]	SR/NMA	12 weeks	Median (CrI) = 0.58 (0.48–0.67) abrocitinib 200 mg**$	Median (CrI) = 0.10 (0.09–0.11)**$	Not estimable	Low (imprecision, indirectness)	Difference in favour of abrocitinib 200 mg; but imprecise and indirect data⇗
Fadlalmola 2021[8]	SR	12 weeks	291/600 (48.5) abrocitinib 100 mg	60/334 (17.9)	RR = 2.74 [1.99, 3.79]	Low (inconsistency, study limitations)	Difference in favour of abrocitinib 100 mg; but inconsistent data of low quality⇗
Fadlalmola 2021[8]	SR	12 weeks	375/574 (65.3) abrocitinib 200 mg	60/334 (17.9)	RR = 4.04 [2.55, 6.42]	Low (inconsistency)	Difference in favour of abrocitinib 200 mg; but heterogenous data of low quality⇗
Meher 2021[10]	SR	12 weeks	291/600 (48.5) abrocitinib 100 mg	60/334 (17.9)	RR = 2.74 [1.99, 3.79]	Low (inconsistency)	Difference in favour of abrocitinib 100 mg; but inconsistent data⇗
Meher 2021[10]	SR	12 weeks	375/574 (65.3) abrocitinib 200 mg	60/334 (17.9)	RR = 4.04 [2.55, 6.42]	Low (inconsistency)	Difference in favour of abrocitinib 200 mg; but heterogenous data⇗
Pereyra-Rodriguez 2021[9]	SR/NMA	12 weeks	Not estimable upadacitinib 15 mg	Not estimable	OR = 10.89 [8.13, 14.59]**	Low (imprecision, indirectness)	Difference in favour of upadacitinib 15 mg; but imprecise and indirect data⇗

First author year	Type of study	Follow-up time	Intervention	Comparator/placebo (unless otherwise specified)	Effect estimate with 95% CIs, e.g., risk ratio, odds ratio, risk difference	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate n/N (%) or mean/median (SD)				
Pereyra-Rodriguez 2021[9]	SR/NMA	12 weeks	Not estimable upadacitinib 30 mg	Not estimable	OR = 18.90 [13.94, 25.62]**	Low (imprecision, indirectness)	Difference in favour of upadacitinib 30 mg; but imprecise and indirect data⇗
Pereyra-Rodriguez 2021[9]	SR/NMA	12 weeks	Not estimable abrocitinib 100 mg	Not estimable	OR = 5.14 [3.21, 8.23]**	Low (imprecision, indirectness)	Difference in favour of abrocitinib 100 mg; but imprecise and indirect data⇗
Pereyra-Rodriguez 2021[9]	SR/NMA	12 weeks	Not estimable abrocitinib 200 mg	Not estimable	OR = 11.26 [7.02, 18.05]**	Low (imprecision, indirectness)	Difference in favour of abrocitinib 200 mg; but imprecise and indirect data⇗
Pereyra-Rodriguez 2021[9]	SR/NMA	12 weeks	Not estimable baricitinib 2 mg	Not estimable	OR = 2.76 [1.73, 4.40]**	Low (imprecision, indirectness)	Difference in favour of baricitinib 2 mg; but imprecise and indirect data⇗
Pereyra-Rodriguez 2021[9]	SR/NMA	12 weeks	Not estimable baricitinib 4 mg	Not estimable	OR = 3.67 [2.35, 5.75]**	Low (imprecision, indirectness)	Difference in favour of baricitinib 4 mg; but imprecise and indirect data⇗
EASI-50 (Monoclonal antibodies)							
Snast 2018[2]	SR	12 weeks	99/140 (70.7) Tralokinumab^	25/41 (60.9)	RR = 0.75 [0.47, 1.19]***	Low (imprecision, study limitations)	No difference shown⇔

First author year	Type of study	Follow-up time	Intervention	Comparator/placebo (unless otherwise specified)	Effect estimate with 95% CIs, e.g., risk ratio, odds ratio, risk difference	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate n/N (%) or mean/median (SD)				
EASI-50 (JAK inhibitors)							
Kerschbaumer 2020[4]	SR	16 weeks	21/37 (56.7) baricitinib 2 mg	18/49 (36.7)	RR = 0.68 [0.45, 1.05]***	Low (imprecision, study limitations)	No difference shown⇔
Kerschbaumer 2020[4]	SR	16 weeks	23/38 (60.5) baricitinib 4 mg	18/49 (36.7)	RR = 0.62 [0.40, 0.98]***	Low (imprecision, study limitations)	Difference in favour of baricitinib; but imprecise data at a high risk of bias⇗
Investigators' Global Assessment (Monoclonal antibodies)							
Sawangjit 2020[1]	SR/NMA	Short-term (≤16 weeks)	29/153 (18.9) tralokinumab	6/51 (11.7)	RR = 1.61 [0.71,3.66]**	Low (imprecision, study limitations)	No difference shown⇔
Snast 2018[2]	SR	12 weeks	29/152 (19) tralokinumab^	6/50 (12)	RR = 0.92 [0.81, 1.05]***	Low (imprecision, study limitations)	No difference shown⇔
Silverberg 2021[7]	SR/NMA	12 weeks	Not estimable tralokinumab 300 mg**	Not estimable	OR = 2.58 [0.80, 9.63]	Low (imprecision, indirectness)	No difference shown⇔
Pereyra-Rodriguez 2021[9]	SR/NMA	12 weeks	Not estimable tralokinumab 300 mg	Not estimable	OR = 2.37 [1.63, 3.44]**	Low (imprecision, indirectness)	Difference in favour of tralokinumab 300 mg; but imprecise and indirect data⇗

First author year	Type of study	Follow-up time	Intervention	Comparator/placebo (unless otherwise specified)	Effect estimate with 95% CIs, e.g., risk ratio, odds ratio, risk difference	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate n/N (%) or mean/median (SD)				
Investigators' Global Assessment (JAK inhibitors)							
Sawangjit 2020[1]	SR/NMA	Short-term (≤16 weeks)	50/211 (23.6) abrocitinib	4/56 (7.1)	RR = 3.32 [1.25, 8.79]**	Low (imprecision, study limitations)	Difference in favour of abrocitinib; imprecise data⇗
Zhou 2021[5]	SR	12 weeks	97/365 (26.5) abrocitinib 100 mg	16/205 (7.8)	RR = 3.37 [2.04, 5.55] ***	Moderate (imprecision)	Difference in favour of abrocitinib 100 mg; but imprecise data⇗
Zhou 2021[5]	SR	12 weeks	147/356 (41.2) abrocitinib 200 mg	16/205 (7.8)	RR = 5.19 [3.19, 8.44] ***	Moderate (imprecision)	Difference in favour of abrocitinib 200 mg; but imprecise data⇗
Silverberg 2021[7]	SR/NMA	12 weeks	Not estimable abrocitinib 100 mg**	Not estimable	OR = 5.11 [3.89, 6.57]**	Low (imprecision, indirectness)	Difference in favour of abrocitinib 100 mg; but imprecise and indirect data⇗
Silverberg 2021[7]	SR/NMA	12 weeks	Not estimable abrocitinib 200 mg**	Not estimable	OR = 9.96 [7.77, 12.59]**	Low (imprecision, indirectness)	Difference in favour of abrocitinib 200 mg; but imprecise and indirect data⇗
Silverberg 2021[7]	SR/NMA	12 weeks	Not estimable baricitinib 2 mg**	Not estimable	OR = 1.81 [1.16, 2.75]	Low (imprecision, indirectness)	Difference in favour of baricitinib 2 mg; but imprecise and indirect data⇗

First author year	Type of study	Follow-up time	Intervention	Comparator/placebo (unless otherwise specified)	Effect estimate with 95% CIs, e.g., risk ratio, odds ratio, risk difference	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate n/N (%) or mean/median (SD)				
Silverberg 2021[7]	SR/NMA	12 weeks	Not estimable baricitinib 4 mg**	Not estimable	OR = 2.69 [1.84, 3.91]	Low (imprecision, indirectness)	Difference in favour of baricitinib 4 mg; but imprecise and indirect data⇗
Fadlalmola 2021[8]	SR	12 weeks	177/595 (29.7) abrocitinib 100 mg	32/329 (9.7)	RR = 3.03 [2.14, 4.30]	Low (imprecision, study limitations)	Difference in favour of abrocitinib 100 mg; but imprecise data of low quality⇗
Fadlalmola 2021[8]	SR	12 weeks	252/577 (43.6) abrocitinib 200 mg	32/329 (9.7)	RR = 4.44 [3.16, 6.24]	Low (imprecision, study limitations)	Difference in favour of abrocitinib 200 mg; but imprecise data of low quality⇗
Meher 2021[10]	SR	12 weeks	183/600 (30.5) abrocitinib 100 mg	34/334 (10.1)	RR = 2.94 [2.10, 4.13]	Low (imprecision)	Difference in favour of abrocitinib 100 mg; but imprecise⇗
Meher 2021[10]	SR	12 weeks	253/575 (44) abrocitinib 200 mg	34/334 (10.1)	RR = 4.18 [3.00, 5.81]	Low (imprecision)	Difference in favour of abrocitinib 200 mg; but imprecise data⇗
Pereyra-Rodriguez 2021[9]	SR/NMA	12 weeks	Not estimable upadacitinib 15 mg	Not estimable	OR = 10.95 [7.52, 15.94]**	Low (imprecision, indirectness)	Difference in favour of upadacitinib 15 mg; but imprecise and indirect data⇗
Pereyra-Rodriguez 2021[9]	SR/NMA	12 weeks	Not estimable upadacitinib 30 mg	Not estimable	OR = 19.13 [13.14, 27.85]**	Low (imprecision, indirectness)	Difference in favour of upadacitinib 30 mg; but imprecise and indirect data⇗

First author year	Type of study	Follow-up time	Intervention	Comparator/placebo (unless otherwise specified)	Effect estimate with 95% CIs, e.g., risk ratio, odds ratio, risk difference	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate n/N (%) or mean/median (SD)				
Pereyra-Rodriguez 2021[9]	SR/NMA	12 weeks	Not estimable abrocitinib 100 mg	Not estimable	OR = 4.26 [2.43, 7.46]**	Low (imprecision, indirectness)	Difference in favour of abrocitinib 100 mg; but imprecise and indirect data⇗
Pereyra-Rodriguez 2021[9]	SR/NMA	12 weeks	Not estimable abrocitinib 200 mg	Not estimable	OR = 8.04 [4.62, 13.96]**	Low (imprecision, indirectness)	Difference in favour of abrocitinib 200 mg; but imprecise and indirect data⇗
Pereyra-Rodriguez 2021[9]	SR/NMA	12 weeks	Not estimable baricitinib 2 mg	Not estimable	OR = 2.52 [1.41, 4.50]**	Low (imprecision, indirectness)	Difference in favour of baricitinib 2 mg; but imprecise and indirect data⇗
Pereyra-Rodriguez 2021[9]	SR/NMA	12 weeks	Not estimable baricitinib 4 mg	Not estimable	OR = 3.70 [2.15, 6.37]**	Low (imprecision, indirectness)	Difference in favour of baricitinib 4 mg; but imprecise and indirect data⇗

* = from the pair-wise meta-analyses. ** = network estimate. *** = own re-calculation, for more details, please refer to the appendix 2. ^ = all doses combined. ^^ = combination therapy. $ = Estimate is the median proportion of patients reaching the EASI-50 or EASI-75 thresholds in the studies included in the network meta-analysis.

CI = confidence interval; CrI = credible interval; EASI-50 or EASI-75 = Eczema Area and Severity Index (≥50% or ≥75% reduction in EASI score from baseline; a weighted score (0 to 72) of 4 affected areas i.e., head and neck, trunk, upper and lower extremities is given where 0 = no eczema; 7.1-21 = moderate; 21.1-50 = severe; and 50.1-72 = very severe)); NMA = network meta-analysis; OR = odds ratio; RCT = randomised controlled trial; RD = risk difference; RR = risk ratio; SR = systematic review.

3.5 FAQ 3: WILL IT IMPACT MY QUALITY OF LIFE?

This section explains whether the two classes of medications i.e., monoclonal antibodies and JAK inhibitors influence quality of life. The included trials typically measured the outcome with disease-specific questionnaires e.g., Dermatology Life Quality Index (DLQI), Patient Oriented Eczema Measure or generic ones i.e., EQ-5D. Five studies provided quantitative data pertaining to these outcomes with mixed findings.[5-8, 11]

3.5.1 Dermatology Life Quality Index (DLQI)

Monoclonal antibodies

Tralokinumab

Silverberg 2021[7] reported that there was a greater improvement in DLQI scores following tralokinumab 300 mg plus topical corticosteroids compared with placebo plus topical corticosteroids at 12 weeks follow-up (MD = -3.53; 95% CI -6.68 to -0.44). The certainty of the evidence was low for this outcome due to imprecision and indirectness (see Table 5).

Mostafa et al. 2021[11] performed a SR of existing studies of novel systemic agents for atopic dermatitis which specifically reported QoL outcomes. The authors searched two databases from inception until March 2021 and included 16 studies (published in 13 papers) of predominantly high methodological quality. The authors reported that there was a greater improvement in DLQI scores following tralokinumab (every 2 weeks) compared with placebo at 16 weeks follow-up (least square (MD) = -2.97; 95% credible interval (CrI) -3.96 to -1.97). The certainty of the evidence was low for this outcome due to imprecision and indirectness (see Table 5).

For monoclonal antibodies, both studies found improvements in quality of life (QOL) (measured with Dermatology Life Quality Index) compared with placebo at short-term follow-up (up to 16 weeks).[7, 11]

Janus kinase (JAK) inhibitors

Abrocitinib

Meta-analysis of three trials [16-18] (identified in Zhou 2021 [5]) found that there was a greater improvement in Dermatology Life Quality Index (DLQI) following abrocitinib 100 mg and 200 mg compared with placebo at 12 weeks follow-up (standardised mean difference (SMD) = -0.57; 95% CI -0.80 to -0.34 and -0.78; 95% CI -1.02 to -0.53 respectively). The certainty of the evidence was low for this outcome due to imprecision and inconsistency (see Table 5).

Silverberg 2021[7] reported that there was a greater improvement in DLQI scores following abrocitinib (100 mg and 200 mg) compared with placebo at 12 weeks follow-up (MD = -3.69; 95% CrI -6.06 to -1.14 and MD = -5.46; 95% CrI -7.87 to -2.94 respectively). The certainty of the evidence was low for this outcome due to imprecision and indirectness (see Table 5).

Fadlalmola 2021[8] reported there was a greater improvement in DLQI following abrocitinib 100 mg and 200 mg compared with placebo at 12 weeks follow-up (MD = -2.99; 95% CI -3.88 to -2.09 and MD = -5.07; 95% CI -5.94 to -4.20 respectively). The certainty of the evidence was low for this outcome due to imprecision and study limitations (see Table 5).

Mostafa et al. 2021[11] reported that there was a greater improvement in DLQI scores following abrocitinib (100 mg and 200 mg) compared with placebo at 16 weeks follow-up (least square MD = -

2.95; 95% CrI -4.10 to -1.80 and least square MD = -3.94; 95% CrI -4.94 to -2.94 respectively). The certainty of the evidence was low for this outcome due to imprecision and indirectness (see Table 5).

Baricitinib

Silverberg 2021[7] reported that there was a greater improvement in DLQI scores following baricitinib 4 mg plus topical corticosteroids compared with placebo plus topical corticosteroids (MD = -2.70; 95% CrI -4.46 to -0.86); and no difference between baricitinib 2 mg plus topical corticosteroids compared with placebo plus topical corticosteroids at 12 weeks follow-up (MD = -1.43; 95% CrI -3.20 to 0.44). The certainty of the evidence was low for this outcome due to imprecision and indirectness (see Table 5).

Mostafa et al. 2021[11] reported that there was a greater improvement in DLQI scores following baricitinib 1mg, 2 mg and 4 mg compared with placebo (least square MD = -1.75; 95% CrI -2.91 to -0.59, least square MD = -2.61; 95% CrI -3.61 to -1.61 and least square MD = -3.94; 95% CrI -4.94 to -2.94 respectively) at 16 weeks follow-up. The certainty of the evidence was low for this outcome due to imprecision and indirectness (see Table 5).

For JAK inhibitors, all but one studies found improvements in quality of life (QOL) (measured with Dermatology Life Quality Index) compared with placebo at short-term follow-up (up to 16 weeks).[5, 7, 8, 11]

3.5.2 Euro-QoL 5-Dimension Scale (EQ -5D)

Janus kinase (JAK) inhibitors

Abrocitinib

Silverberg 2021[6] pooled data from the placebo-controlled phase IIb and III studies of abrocitinib monotherapy on patient-reported outcomes in adolescents and adults with moderate-to-severe AD. They reported that compared with placebo, there were no between-group differences in life quality measured with Euro-QoL 5-Dimension Scale (EQ -5D) following abrocitinib 100 mg and 200 mg at 12 weeks follow-up (SMD = -0.07; 95% CI -0.26 to 0.13 and SMD = -0.14; 95% CI -0.33 to 0.05 respectively). The certainty of the evidence was moderate for this outcome due to imprecision.

3.5.3 Patient Oriented Eczema Measure (POEM)

Monoclonal antibodies

Tralokinumab

Mostafa et al. 2021[11] reported no differences in QOL measured with POEM scores between tralokinumab (every 2 weeks) compared with placebo at 16 weeks follow-up (least square MD = -1.93; 95% CrI -4.22 to 0.36). The certainty of the evidence was low for this outcome due to imprecision and indirectness (see Table 5).

Janus kinase (JAK) inhibitors

Abrocitinib

Mostafa et al. 2021[11] reported that there was a greater improvement in POEM scores following abrocitinib (100 mg and 200 mg) compared with placebo at 16 weeks follow-up (least square MD = -4.22; 95% CrI -6.86 to -1.58 and least square MD = -7.62; 95% CrI -10.26 to -4.98 respectively). The certainty of the evidence was low for this outcome due to imprecision and indirectness (see Table 5).

Baricitinib

Mostafa et al. 2021[11] reported that there was a greater improvement in DLQI scores following baricitinib 2 mg and 4 mg compared with placebo (least square MD = -4.02; 95% CrI -6.31 to -1.72 and least square MD = -5.49; 95% CrI -7.78 to -3.19 respectively); and no difference for baricitinib 1mg at 16 weeks follow-up. The certainty of the evidence was low for this outcome due to imprecision and indirectness (see Table 5).

For the two JAK inhibitors i.e., abrocitinib and baricitinib, all doses except baricitinib 1mg found improvements in QOL (measured with POEM) compared with placebo at short-term follow-up (up to 16 weeks).[11]

Table 5: FAQ 3 – Evidence synthesis

First author year	Type of study	Follow-up time	Intervention N/Mean (SD)	Comparator N/Mean (SD)	Effect estimate with 95% CIs or CrI	Certainty – quality of evidence (reason(s) for downgrading))	Assessment for use in decision aid
Dermatology Life Quality Index (Monoclonal antibodies)							
Silverberg 2021[7]	SR/NMA	12 weeks	Not estimable tralokinumab 300 mg+TCS	Not estimable placebo +TCS	MD = -3.53 [-6.68, -0.44]**	Low (imprecision, indirectness)	Difference in favour of tralokinumab 300 mg; but imprecise and indirect data⇗
Mostafa 2021[11]	SR/NMA	16 weeks	Not estimable tralokinumab 300 mg	Not estimable placebo	Least square MD = -2.97 [-3.96, -1.97]	Low (imprecision, indirectness)	Difference in favour of tralokinumab; but imprecise and indirect data⇗
Dermatology Life Quality Index (JAK inhibitors)							
Zhou 2021[5]	SR	12 weeks	350 abrocitinib 100 mg	203 placebo	SMD = -0.57 [-0.80, -0.34]*	Low (imprecision, inconsistency)	Difference in favour of abrocitinib 100 mg; but imprecise and heterogenous data⇗
Zhou 2021[5]	SR	12 weeks	348 abrocitinib 200 mg	203 placebo	SMD = -0.78 [-1.02, -0.53]*	Low (imprecision, inconsistency)	Difference in favour of abrocitinib 200 mg; but imprecise and heterogenous data⇗
Silverberg 2021[7]	SR/NMA	12 weeks	Not estimable abrocitinib 100 mg	Not estimable placebo	MD = -3.69 [-6.06, -1.14]**	Low (imprecision, indirectness)	Difference in favour of abrocitinib 100 mg; but imprecise and indirect data⇗
Silverberg 2021[7]	SR/NMA	12 weeks	Not estimable abrocitinib 200 mg	Not estimable placebo	MD = -5.46 [-7.87, -2.94]**	Low (imprecision, indirectness)	Difference in favour of abrocitinib 200 mg; but imprecise and indirect data⇗
Silverberg 2021[7]	SR/NMA	12 weeks	Not estimable baricitinib 2 mg+TCS	Not estimable placebo+TCS	MD = -1.43 [-3.20, 0.44]**	Low (imprecision, indirectness)	No difference shown⇔

First author year	Type of study	Follow-up time	Intervention N/Mean (SD)	Comparator N/Mean (SD)	Effect estimate with 95% CIs or CrI	Certainty – quality of evidence (reason(s) for downgrading))	Assessment for use in decision aid
Silverberg 2021[7]	SR/NMA	12 weeks	Not estimable baricitinib 4 mg+TCS	Not estimable placebo +TCS	MD = -2.70 [-4.46, -0.86]**	Low (imprecision, indirectness)	Difference in favour of baricitinib 4 mg; but imprecise and indirect data⇗
Fadlalmola 2021[8]	SR	12 weeks	499 abrocitinib 100 mg	261 placebo	MD = -2.99 [-3.88, -2.09]	Low (imprecision, study limitations)	Difference in favour of abrocitinib 100 mg; but imprecise data of low quality⇗
Fadlalmola 2021[8]	SR	12 weeks	484 abrocitinib 200 mg	261 placebo	MD = -5.07 [-5.94, -4.20]	Low (imprecision, study limitations)	Difference in favour of abrocitinib 200 mg; but imprecise data of low quality⇗
Mostafa 2021[11]	SR/NMA	16 weeks	Not estimable abrocitinib 100 mg	Not estimable placebo	Least square MD = -2.95 [-4.10, -1.80]	Low (imprecision, study limitations)	Difference in favour of abrocitinib 100 mg; but imprecise data of low quality⇗
Mostafa 2021[11]	SR/NMA	16 weeks	Not estimable abrocitinib 200 mg	Not estimable placebo	Least square MD = -3.94 [-4.94, -2.94]	Low (imprecision, study limitations)	Difference in favour of abrocitinib 200 mg; but imprecise data of low quality⇗
Mostafa 2021[11]	SR/NMA	16 weeks	Not estimable baricitinib 1mg	Not estimable placebo	Least square MD = -1.75 [-2.91, -0.59]	Low (imprecision, indirectness)	Difference in favour of baricitinib 1mg; but imprecise and indirect data⇗
Mostafa 2021[11]	SR/NMA	16 weeks	Not estimable baricitinib 2 mg	Not estimable placebo	Least square MD = -2.61 [-3.61, -1.61]	Low (imprecision, indirectness)	Difference in favour of baricitinib 2 mg; but imprecise and indirect data⇗

First author year	Type of study	Follow-up time	Intervention N/Mean (SD)	Comparator N/Mean (SD)	Effect estimate with 95% CIs or CrI	Certainty – quality of evidence (reason(s) for downgrading))	Assessment for use in decision aid
Mostafa 2021[11]	SR/NMA	16 weeks	Not estimable baricitinib 4 mg	Not estimable placebo	Least square MD = -3.94 [-4.94, -2.94]	Low (imprecision, indirectness)	Difference in favour of baricitinib 4 mg; but imprecise and indirect data⇗
EQ-5D visual analogue scale (JAK inhibitors)							
Silverberg 2021[6]	SR	12 weeks	314 abrocitinib 100 mg	155 placebo	SMD = -0.07 [-0.26, 0.13]*	Moderate (imprecision)	No difference shown⇔
Silverberg 2021[6]	SR	12 weeks	309 abrocitinib 200 mg	155 placebo	SMD = -0.14 [-0.33, 0.05]*	Moderate (imprecision)	No difference shown⇔
Patient Oriented Eczema Measure (monoclonal antibodies)							
Mostafa 2021[11]	SR/NMA	16 weeks	Not estimable tralokinumab 300 mg	Not estimable placebo	Least square MD = -1.93 [-4.22, 0.36]	Low (imprecision, indirectness)	No difference shown⇔
Patient Oriented Eczema Measure (JAK inhibitors)							
Mostafa 2021[11]	SR/NMA	16 weeks	Not estimable abrocitinib 100 mg	Not estimable placebo	Least square MD = -4.22 [-6.86, -1.58]**	Low (imprecision, study limitations)	Difference in favour of abrocitinib 100 mg; but imprecise data of low quality⇗
Mostafa 2021[11]	SR/NMA	16 weeks	Not estimable abrocitinib 200 mg	Not estimable placebo	Least square MD = -7.62 [-10.26, -4.98]**	Low (imprecision, study limitations)	Difference in favour of abrocitinib 200 mg; but imprecise data of low quality⇗
Mostafa 2021[11]	SR/NMA	16 weeks	Not estimable baricitinib 1mg	Not estimable placebo	Least square MD = -2.28 [-4.93, 0.38]**	Low (imprecision, indirectness)	No difference shown⇔
Mostafa 2021[11]	SR/NMA	16 weeks	Not estimable baricitinib 2 mg	Not estimable placebo	Least square MD = -4.02 [-6.31, -1.72]**	Low (imprecision, indirectness)	Difference in favour of baricitinib 2 mg; but imprecise and indirect

First author year	Type of study	Follow-up time	Intervention N/Mean (SD)	Comparator N/Mean (SD)	Effect estimate with 95% CIs or CrI	Certainty – quality of evidence (reason(s) for downgrading))	Assessment for use in decision aid
							data⇗
Mostafa 2021[11]	SR/NMA	16 weeks	Not estimable baricitinib 4 mg	Not estimable placebo	Least square MD = -5.49 [-7.78, -3.19]**	Low (imprecision, indirectness)	Difference in favour of baricitinib 4 mg; but imprecise and indirect data⇗

* = own re-calculation, for more details, please refer to the appendix 2. ** = network estimate; *** = loading dose 600 mg; ECZTRA 3 trial included TCS, ECZTRA 1 and 2 did not.
CI = confidence interval; CrI = credible interval; MD = standardised mean difference; RCT = randomised controlled trial; SD = standard deviation; SMD = standardised mean difference; TCS = topical corticosteroids.

3.6 FAQ 4: WHAT ARE THE RISKS OR SIDE EFFECTS?

This section explains whether a specific type of medications is associated with treatment-emergent (TRAE) or serious adverse events (SAE). Eight studies reported on these outcomes, with mixed findings.[1-3, 5, 7-10] The certainty of the evidence was very low for this FAQ due to imprecision or indirectness (see Table 6).

3.6.1 Treatment-emergent/ treatment-related adverse events (TRAE)

Janus kinase (JAK) inhibitors

Abrocitinib

Silverberg 2021[7] reported that there no between-group differences in treatment-related adverse events (TRAE) following abrocitinib (100 mg and/or 200 mg) compared with placebo at 12 weeks follow-up (OR = 1.56; 95% CrI 0.72 to 3.39 and OR = 2.09; 95% CrI 0.96 to 4.54 respectively). The certainty of the evidence was low for this outcome due to imprecision and indirectness (see Table 6).

Meher et al. 2021[10] reported that there no between-group differences in TRAE following abrocitinib 100 mg; and lower rate following placebo compared with abrocitinib 200 mg at 12 weeks follow-up (RR = 1.09; 95% CI 0.94 to 1.28 and RR = 1.24; 95% CI 1.10 to 1.40 respectively). The certainty of the evidence was moderate for this outcome due to imprecision (see Table 6).

Baricitinib

Silverberg 2021[7] reported that there no between-group differences in TRAE following baricitinib 2 mg plus topical corticosteroids compared with placebo plus topical corticosteroids at 12 weeks follow-up (OR = 1.56; 95% CrI 0.63 to 3.36); and a higher rate of TRAE for baricitinib 4 mg plus topical corticosteroids compared with placebo and topical corticosteroids at 12 weeks follow-up (OR = 2.33; 95% CrI 1.03 to 5.55 respectively). The certainty of the evidence was low for this outcome due to imprecision and indirectness (see Table 6).

For JAK inhibitors, the absolute numbers for TRAE were inestimable. However, both studies Silverberg 2021[7] and Meher 2021[10] found higher rates of TRAE baricitinib 4 mg + topical corticosteroids and abrocitinib 200 mg respectively at 12 weeks follow-up when compared with placebo and topical corticosteroids.

3.6.2 Serious adverse events (SAE)

Monoclonal antibodies

Tralokinumab

Snast 2018[2] reported there were no between-group differences in serious adverse events (SEA) between tralokinumab groups (all doses combined) compared with placebo at 12 weeks follow-up (3.2% versus 3.9%). The certainty of the evidence was low for this outcome due to imprecision and study limitations.

Sawangjit 2020 [1] reported that there were no between-group differences in SAE following tralokinumab when compared with placebo at short-term (≤16 weeks) follow-up (3.2% versus 1.9%). The certainty of the evidence was low for this outcome due to imprecision and study limitations (see Table 6).

Pereyra-Rodriguez 2021[9] found that there were no between-group differences in SAE following tralokinumab 300 mg (monotherapy) compared with placebo at 12 weeks follow-up (OR = 1.26; 95%

CI 0.65 to 2.43). The certainty of the evidence was low for this outcome due to imprecision and indirectness (see Table 6).

For monoclonal antibodies, the absolute numbers for SAE were inestimable. However, all three studies (Sawangjit 2020[1], Snast 2018[2] and Pereyra-Rodriguez 2021[9]) consistently found no between-group differences in SEA between tralokinumab when compared with placebo at short-term follow-up (up to 16 weeks).Janus kinase (JAK) inhibitors

Abrocitinib

Sawangjit 2020 [1] reported that there were no between-group differences in serious adverse events (SAE) following abrocitinib when compared with placebo at short-term (≤16 weeks) follow-up (3.3% versus 3.5%). The certainty of the evidence was low for this outcome due to imprecision and study limitations (see Table 6).

Meta-analysis of three trials [16-18] (identified in Zou 2021[5]) found no between-group differences in SAE following abrocitinib 100 mg and 200 mg compared with placebo at 12 weeks follow-up (3.5% and 2.4% versus 2.8%respectively). The certainty of the evidence was moderate for this outcome due to imprecision (see Table 6).

Fadlalmola 2021[8] reported no between-group differences in SAE following abrocitinib 100 mg and 200 mg compared with placebo at 12 weeks follow-up (2.4% and 1.5% versus 3.2%respectively). The certainty of the evidence was low for this outcome due to imprecision and study limitations (see Table 6).

Pereyra-Rodriguez 2021[9] found that there were no between-group differences in SAE following abrocitinib 100 mg or 200 mg (monotherapy) compared with placebo at 12 weeks follow-up (OR = 1.01; 95% CI 0.31 to 3.32 and OR = 1.43; 95% CI 0.41 to 4.97 respectively). The certainty of the evidence was low for this outcome due to imprecision and indirectness (see Table 6).

Baricitinib

Sawangjit 2020 [1] reported that there were no between-group differences in SAE following baricitinib when compared with placebo at short-term (≤16 weeks) follow-up (4% versus 0%). The certainty of the evidence was low for this outcome due to imprecision and study limitations (see Table 6).

Pereyra-Rodriguez 2021[9] reported that there was a lower rate of at least one SAE following baricitinib 2 mg or/and 4 mg (monotherapy) compared with placebo at 12 weeks follow-up (OR = 0.23; 95% CI 0.07 to 0.79 and OR = 0.08; 95% CI 0.02 to 0.26 respectively. The certainty of the evidence was low for this outcome due to imprecision and indirectness (see Table 6).

Siegels 2021[3] reported that there was a lower rate of SAE (albeit statistically not significant) following baricitinib 2 mg or/and 4 mg (combination therapy) compared with placebo and topical corticosteroids at 16 weeks follow-up (0.7% and 1.7% versus 2.7%respectively). The certainty of the evidence was low for this outcome due to imprecision (see Table 6).

Upadacitinib

Siegels 2021[3] reported that there were no between-group differences in SAE following upadacitinib when compared with placebo at 16 weeks follow-up (3.3% versus 3.5%). The certainty of the evidence was low for this outcome due to imprecision and study limitations (see Table 6).

Pereyra-Rodriguez 2021[9] found that there were no between-group differences in SAE following upadacitinib 15 mg or 30 mg (monotherapy) compared with placebo at 12 weeks follow-up (OR = 0.50; 95% CI 0.23 to 1.11 and OR = 0.96; 95% CI 0.46 to 1.99 respectively). The certainty of the evidence was low for this outcome due to imprecision and indirectness (see Table 6).

For JAK inhibitors, SAE ranged from 0.7% to 4% at short-term follow-up (up to 16 weeks). In comparison, these numbers for placebo ranged from 0% to 3.5%.

Table 6: FAQ 6 – Evidence synthesis

First author year	Type of study	Follow-up time	Intervention	Comparator	Effect estimate with 95% CIs or CrI, e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate (n/N)				
Treatment-emergent adverse events (JAK inhibitors)							
Silverberg 2021[7]	SR/NMA	12 weeks	Not estimable abrocitinib 100 mg	Not estimable placebo	OR = 1.56 [0.72, 3.39]**	Low (imprecision, indirectness)	No difference shown⇔
Silverberg 2021[7]	SR/NMA	12 weeks	Not estimable abrocitinib 200 mg	Not estimable placebo	OR = 2.09 [0.96, 4.54]**	Low (imprecision, indirectness)	No difference shown⇔
Silverberg 2021[7]	SR/NMA	12 weeks	Not estimable baricitinib 2 mg+TCS	Not estimable placebo+TCS	OR = 1.56 [0.63, 3.36]**	Low (imprecision, indirectness)	No difference shown⇔
Silverberg 2021[7]	SR/NMA	12 weeks	Not estimable baricitinib 4 mg+TCS	Not estimable placebo+TCS	OR = 2.33 [1.03, 5.55]**	Low (imprecision, indirectness)	Difference in favour of placebo; but imprecise and indirect data⇗
Meher 2021[10]	SR	12 weeks	328/552 (59.4) abrocitinib 100 mg	156/286 (54.5)	RR = 1.09 [0.94, 1.28]	Moderate (imprecision)	No difference shown⇔
Meher 2021[10]	SR	12 weeks	362/535 (67.6) abrocitinib 200 mg	156/286 (54.5)	RR = 1.24 [1.10, 1.40]	Moderate (imprecision)	Difference in favour of placebo; but imprecise⇗
Serious adverse events (Monoclonal antibodies)							
Sawangjit 2020[1]	SR/NMA	Short-term (≤16 weeks)	5/153 (3.2) Tralokinumab	1/51 (1.9)	RR = 1.67 [0.20, 13.93]	Low (imprecision, study limitations)	No difference shown⇔

First author year	Type of study	Follow-up time	Intervention	Comparator	Effect estimate with 95% CIs or CrI, e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate (n/N)				
Snast 2018[2]	SR	12 weeks	5/153 (3.2) Tralokinumab^	2/51 (3.9)	RR = 0.83 [0.17, 4.16]*	Low (imprecision, study limitations)	No difference shown⇔
Pereyra-Rodriguez 2021[9]	SR/NMA	12 weeks	Not estimable tralokinumab 300 mg	Not estimable	OR = 1.26 [0.65, 2.43]**	Low (imprecision, indirectness)	No difference shown⇔
Serious adverse events (JAK inhibitors)							
Sawangjit 2020[1]	SR/NMA	Short-term (≤16 weeks)	3/75 (4) Baricitinib	0/49 (0)	RR = 4.61 [0.24, 87.25]	Low (imprecision, study limitations)	No difference shown⇔
Sawangjit 2020[1]	SR/NMA	Short-term (≤16 weeks)	7/211 (3.3) Abrocitinib	2/56 (3.5)	RR = 0.93 [0.20, 4.35]	Low (imprecision, study limitations)	No difference shown⇔
Siegels 2021[3]	SR	16 weeks	3/126 (2.3) upadacitinib ^	1/40 (2.5)	RR = 0.95 [0.10, 8.90]*	Low (imprecision, study limitations)	No difference shown⇔
Siegels 2021[3]	SR	16 weeks	2/283 (0.7) baricitinib 2 mg	15/542 (2.7)	RR = 0.26 [0.06, 1.11]*	Low (imprecision)	No difference shown⇔
Siegels 2021[3]	SR	16 weeks	5/286 (1.7) baricitinib 4 mg	15/542 (2.7)	RR = 0.63 [0.23, 1.72]*	Low (imprecision)	No difference shown⇔
Zhou 2021[5]	SR	12 weeks	13/370 (3.5) abrocitinib 100 mg	6/211 (2.8)	RR = 1.25 [0.47, 3.30]*	Moderate (imprecision)	No difference shown⇔

First author year	Type of study	Follow-up time	Intervention	Comparator	Effect estimate with 95% CIs or CrI, e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate (n/N)				
Zhou 2021[5]	SR	12 weeks	9/364 (2.4) abrocitinib 200 mg	6/211 (2.8)	RR = 0.91 [0.33, 2.54]*	Moderate (imprecision)	No difference shown⇔
Fadlalmola 2021[8]	SR	12 weeks	15/608 (2.4) abrocitinib 100 mg	11/342 (3.2)	OR = 0.81 [0.38, 1.73]	Low (imprecision, study limitations)	No difference shown⇔
Fadlalmola 2021[8]	SR	12 weeks	9/590 (1.5) abrocitinib 200 mg	11/342 (3.2)	OR = 0.50 [0.22, 1.16]	Low (imprecision, study limitations)	No difference shown⇔
Pereyra-Rodriguez 2021[9]	SR/NMA	12 weeks	Not estimable baricitinib 2 mg	Not estimable	OR = 0.23 [0.07, 0.79]**	Low (imprecision, indirectness)	Difference in favour of baricitinib 2 mg; but imprecise and indirect data⇗
Pereyra-Rodriguez 2021[9]	SR/NMA	12 weeks	Not estimable baricitinib 4 mg	Not estimable	OR = 0.08 [0.02, 0.26]**	Low (imprecision, indirectness)	Difference in favour of baricitinib 4 mg; but imprecise and indirect data⇗
Pereyra-Rodriguez 2021[9]	SR/NMA	12 weeks	Not estimable upadacitinib 15 mg	Not estimable	OR = 0.50 [0.23, 1.11]**	Low (imprecision, indirectness)	No difference shown⇔
Pereyra-Rodriguez 2021[9]	SR/NMA	12 weeks	Not estimable upadacitinib 30 mg	Not estimable	OR = 0.96 [0.46, 1.99]**	Low (imprecision, indirectness)	No difference shown⇔
Pereyra-Rodriguez 2021[9]	SR/NMA	12 weeks	Not estimable abrocitinib 100 mg	Not estimable	OR = 1.01 [0.31, 3.32]**	Low (imprecision, indirectness)	No difference shown⇔
Pereyra-Rodriguez	SR/NMA	12 weeks	Not estimable abrocitinib	Not estimable	OR = 1.43 [0.41, 4.97]**	Low (imprecision, indirectness)	No difference shown⇔

First author year	Type of study	Follow-up time	Intervention	Comparator	Effect estimate with 95% CIs or CrI, e.g. mean/median difference, risk ratio, odds ratio	Certainty – quality of evidence (reason for downgrading)	Assessment for use in decision aid
			Proportion with event Intervention/control group event rate (n/N)				
2021[9]			200 mg				
* = own re-calculation, for more details, please refer to the appendix 2. ** = network estimate. ^ = all doses combined. CI = confidence interval; CrI = credible interval; NMA = network meta-analysis; OR = odds ratio; RCT = randomised controlled trial; RR = risk ratio; SR = systematic review.							

3.7 FAQ 5: WHAT IF I AM PREGNANT OR WANT TO GET PREGNANT?

There were no studies to answer this FAQ.

4. DISCUSSION

4.1 SUMMARY OF MAIN FINDINGS

Low or moderate certainty (imprecise, inconsistent, indirect or at a high/unclear risk of bias) evidence suggests inconsistent findings for all FAQs/outcomes.

In general, there was a large body of evidence that provided data for FAQs 2-4; and no data for FAQ 5 (what if a woman is or want to get pregnant).

Regarding the FAQ 2, all three studies found that monoclonal antibodies i.e., tralokinumab reduced the common symptoms of the disease (measured with EASI-75) compared with placebo at short-term follow-up (up to 16 weeks) based on imprecise and indirect (low quality) evidence.[1, 7, 9] One study found no between-group differences in improving EASI-50 following tralokinumab compared with placebo at 12 weeks follow-up based on low quality evidence.[2]. The findings were inconsistent for improvements in symptoms measured with Investigators' Global Assessment (IGA); with three studies reporting no between group differences, and one study favouring tralokinumab 300 mg (monotherapy) compared with placebo at 12 weeks follow-up.[9] All four studies were based on low certainty of the evidence (imprecise and indirect).

For JAK inhibitors, all studies consistently favoured abrilumab, baricitinib and upadacitinib in reducing the symptoms (measured with EASI-75) compared with placebo at short-term follow-up (up to 16 weeks) based on imprecise, inconsistent, indirect or at a high/unclear risk of bias (low to moderate quality) evidence. However, the findings were less consistent for improvements in symptoms measured with Investigators' Global Assessment (IGA). One study found no differences in improving the outcomes between baricitinib 2 mg or 4 mg compared with placebo at 16 weeks follow-up based on moderate certainty evidence.[4] In contrast, the remaining six studies reported greater reductions of symptoms measured with IGA at short-term follow-up (up to 16 weeks) based on low to moderate certainty evidence.[1, 5, 7-10]

Medium size body of evidence i.e., five studies provided data for FAQ 3 with mixed findings for both classes of drugs.[5-8, 11] For instance, for tralokinumab, both studies found improved QOL measured with DLQI compared with placebo;[7, 11] and no between-group differences as measured with Patient Oriented Eczema Measure at short-term follow-ups (ranging from 12 to 16 weeks).

For both JAK inhibitors i.e., abrilumab, baricitinib, almost all studies reported improved QOL measured with DLQI compared with placebo; and there were no between-group differences as measured with EQ-5D at short-term follow-ups (ranging from 12 to 16 weeks).[5, 7, 8, 11] The certainty of the evidence varied from low to moderate (predominantly low) with all four reasons for downgrading including imprecision, inconsistency, indirectness or risk of bias/study limitations. All except one (a network estimate for baricitinib 1mg [11]) improved QOL measured with POEM compared with placebo at 16 weeks follow-up. No studies reported QOL data for upadacitinib.

Large body of evidence provided data for FAQ 6 with mixed findings. For instance, there were higher rates of TRAE for both JAK inhibitors i.e., abrilumab, baricitinib when compared with placebo (with abrocitinib 200 mg and baricitinib 4 mg+topical corticosteroids reaching statistical significance) based on low to moderate certainty of the evidence. No studies reported TRAE data for tralokinumab. For SAE, two studies found higher rates of SAE for tralokinumab compared with placebo,[1, 9] whereas one study reported the opposite findings at follow-ups ranging from 12 to 16 weeks based on low certainty of the evidence.[2] For JAK inhibitors, the majority of the studies reported lower rates of SAE for the

intervention groups (with baricitinib 2 mg and 4 mg reaching statistical significance) as compared with placebos based on low to moderate certainty of the evidence.

4.2 STRENGTH, LIMITATIONS AND UNCERTAINTIES

This report has several strengths including a comprehensive search of the most up-to-date literature, no language restrictions, and a large amount of data, especially for FAQs 2,3 and 4. However, this review has limitations too including lack of data for FAQ 5, and predominantly low certainty evidence.

REFERENCES

[1] Sawangjit R, Dilokthornsakul P, Lloyd-Lavery A, Lai NM, Dellavalle R, Chaiyakunapruk N. Systemic treatments for eczema a network meta-analysis. Cochrane Database of Systematic Reviews 2020, Issue 9. Art. No.: CD013206. DOI: 10.1002/14651858.CD013206.pub2.

[2] Snast I, Reiter O, Hodak E, Friedland R, Mimouni D, Leshem YA. Are biologics efficacious in atopic dermatitis? A systematic review and meta-analysis. Am J Clin Dermatol 2018;19(2):145-65.

[3] Siegels D, Heratizadeh A, Abraham S, Binnmyr J, Brockow K, Irvine AD, et al. Systemic treatments in the management of atopic dermatitis: a systematic review and meta-analysis. Allergy 2021;76(4):1053-76.

[4] Kerschbaumer A, Smolen JS, Nash P, Doerner T, Dougados M, Fleischmann R, et al. Points to consider for the treatment of immune-mediated inflammatory diseases with Janus kinase inhibitors: a systematic literature research. RMD Open 2020;6(3):e001374.

[5] Zhou S, Qi F, Gong Y, Zhang J, Zhu B. Biological therapies for atopic dermatitis: a systematic review. Dermatology (Basel) 2021;237(4):542-52.

[6] Silverberg JI, Thyssen JP, Simpson EL, Yosipovitch G, Stander S, Valdez H, et al. Impact of oral abrocitinib monotherapy on patient-reported symptoms and quality of life in adolescents and adults with moderate-to-severe atopic dermatitis: a pooled analysis of patient-reported outcomes. Am J Clin Dermatol 2021;22(4):541-54.

[7] Silverberg JI, Thyssen JP, Fahrbach K, Mickle K, Cappelleri JC, Romero W, et al. Comparative efficacy and safety of systemic therapies used in moderate-to-severe atopic dermatitis: a systematic literature review and network meta-analysis. J Eur Acad Dermatol Venereol 2021;35(9):1797-810.

[8] Fadlalmola HA, Albadrani MS, Elhusein AM, Mohamedsalih WE, Swamy VDS, Mamanao DM. Effectiveness and safety of abrocitinib in patients with moderate-to-severe atopic dermatitis: a systematic review and meta-analysis of randomized clinical trials. Dermatol Res Pract 2021;2021:8382761.

[9] Pereyra-Rodriguez JJ, Alcantara-Luna S, Domínguez-Cruz J, Galán-Gutiérrez M, Ruiz-Villaverde R, Vilar-Palomo S, et al. Short-term effectiveness and safety of biologics and small molecule drugs for moderate to severe atopic dermatitis: a systematic review and network meta-analysis. Life (Basel) 2021;11(9):927.

[10] Meher BR, Mohanty RR, Padhy BM. Efficacy and safety of abrocitinib for the treatment of moderate-to-severe atopic dermatitis: a meta-analysis of randomized clinical trials. J Dermatolog Treat 2021;Epub ahead of print.

[11] Mostafa N, Phan K, Lai B, Smith SD. Comparing quality of life outcomes of JAK inhibitors and biological treatments for atopic dermatitis: a systematic review and network meta-analysis. Expert Rev Clin Pharmacol 2021;14(11):1435-44.

[12] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.

[13] Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ 2021;372:n160.

[14] Wyant T, Fedyk E, Abhyankar B. An overview of the mechanism of action of the monoclonal antibody vedolizumab. J Crohns Colitis 2016;10(12):1437-44.

[15] European Medicines Agency. EMA starts safety review of Janus kinase inhibitors for inflammatory disorders. News 11/02/2022 [Internet]. Amsterdam, The Netherlands: European Medicines Agency, 2022 [accessed 25.2.22]. Available from: https://www.ema.europa.eu/en/news/ema-starts-safety-review-janus-kinase-inhibitors-inflammatory-disorders

[16] Gooderham MJ, Forman SB, Bissonnette R, Beebe JS, Zhang W, Banfield C, et al. Efficacy and safety of oral Janus kinase 1 inhibitor abrocitinib for patients with atopic dermatitis: a phase 2 randomized clinical trial. JAMA Dermatol 2019;155(12):1371-9.

[17] Simpson EL, Sinclair R, Forman S, Wollenberg A, Aschoff R, Cork M, et al. Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. Lancet 2020;396(10246):255-66.

[18] Silverberg JI, Simpson EL, Thyssen JP, Gooderham M, Chan G, Feeney C, et al. Efficacy and safety of abrocitinib in patients with moderate-to-severe atopic dermatitis: a randomized clinical trial. JAMA Dermatol 2020;156(8):863-73.

APPENDIX 1: SEARCH STRATEGIES

Supplemental Table 1: Systematic reviews and guideline search results

Database	Dates	Results
CDSR	Issue 2, February 2022	1
KSR Evidence	up to 22 February 2022	19
Epistemonikos	up to 22 February 2022	34
INAHTA	up to 22 February 2022	0
NICE Evidence	up to 22 February 2022	18
NICE Guidance	up to 22 February 2022	10
GIN	up to 22 February 2022	7
ECRI	up to 22 February 2022	0
Trip	up to 22 February 2022	16
CADTH	up to 22 February 2022	0
Total		**105**
Total after de-duplication		**65**

Search strategies

Cochrane Database of Systematic Reviews (CDSR) (Wiley): Issue 2 of 12, February 2022
Searched: 22.2.22

#1 MeSH descriptor: [Neurodermatitis] explode all trees 74
#2 MeSH descriptor: [Dermatitis, Atopic] explode all trees 1956
#3 (neurodermatit* or "neuro dermatit*" or (lichen NEAR/3 chronic*)):ti,ab,kw 161
#4 ((atopic* or infantile or childhood) NEAR/3 (eczema* or dermatit*)):ti,ab,kw 5371
#5 #1 or #2 or #3 or #4 5491
#6 (baricitinib or olumiant or "incb 028050" or "incb 28050" or incb028050 or incb28050 or "ly 3009104" or ly3009104 or 1187594−09−7):ti,ab,kw 518
#7 (upadacitinib or "abt 494" or abt494 or rinvoq or 1310726−60−3 or 1607431−21−9):ti,ab,kw 454
#8 (abrocitinib or cibinqo or 1622902−68−4):ti,ab,kw 61
#9 (tralokinumab or adtralza or "cat 354" or cat354 or "lp 0162" or lp0162 or 1044515−88−9):ti,ab,kw 127
#10 #6 or #7 or #8 or #9 1155
#11 #5 and #10 in Cochrane Reviews, Cochrane Protocols 1

KSR Evidence (Internet): Database last updated 22 February 2022
https://ksrevidence.com/
Searched: 22.2.22

1 neurodermatit* or "neuro dermatit*" or (lichen near/3 chronic*) in All text 15 results
2 (atopic* or infantile or childhood) near/3 (eczema* or dermatit*) in All text 401 results
3 #1 or #2 in All text 412 results

4 baricitinib or olumiant or "incb 028050" or "incb 28050" or incb028050 or incb28050 or "ly 3009104" or ly3009104 in All text 62 results
5 upadacitinib or "abt 494" or abt494 or rinvoq in All text 43 results
6 abrocitinib or cibinqo in All text 11 results
7 tralokinumab or adtralza or "cat 354" or cat354 or "lp 0162" or lp0162 in All text 12 results
8 #4 or #5 or #6 or #7 in All text 95 results
9 #3 and #8 in All text 19 results
Search run Tue Feb 22 2022

Epistemonikos (Internet): up to 22 February 2022
https://www.epistemonikos.org/en/
Searched: 22.2.22

(neurodermatitis OR "neuro dermatitis" OR neurodermatitides OR "neuro dermatitides" OR "lichen simplex" OR "atopic dermatitis" OR "atopic eczema" OR "infantile dermatitis" OR "infantile eczema" OR "childhood dermatitis" OR "childhood eczema") AND (baricitinib OR olumiant OR "incb 028050" OR "incb 28050" OR incb028050 OR incb28050 OR "ly 3009104" OR ly3009104 OR upadacitinib OR "abt 494" OR abt494 OR rinvoq OR abrocitinib OR cibinqo OR tralokinumab OR adtralza OR "cat 354" OR cat354 OR "lp 0162" OR lp0162)
Records retrieved 34

International HTA Database (INAHTA): up to 22 February 2022
https://database.inahta.org/
Searched: 22.2.22

1 "Neurodermatitis"[mh] 0
2 "Dermatitis, Atopic"[mh] 24
3 neurodermatitis OR "neuro dermatitis" OR neurodermatitides OR "neuro dermatitides" OR "lichen simplex" OR "atopic dermatitis" OR "atopic eczema" OR "infantile dermatitis" OR "infantile eczema" OR "childhood dermatitis" OR "childhood eczema" 27
4 #3 OR #2 OR #1 29
5 baricitinib OR olumiant OR "incb 028050" OR "incb 28050" OR incb028050 OR incb28050 OR "ly 3009104" OR ly3009104 OR upadacitinib OR "abt 494" OR abt494 OR rinvoq OR abrocitinib OR cibinqo OR tralokinumab OR adtralza OR "cat 354" OR cat354 OR "lp 0162" OR lp0162 8
6 #5 AND #4 0

NICE Evidence Search (Internet): up to 22 February 2022
https://www.evidence.nhs.uk/
Searched: 22.2.22

Search terms	Results (Guidance; Systematic Reviews)
neurodermatitis	5
"neuro dermatitis"	0

dermatitis (baricitinib or upadacitinib or abrocitinib or tralokinumab)	11
eczema (baricitinib or upadacitinib or abrocitinib or tralokinumab)	8
"lichen simplex" (baricitinib or upadacitinib or abrocitinib or tralokinumab)	0
Total retrieved	**34**
Total after removal of duplicates	**18**

National Institute for Health and Care Excellence (NICE): Guidelines: up to 22 February 2022
https://www.nice.org.uk/
Searched: 22.1.21

NICE Guidance; Conditions and diseases; Skin conditions; Eczema

Guidance 3
Guidance In Development 5
Quality standards 1
Pathways 1

Total 10

Guidelines International Network (GIN). International Guidelines Library (Internet): up to 22 February 2022
https://g-i-n.net/international-guidelines-library/
Searched: 22.2.22

neurodermatitis
atopic dermatitis
atopic eczema
infantile eczema
childhood eczema
baricitinib
upadacitinib
abrocitinib
tralokinumab
7 records retrieved

ECRI Institute Guidelines Trust (Internet): up to 22 February 2022
https://guidelines.ecri.org/
Searched: 22.2.22

neurodermatitis
atopic dermatitis
atopic eczema
infantile eczema
childhood eczema
baricitinib

upadacitinib
abrocitinib
tralokinumab
0 records retrieved

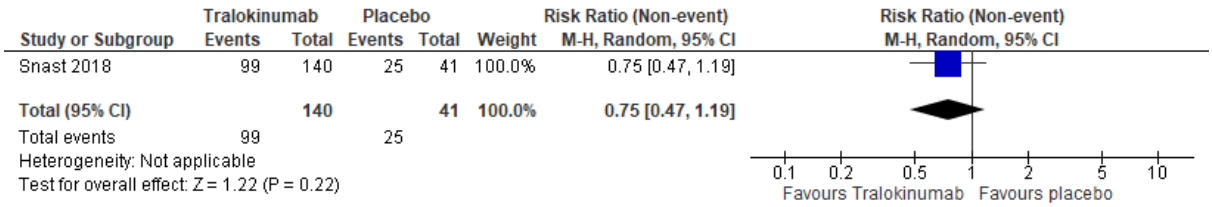
Trip Database: up to 22 February 2022
https://www.tripdatabase.com/
Searched: 2.2.22

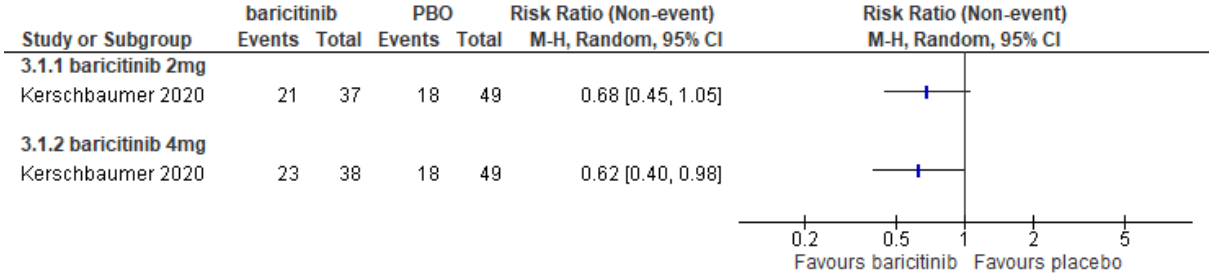
(neurodermatitis OR "neuro dermatitis" OR neurodermatitides OR "neuro dermatitides" OR "lichen simplex" OR "atopic dermatitis" OR "atopic eczema" OR "infantile dermatitis" OR "infantile eczema" OR "childhood dermatitis" OR "childhood eczema") AND (baricitinib OR olumiant OR "incb 028050" OR "incb 28050" OR incb028050 OR incb28050 OR "ly 3009104" OR ly3009104 OR upadacitinib OR "abt 494" OR abt494 OR rinvoq OR abrocitinib OR cibinqo OR tralokinumab OR adtralza OR "cat 354" OR cat354 OR "lp 0162" OR lp0162)
Guidelines: 16 records retrieved

Canadian Agency for Drugs and Technologies in Health (CADTH): up to 22 February 2022
https://www.cadth.ca/
Searched: 22.2.22

neurodermatitis
"atopic dermatitis"
"atopic eczema"
"infantile eczema"
"childhood eczema"
baricitinib
upadacitinib
abrocitinib
tralokinumab
Advanced Search; Project Line; Health Technology Assessment
0 records retrieved

APPENDIX 2: OWN CALCULATIONS WITH REVIEW MANAGER 5.4.1





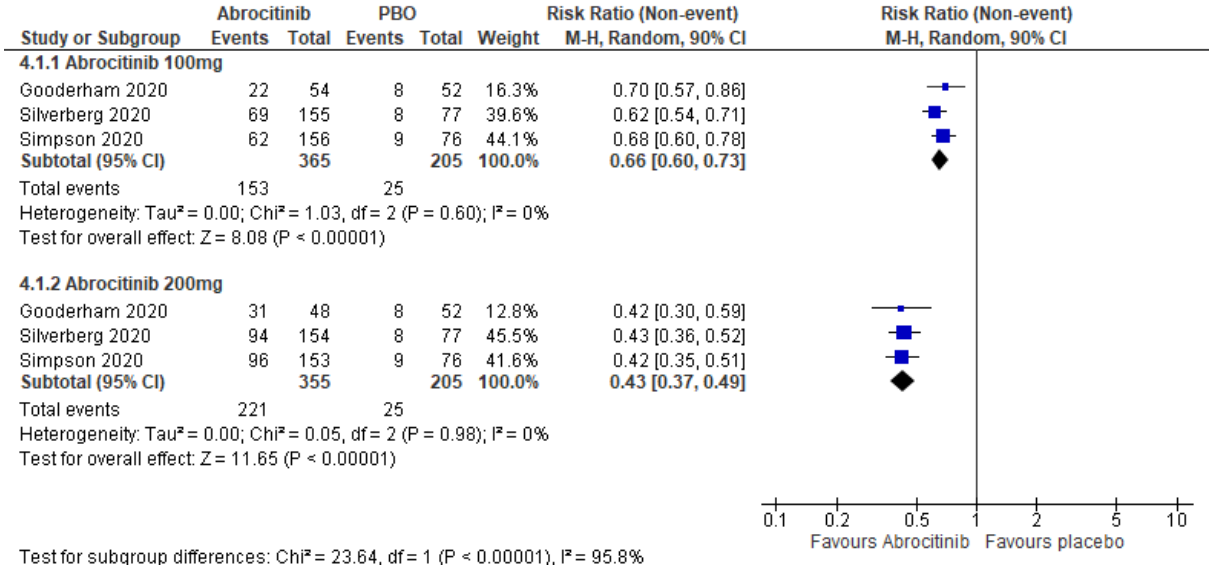
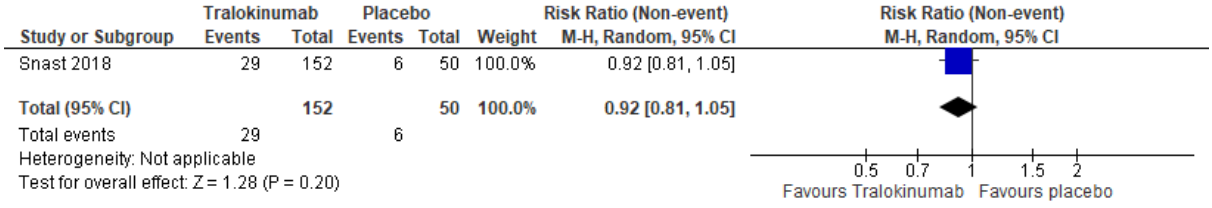


Figure footnote: Outcome: EASI-50 or 75 (refer to Table 4)



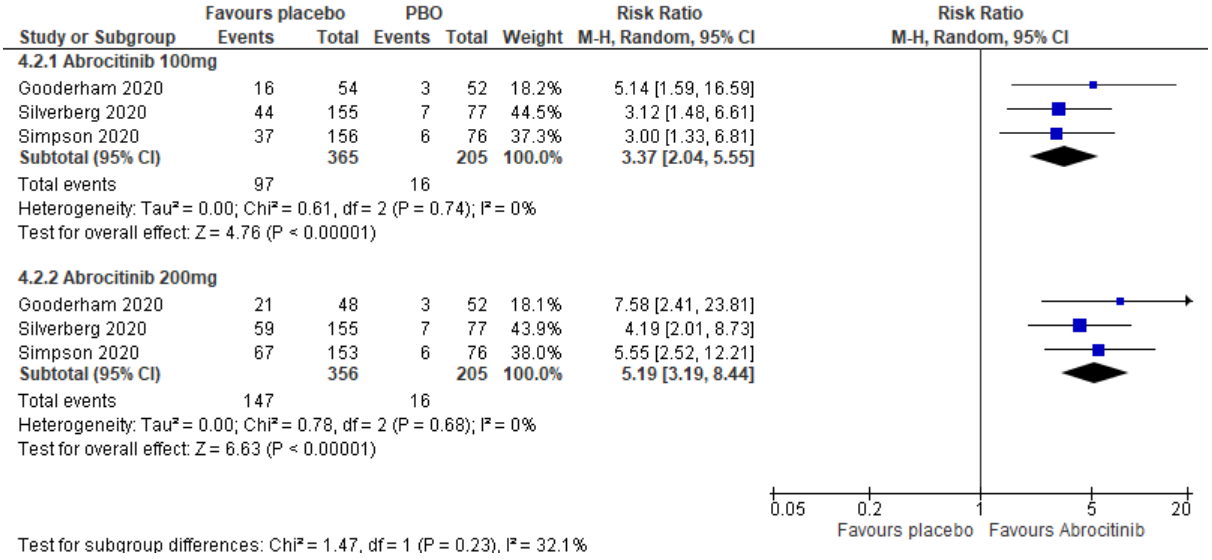


Figure footnote: Outcome: Investigator's Global Assessment (refer to Table 4)

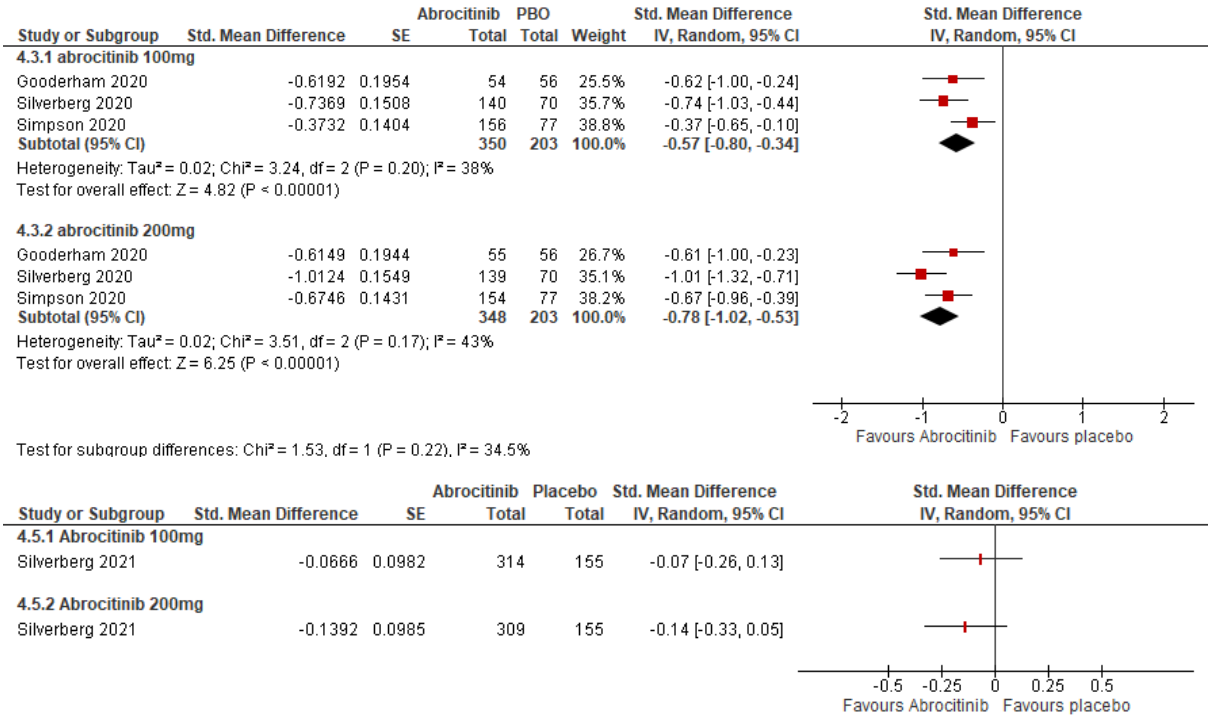
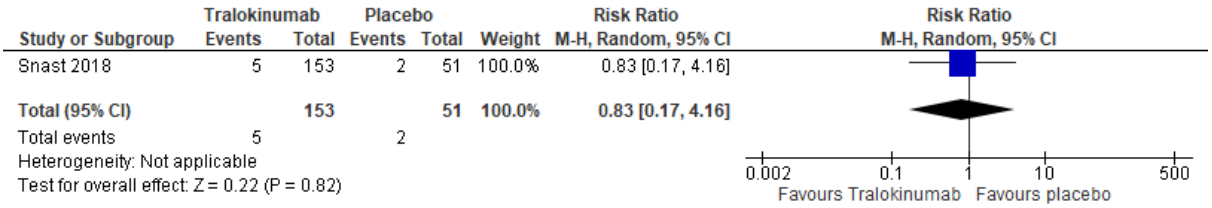


Figure footnote: Outcome: Quality of life (refer to Table 5)



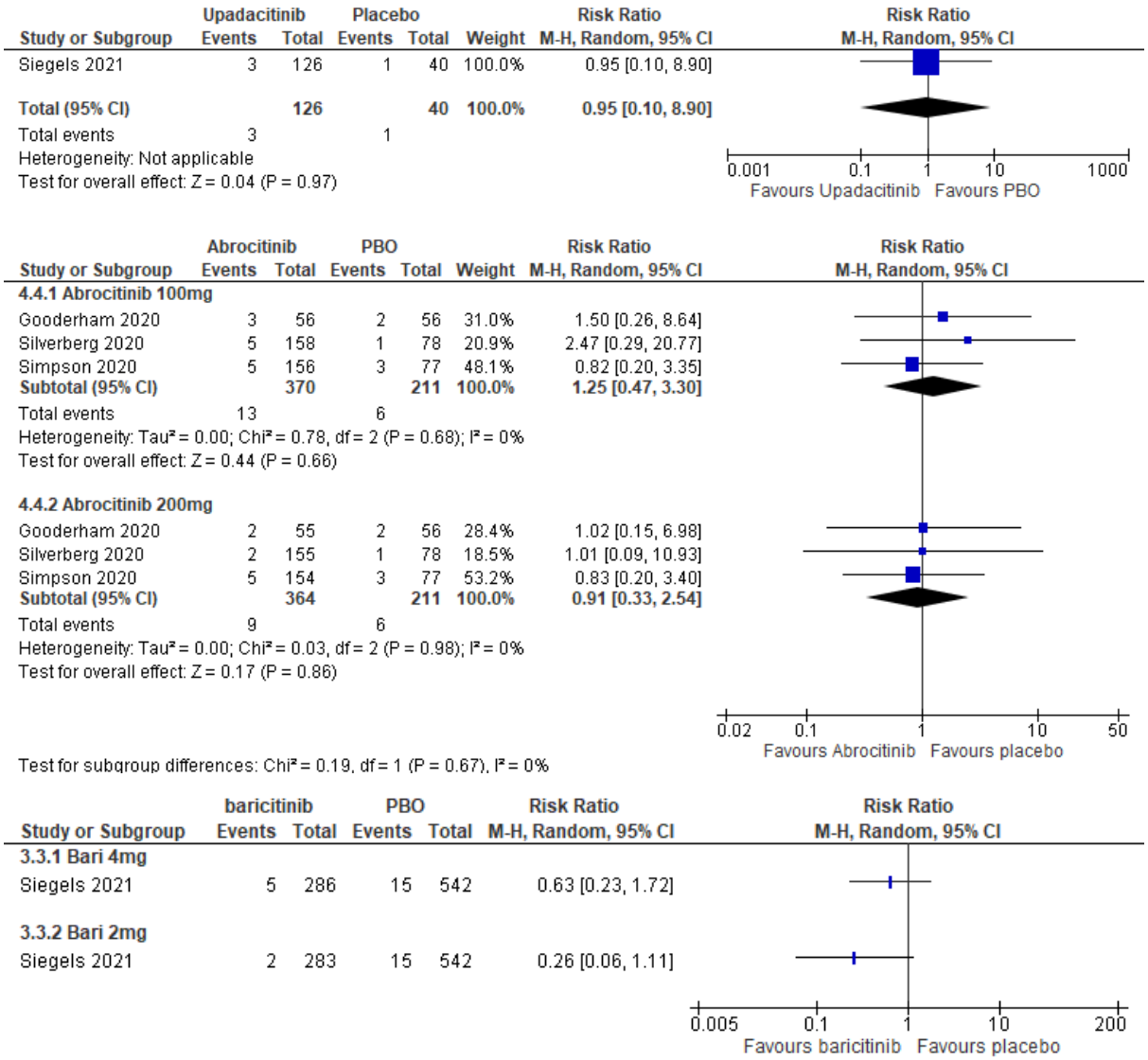


Figure footnote: Outcome: Serious adverse events (refer to Table 6)