A report for Universitätsklinikum Schleswig-Holstein/Campus Kiel on Shared Decision Making for the treatment of moderate to severe plaque psoriasis

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AE	Adverse event
BSA	Body surface area
CDSR	Cochrane Database of Systematic Reviews
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
DARE	Database of Abstracts of Reviews of Effects
DLQI	Dermatology Life Quality Index
EMA	European Medicines Agency
FAQ	Frequently asked question
GIN	Guidelines International Network
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HTA	Health technology assessment
KSR	Kleijnen Systematic Reviews Ltd
MA	Meta-analysis
MD	Mean difference
MTC	Mixed treatment comparison
Mth	Month
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
PASI	Psoriasis Area and Severity Index score
PICOS	Participants, intervention, comparators, outcomes, and study design
PRISMA	Preferred reporting items for systematic reviews and meta-analysis
RCT	Randomised controlled trial
SDM	Shared decision making
SAE	Serious adverse event
SC	Subcutaneous
SR	Systematic review
Wk	Week
Yr	Year

1. PROJECT OBJECTIVE

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

To support this, Kleijnen Systematic Reviews Ltd (KSR) has prepared an evidence report with a synthesis of the literature underpinning the supporting evidence table of the relevant treatment options.

The objective of this evidence report is to present a comparative summary of outcomes resulting from the treatment of moderate to severe plaque psoriasis.

In consultation with the commissioner, and with additional input from the literature, five frequently asked questions (FAQs) of most concern to patients were grouped into five main questions. These five following questions are addressed in this report:

1. **What does the treatment involve?**
   - 1.1. What does my treatment involve?
   - 1.2. Will I be treated at home?
2. **Will it help my symptoms?**
   - 2.1. Will the treatment help my symptoms (redness, itching, pruritus, pain, Psoriasis Area and Severity Index score [PASI])?
   - 2.2. How long will it take before I see an improvement in my symptoms?
3. **Will it help maintain remission of my disease?**
   - 3.1. Will my disease return?
4. **How will the treatment impact on my quality of life?**
   - 4.1. How will the treatment affect my quality of life?
5. **What are the risks and side effects?**
   - 5.1. What side effects might I experience from my treatment?
   - 5.2. Are there any serious risks associated with my treatment?

2. METHODS

2.1 INCLUSION CRITERIA

The research question underpinning the literature searches for this topic was developed in conjunction with clinical departments at Universitätsklinikum Schleswig-Holstein/Campus Kiel. The question was framed in terms of participants, intervention, comparators, outcomes, and study design (PICOS), see Table 1.

As detailed below, literature searches were carried out using a stepwise approach to identify relevant studies according to study design. In the first step, searches aimed to identify relevant systematic reviews and guidelines. For this project, no further topic-wide searches for randomised controlled trials (RCTs) or observational studies were conducted as relevant results were extracted from the identified systematic reviews, guidelines, and patient information (website and leaflets).

Table 1: Inclusion/exclusion criteria for evidence selection

Item	Included	Excluded
Population	Adults >18yrs Moderate to severe psoriasis vulgaris (defined as Body Surface Area (BSA) OR Psoriasis Area and Severity Index (PASI) > 10 AND Dermatology Life Quality Index (DLQI) >10)	Non-plaque type psoriasis Parapsoriasis
Treatments	Any of the following specific therapies in addition to standard care including active substance-free topical applications (emollients); topical preparations of urea (3-10%); and lifestyle modifications (weight control; smoking cessation; avoidance of food or environmental triggers). Conventional systemic therapy*: ○ Fumaric acid esters ○ Methotrexate Biologics: ○ Anti-TNF alpha (etanercept, infliximab, adalimumab, certolizumab) and their biosimilars ○ Anti-IL12/23 (ustekinumab) ○ Anti-IL17 (secukinumab, ixekizumab, brodalumab) ○ Anti-IL23 (guselkumab, tildrakizumab, risankizumab, apremilast [second-line only]) Biosimilars of the above (where relevant) are included where relevant.	Ciclosporin and Acitretin* Any other treatment not listed as an included treatment (except for biosimilars of included treatments which are eligible for inclusion)
Outcomes	FAQ 1: What does the treatment involve? ○ Administration	

Item	Included	Excluded
	○ Frequency of dosing during induction and maintenance phases ○ Duration of the interventions ○ Onset of action ○ Contraindications FAQ 2: Will it help my symptoms? ○ Pruritus ○ Itching ○ Redness ○ Psoriasis Area and Severity Index score (PASI) FAQ 3: Will it help maintain remission of my disease? ○ Resolution of psoriasis affected skin ○ Relapse rate FAQ 4: How will the treatment impact on my quality of life? ○ Any generic health related quality of life (HRQoL) tools including but not limited to SF-36 Disease specific HRQOL tools: Dermatology Life Quality Index (DLQI); FAQ 5: What are the risks and side effects? ○ Treatment related adverse events (AEs) ○ Serious adverse events (SAEs)	
Study design	The following will be considered if published in the last 5yrs – 2015 onwards): ○ Systematic reviews with or without meta-analyses or NMA/MTC ○ Guidelines ○ Decision aids Priority has been given to the most up to date (i.e. 2018 onwards) and relevant (i.e. closet match to the PICOS) publications. Only English and German language publications have been included.	
* Conventional treatments - Ciclosporin and Acitretin – are not of primary relevance to Germany and will not be included in the review, but will be included in the background section of the report		

In consultation with the commissioner, questions frequently asked by patients, in respect of outcomes identified in the literature, were developed into an evidence table outline.

2.2 LITERATURE SEARCHES

Literature searches were carried out to identify relevant systematic reviews and evidence-based guidelines on the systemic therapy of adult patient with moderate to severe psoriasis. To inform FAQs a second targeted database search on psoriasis and shared decision making was also undertaken.

The search strategies were developed specifically for each database and the keywords adapted according to the configuration of each database. Searches were limited by date range

for systematic reviews and guidelines to 2015-2020. Targeted searches on shared decision-making and psoriasis were also limited to the last five years as current and up-to-date evidence in this area was most relevant. Searches were not limited by language or publication status.

2.3 SEARCH SOURCES

Systematic reviews and guidelines

The following systematic review specific databases were searched from 2015 to present:

- Cochrane Database of Systematic Reviews (CDSR) (Wiley): up to 2020/08/Iss8
- Database of Abstracts of Reviews of Effects (DARE) (www.crd.york.ac.uk): up to 2015/03
- Health Technology Assessment (HTA) database (www.crd.york.ac.uk): up to 2018/03
- INAHTA (https://database.inahta.org/): up to 2020/08/18
- KSR Evidence (KSR): up to 2020/08/14
- Epistemonikos (www.epistemonikos.org): up to 2020/08/19

The following guidelines resources were searched from 2015 to present:

- Guidelines International Network (G-I-N) (www.g-i-n.net): up to 2020/08/18
- NHS Evidence (www.evidence.nhs.uk): up to 2020/08/18
- ECRI Guidelines Trust (https://guidelines.ecri.org/): up to 2020/08/18
- NICE (www.nice.org.uk): up to 2020/08/18

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

Targeted searches

To identify questions relevant to shared decision making, targeted searches were undertaken in the following databases from 2015 to present:

- EMBASE (Ovid): 1974-2020/08/14
- MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily: 1946- 2020/08/14
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): up to 2020/08/Iss8

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

Handling of citations

Identified references from the bibliographic database searches were downloaded into EndNote bibliographic management software for further assessment and handling.

Supplementary searches

In addition, key websites of organisations supporting patients with psoriasis were searched to identify patient friendly information and leaflets about psoriasis and its treatment. These included:

- National Psoriasis Foundation Website (https://www.psoriasis.org/)
- British Association of Dermatologists (BAD) Website (https://www.bad.org.uk/)

Given the abundance of secondary research in this topic area (i.e. systematic reviews, NMA, guidelines etc.), no further supplementary searches were carried out for primary studies (including randomised controlled trials (RCTs) and observational studies).

2.4 METHODS OF DATA SELECTION, PRIORITISATION, EXTRACTION AND ANALYSIS

Data selection

Given the large number of retrieved references, a stepwise approach to screening was used to identify the most recent and relevant evidence. Two reviewers independently inspected the title and abstract of each reference identified by the search and determined the potential relevance of each article. Screening focused on references from 2018 onwards, with the intention of expanding this to include all the references from 2015 onwards if necessary. For potentially relevant articles, or in cases of disagreement, the full article was obtained, independently inspected, and inclusion criteria applied. Any disagreements were resolved through discussion.

Data extraction

An evidence hierarchy was used to select the most appropriate study(ies) to populate the evidence table. Where more than one study could provide evidence for the table, the most relevant studies were extracted using the following criteria: recency (most recent preferred), quality (highest quality preferred), representativeness (populations representative of the general target population preferred), and completeness (comparison between the most number of relevant treatments).

For each study, data were extracted by one reviewer and checked by another. Any disagreements were resolved by consensus.

3. RESULTS

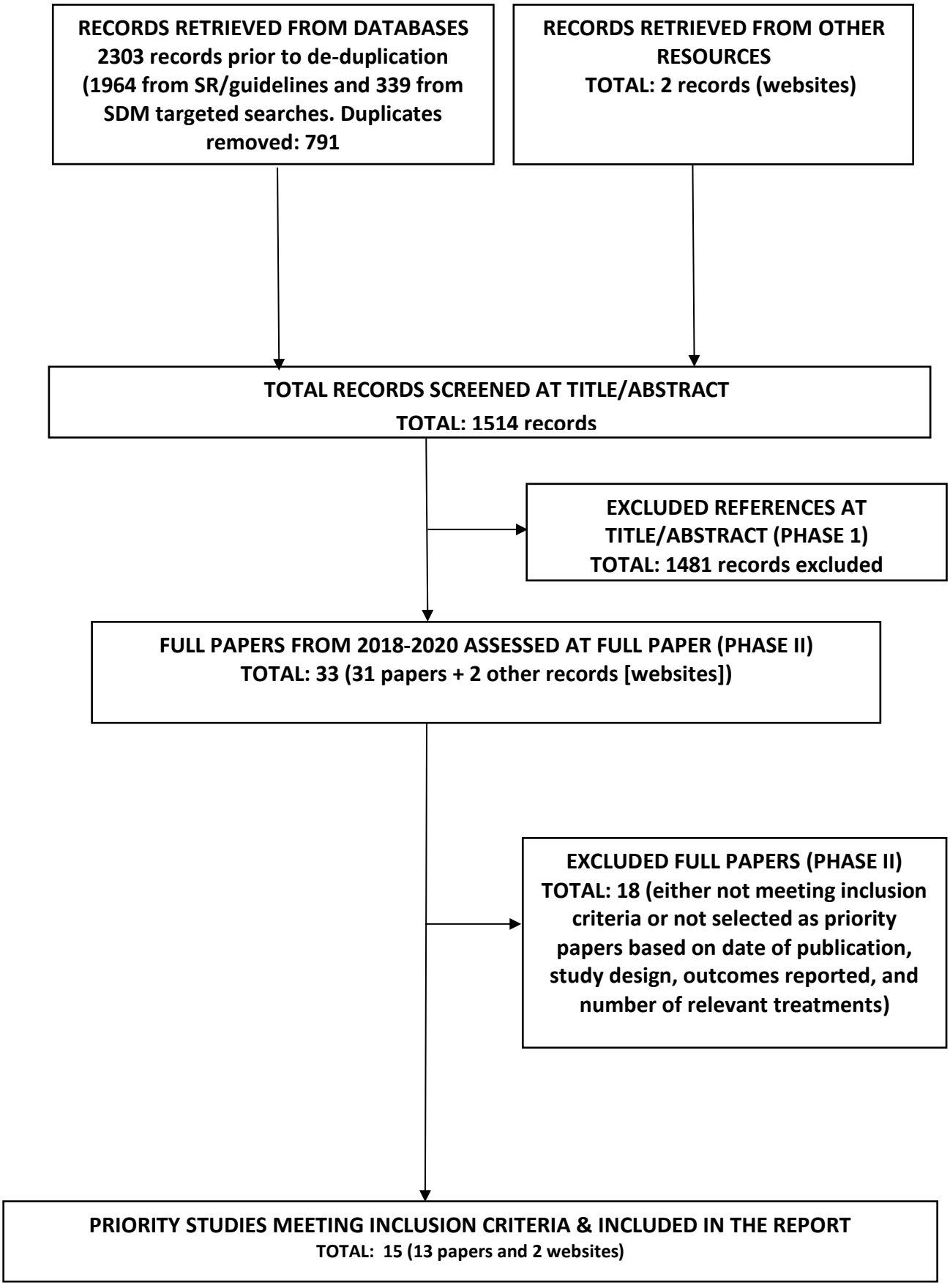
3.1 LITERATURE SEARCHES AND INCLUSION ASSESSMENT

For this evidence report, systematic searches for systematic reviews and guidelines were supplemented by hand searches.

Literature searches for systematic reviews, meta-analyses, NMA, SDM tools and evidence-based guidelines from 2015 onwards were conducted between 17 to 19 August 2020. A total of 2,303 database records and two website resources were identified and after de-duplication, 1,514 records were screened by two reviewers and full papers were obtained for 31 citations and two websites. During full paper screening 13 articles were selected as priority records for inclusion in the report based on the following criteria: date of publication, study design, outcomes reported, and number of relevant treatments compared. In addition, two patient-friendly websites were included; these provided additional background information on what the different treatments involve.

A summary of the study selection process is reported in Figure 1.

Figure 1: Summary of study selection process



3.2 Overview of the evidence

The relevant treatments of interest were:

- Conventional systemic therapy*:
  - Fumaric acid esters
  - Methotrexate
- Biologics:
  - Anti-TNF alpha (etanercept, infliximab, adalimumab, certolizumab) and their biosimilars
  - Anti-IL12/23 (ustekinumab)
  - Anti-IL17 (secukinumab, ixekizumab, brodalumab)
  - Anti-IL23 (guselkumab, tildrakizumab, risankizumab, apremilast [second-line only])

In addition, background information on UVA/UVB phototherapy and other supportive treatments including lifestyle changes was included, though these were not included in the main treatment comparisons.

The five FAQs of most concern to patients were developed into an evidence table outline (see Table 2). The key evidence sources used to support each of the FAQs are shown in Table 3. These included seven systematic reviews, five of which included network meta-analyses comparing different treatment options. In addition, two guidelines and two websites including patient friendly treatment summaries and/or leaflets were included.

Table 2: List of FAQs

FAQ #	FAQ Details	Evidence
1	**WHAT DOES THE TREATMENT INVOLVE?**	
	1.1 What does my treatment involve?	• Websites and patient friendly leaflets[1, 2] • Systematic review[3] • Guideline[4]
	1.2 Will I be treated at home?	
2	**WILL IT HELP MY SYMPTOMS?**	
	2.1 Will the treatment help my symptoms (redness, itching, pruritus, pain, Psoriasis Area and Severity Index score [PASI])?	• Systematic reviews with NMA reporting on Psoriasis Area Severity Index (PASI)[3, 5-7]
	2.2 How long will it take before I see an improvement in my symptoms?	• Systematic reviews with NMA reporting on shorter term (12-16 weeks) and longer term (1 year) effects on PASI*[5, 7]
3	**WILL IT HELP MAINTAIN REMISSION OF MY DISEASE?**	
	2.1 Will my disease return?	• Websites and patient friendly leaflets[1, 2] • Background papers[8-10]
4	**HOW WILL THE TREATMENT IMPACT ON MY QUALITY OF LIFE?**	
	4.1 How will the treatment affect my quality of life?	• Systematic reviews assessing the Dermatology Life Quality Index (DLQI)[3, 5]
5	**WHAT ARE THE RISKS AND SIDE EFFECTS?**	
	5.1 What side effects might I experience from my treatment?	• Websites and patient friendly leaflets [1, 2] • Systematic reviews with NMA of adverse events [3, 11] • Guidelines[4, 12]
	5.2 Are there any serious risks associated with my treatment?	• Systematic reviews with NMA of adverse events[1, 2] • Websites and patient friendly leaflets[3, 11] • Guidelines[4, 12]

***** PASI is a quantitative rating score for measuring the severity of psoriatic lesions based on area coverage and plaque appearance; the score is based on the assessment of three characteristics (erythema; induration/thickness and scaling) of the lesions

NOTE: the scoping document states: "As background information an overview of the therapy options should be provided (see figure from the German S3 guideline). This includes:
- Avoidance of trigger factors (weight reduction, smoking cessation)
- Basic therapy (which any patient receives as accompanying treatment - includes topical application of the active substance-free ointment bases as well as the topical preparations of urea (3-10%))
- topical and phototherapy (which can be given as add on to systemic therapy)"

Information to address this has been taken from Ko 2019[13] – Cochrane review evaluating lifestyle interventions and comparing these treatments to no treatment or active treatments

NOTE: the scoping document states: "It is important to mention that some biologics and apremilast are only applied second-line" – this has been included in the report but not as a main comparator and is reported as second-line use only.
NMA network meta-analysis; PASI Psoriasis Area Severity Index

Table 3: Summary of included papers and evidence for each type of treatment

Evidence name	Evidence type	Fumaric acid esters	Methotrexate	Anti-TNF-alpha	Anti-IL23	Anti-IL12/23	Anti-IL-17
Warren RB, See K, Burge R, Zhang Y, Brnabic A, Gallo G, et al. Rapid response of biologic treatments of moderate-to-severe plaque psoriasis: a comprehensive investigation using bayesian and frequentist network meta-analyses. Dermatology & Therapy (Heidelb) 2020;10(1):73-86.	SR with NMA/MTC	No	No	Yes	Yes	Yes	Yes
Warren RB, Gooderham M, Burge R, Zhu B, Amato D, Liu KH, et al. Comparison of cumulative clinical benefits of biologics for the treatment of psoriasis over 16 weeks: results from a network meta-analysis. *J Am Acad Dermatol* 2020;82(5):1138-49.	SR with NMA/MTC	No	No	No	Yes	Yes	Yes
Armstrong AW, Puig L, Joshi A, Skup M, Williams D, Li J, et al. Comparison of biologics and oral treatments for plaque psoriasis: a meta-analysis. JAMA Dermatol 2020;156(3):258-69.	SR with NMA/MTC	Yes	No	Yes	Yes	Yes	Yes
Yasmeen N, Sawyer LM, Malottki K, Levin LA, Didriksen Apol E, Jemec GB. Targeted therapies for patients with moderate-to-severe psoriasis: a systematic review and network meta-analysis of PASI response at 1 year. J of Dermatological Treatment 2020; Epub ahead of print:1-15.	SR with NMA/MTC	No	No	Yes	Yes	Yes	Yes
Balak DMW, Gerdes S, Parodi A, Salgado-Boquete L. Long-term Safety of Oral Systemic Therapies for Psoriasis: A Comprehensive Review of the Literature. Dermatol Ther (Heidelb) 2020;10(4):589-613.	SR	Yes	Yes	No	No	No	No
Afach S, Chaimani A, Evrenoglou T, Penso L, Brouste E, Sbidian É, et al. Meta-analysis results do not reflect the real safety of biologics in psoriasis. The British journal of dermatology 2020.	SR	No	No	Yes	Yes	Yes	Yes

Evidence name	Evidence type	Fumaric acid esters	Methotrexate	Anti-TNF-alpha	Anti-IL23	Anti-IL12/23	Anti-IL-17
Sbidian E, Chaimani A, Afach S, Doney L, Dressler C, Hua C, et al. Systemic pharmacological treatments for chronic plaque psoriasis a network meta-analysis. Cochrane Database Syst Rev 2020, Issue 1. Art. No.: CD011535. DOI: 10.1002/14651858.CD011535.pub3	SR with NMA/MTC	Yes	Yes	Yes	Yes	Yes	Yes
National Psoriasis Foundation Website (https://www.psoriasis.org/)	Patient information	No	Yes	Yes	Yes	No	Yes
British Association of Dermatologists (BAD) Website (https://www.bad.org.uk/)	Patient information	Yes	Yes	Yes	Yes	No	Yes
Nast A, Amelunxen L, Augustin M, Boehncke W-H, Dressler C, Gaskins M, et al. S3 - Leitlinie zur therapie der psoriasis vulgaris: update 2017 (S3-Leitlinie 013-001) [Internet]: Association of Scientific Medical Societies (AWMF), 2017 Available from: https://www.awmf.org/uploads/tx_szleitlinien/013-001l_S3_Therapie_Psoriasis-vulgaris_2017-12.pdf	German guidelines	Yes	Yes	Yes	Yes	Yes	Yes
Nast A, Smith C, Spuls PI, Avila Valle G, Bata-Csörgö Z, Boonen H, et al. EuroGuiDerm guideline for the systemic treatment of psoriasis vulgaris [Internet]: European Centre for Guidelines Development, European Dermatology Forum, Charite dEBM, 2020 [accessed 20.11.20] Available from: https://www.edf.one/home/Guidelines/EuroGuiDerm-psoriasis-vulgaris.html	European guidelines	Yes	Yes	Yes	Yes	Yes	Yes

3.3 FAQ 1. WHAT DOES THE TREATMENT INVOLVE?

This section covers the administration, frequency of dosing during induction and maintenance phases, duration of the interventions, onsets of action, and contraindications (see Tables 4 and 5).

Psoriasis is a condition which can be affiliated with chronic inflammatory effects effecting the skin or joints.[3] While the cause of the condition is not fully understood, interactions with environmental factors, such as stress, injury, and infections can trigger psoriasis.[3] While the severity of the disease generally fluctuates at the same level across individuals, the evolution of the disease can be unpredictable.[3] This can impact quality of life in patients with psoriasis.[3] While there is no cure for psoriasis, various treatments are available to control the symptoms.[3] For daily practice, a treatment strategy requires a defined induction therapy and a maintenance therapy.[3]

Changes in lifestyle are often recommended as a method for addressing psoriasis.[13] Such lifestyle interventions can include weight reduction, alcohol abstinence, smoking cessation, and exercise.[13] The purpose of the identified lifestyle interventions can include reducing inflammation, reducing free radical production, decreasing the volume of drug distribution, and improving the body composition.[13]

Topical treatments can be used as a first-line treatment for minor psoriasis.[3] Topical therapy can include a corticosteroid applied once daily in addition to a Vitamin D or Vitamin D analogue, also applied once daily, for a four-week period. If topical treatments are ineffective, phototherapy can be utilised.[1, 2] Ultraviolet B (UVB) phototherapy can be given two to three times per week.[1, 2]

Patients with a more moderate form of the disease will proceed to second-line treatment, which can include phototherapy and conventional systemic therapy.[3] Third-line treatments can include biological agents including tumour necrosis factor (TNF) antagonists, the monoclonal antibody ustekinumab targeting interleukin-12 and -23, anti-IL17, and small molecules.[3]

Table 4: A summary of treatments available for the treatment of moderate to severe plaque psoriasis

Conventional Systemic Therapy
Systemic therapy can be offered to patients with any type of psoriasis that cannot be addressed with topical treatments, has a significant impact on patient wellbeing, and if the psoriasis is extensive, or if the condition is associated with significant functional impairment (i.e. on the nails), or phototherapy was ineffective. Methotrexate is generally offered as a first-choice treatment if criteria for systemic therapy are met. The provided dose will typically start at 5-10mg once per week as an oral medication. This will then increase to a maximum dose of 25mg per week.
Biologics
The types of biologics used for treating psoriasis can include Anti-TNF alpha, Anti-IL12/23, Anti-IL17, and Anti-IL23. Biologics are administered as either an injection or as an infusion. The utilised doses for different biologics are provided in the table below.

Conventional Systemic Therapy
Data taken from references[1-4]

Table 5: A summary of treatment regimens for biologic and conventional systematic therapies to treat moderate to severe plaque psoriasis

	Conventional Systemic Therapy	Biologics
What treatments are available? [1]	• **Fumaric acid esters** • **Methotrexate**	• **Anti-TNF alpha (etanercept, infliximab, adalimumab, certolizumab) and their biosimilars.** • **Anti-IL12/23 (ustekinumab)** • **Anti-IL17 (secukinumab, ixekizumab, brodalumab)** • **Anti-IL23 (guselkumab, tildrakizumab, risankizumab)** • **Small molecules (premilast [second-line only])**
Which treatment is right for me? **What are the contraindications?**	**Methotrexate:** Should not be taken by pregnant women or women who are trying to get pregnant (treatment should be stopped three months prior). Should also not be taken by women who are breastfeeding. People who have liver disease should not take methotrexate, and you should not drink alcohol when taking it. **Fumaric acid esters:** Treatment should be avoided in pregnant women and women should avoid getting pregnant whilst undergoing treatment. People who have liver disease of are at risk of serious infections should not take fumaric acid esters.	Which biologic is right for you depends on factors such as comorbidity. Your doctor will discuss with you which biological fits best for you. Certain comorbidities might preclude you from using a specific medication. Evidence on whether biologic treatments are harmful during pregnancy is unclear. In general, biologic treatments are not to be taken by people who have or are at high risk of serious infections, those with a weakened immune systems, those undergoing surgical/dental procedures which may increase their risk of infection, and those with conditions such as inflammatory bowel disease.
How is the treatment administered? **Frequency of dosing during induction**	**Methotrexate:** Tablets are taken orally once a week. **Fumaric acid esters:** Tablets are taken orally once a day. The treatment will take weeks and it may take several months before the psoriasis really improves depending on the dose of medication. If there has not been a	**Etanercept**: Given as an injection under your skin (subcutaneously) using a pre-filled syringe device twice a week. Etanercept works over several weeks and it may take up to three months before someone's psoriasis really improves. If there has not been a considerable improvement after 3 months the medication is stopped. **Infliximab**: Administered as an intravenous infusion into your vein at the hospital. Three infusions will be given in the first 6 weeks, then one infusion

	Conventional Systemic Therapy	Biologics
and maintenance phases **How much of the dose am I getting?** **How frequently do I need to take my dose?** **How long do I take the treatment for?**	considerable improvement after 6 months, the medication should be stopped.	every 8 weeks. If there is no improvement in your psoriasis after 10 weeks, the treatment will be stopped. **Adalimumab**: Given as an injection under your skin (subcutaneously) using a pre-filled syringe device once every 2 weeks. Adalimumab does not work immediately, and it may be 3-12 weeks before you notice any benefit. If there is no improvement in your psoriasis after 16 weeks, the treatment will be stopped. If the response at four months is deemed adequate, treatment would then normally be continued to maintain improvement. **Ustekinumab**: Injected under your skin (subcutaneously) at the beginning of treatment, then again 4 weeks later. After this, injections are every 12 weeks. If there is no improvement in your psoriasis after 16 weeks, the treatment will be stopped. If there is a good response, the treatment will then normally be continued to maintain improvement with an injection once every 12 weeks. **Secukinumab:** Given as an injection under your skin (subcutaneously) using a pre-filled syringe. After the first dose you will continue to receive weekly injections for another four weeks, followed by monthly injections thereafter. The effects will not be seen immediately, and it can take several weeks before you see an improvement of your psoriasis. If after this time, there is no improvement treatment may be stopped. Secukinumab is intended as a long-term treatment to maintain control of your psoriasis. **Ixekizumab**: Given as an injection under your skin (subcutaneously) using a pre-filled syringe. After the first dose you will need to inject every other week for six doses and then after the first 12 weeks of treatment, you will then need to inject every four weeks. Some improvement in your psoriasis may occur in the first few weeks of treatment but it can take 3 months to see the full benefit. If no significant improvement occurs after this time the treatment will be stopped. If you respond this can be continued to maintain long-term control of your psoriasis.

	Conventional Systemic Therapy	Biologics
		Brodalumab: Given as an injection under your skin (subcutaneously) using a pre-filled syringe device once a week for the first three weeks and then every other week. If you respond this can be continued to maintain long-term control of your psoriasis. Some improvement in your psoriasis may occur in the first few weeks of treatment but it can take 3 months to see the full benefit. If no improvement occurs after this time treatment will be stopped. **Guselkumab**: Given as an injection under your skin (subcutaneously) using a pre-filled syringe device. After the first dose a second dose is given 4 weeks later. After this you should inject once every 8 weeks. Some improvement in your psoriasis may occur in the first few weeks of treatment, but it can take 4 months to see the full benefit. If you the psoriasis improves the treatment can be continued to maintain long-term control of your psoriasis. If there is no improvement in your psoriasis after 16 weeks treatment will be stopped. **Tildrakizumab**: Given as an injection under your skin (subcutaneously) using a pre-filled syringe device. After the first dose the second dose should be injected 4 weeks later and then once every 12 weeks. Some improvement in your psoriasis may occur in the first few weeks of treatment, but it can take 7 months to see the full benefit. If there is no significant improvement after this time treatment will be stopped. If you respond this can be continued to maintain long-term control of your psoriasis. **Risankizumab**: Given as an injection under your skin (subcutaneously) using a pre-filled syringe device. After the first dose you will need another 4 weeks later, then you should continue to inject every 12 weeks. Some improvement in your psoriasis may occur in the first few weeks of treatment but it can take 4 months to see the full benefit. If your psoriasis does not improve after this time treatment may be stopped. If you respond, this can be continued to maintain long-term control of your psoriasis. **Certolizumab**: Given as an injection under your skin (subcutaneously) using a pre-filled syringe every two weeks. Patients usually see a response within 16

	Conventional Systemic Therapy	Biologics
		weeks, and treatment may be stopped if there is not improvement in your psoriasis after 16 weeks. **Apremilast**: Given as daily oral tablets. The greatest improvement will be seen in the first 16 weeks of treatment. If no improvement is seen in this period, the doctor may decide to change your treatment.
Can I be treated at home?	Yes.	Yes. A nurse or doctor can show you how to inject yourself. In the case of infliximab, this can be addressed in an outpatient unit.
Do I need a blood test?	**Methotrexate:** When you start taking methotrexate, you may need to get a blood test (to check it is not having any adverse effects on your liver) every two to four weeks for a few months. Then, you are likely need a blood test every one to three months. If a test result shows a problem, you may need to stop taking methotrexate. **Fumaric acid esters:** Before treatment is started, routine blood tests are usually needed to check the full blood count, kidney function and liver function. Additional tests may include HIV and hepatitis virus infection in people who are at risk of these infections. Blood tests will also be needed usually every 3 months and in some cases more frequently to check the treatment is not having any adverse effects.	**Biologics:** Before you start biologics, you will need a blood test prior to starting treatment and then regular tests (generally every 3-6 months) to monitor the effects of the treatment on your body, including the liver.
[1] **Note: Ciclosporin is an option for women who wish to have children and is acceptable during pregnancy considering the risk-benefit ratio.** Data taken from references[1-4]		
Abbreviations: kg kilogram; mg milligram; TNF tumour necrosis factor		

3.4 FAQ 2. WILL IT HELP MY SYMPTOMS?

Will the treatment help my symptoms (redness, itching, pruritus, pain, Psoriasis Area and Severity Index score [PASI])?

And

How long will it take before I see an improvement in my symptoms?

The only evidence from recent systematic reviews was for psoriasis symptoms measured using the PASI scale.[14] This measures redness, thickness, and scale on a five-point scale across four regions of the body, the head, upper extremities, lower extremities, and trunk. It also includes the percentage of the skin in each area covered with psoriasis. These scores are combined into a single score ranging from zero (no disease) to 72 (most severe). In clinical trials the outcomes used are PASI 75, PASI 90 and PASI 100 which reflect a ≥ 75%, ≥ 90% and ≥ 100% improvement in PASI score.[14] PASI 90 reflects the achievement of clear or almost clear skin.[3]

Two systematic reviews were used to compare PASI outcomes at 12-16 weeks[5] with longer term (e.g. one year)[7] outcomes across different treatments (see Tables 6 and 7).

A systematic review and Bayesian network meta-analysis (NMA) of phase III randomised controlled trials (RCTs) evaluating biologic treatments in adults with moderate to severe psoriasis, provided evidence for PASI response up to 12 weeks.[5] Literature was searched up to December 2018 and 32 trials of 11 biologics were included in the analysis. There was no quality assessment of the included trials. PASI outcomes were analysed after two, four, eight and 12 weeks of treatment, results for 12 weeks and treatment rankings are shown in Table 6. IL-17 antagonists had the most rapid treatment effects with ixekizumab and brodalumab having a greater effect on all PASI outcomes at week 8 or earlier compared to other biologics. After 12 weeks of treatment the most effective treatments were ixekizumab (ranked first for PASI 70 and 90 and second for PASI 100), brodalumab (ranked third for PASI 75, second for PASI 90 and first for PASI 100) and risankizumab (ranked second for PASI 75 and third for PASI 90 and 100). The least effective treatment was etanercept. A summary of these findings is reported in Table 6.

A second systematic review with Bayesian NMA[7] provided evidence for PASI response at one year. This included RCTs and extension studies comparing European Medicines Agency (EMA)-approved biologic treatments at their licensed doses with any comparator (placebo, another biologic or non-biologic) in adults with moderate to severe chronic plaque psoriasis. The literature was searched up to September 2019, 88 trials were included in the systematic review and 28 provided outcome data for the analysis. Trial quality was assessed using the Cochrane tool for RCTs and most trials (> 80%) were considered to be at a low risk of bias across all domains with 86% reporting an appropriate method of randomisation and 89% having allocation concealment. Four trials (14%) were considered as high risk of bias due to a

lack of blinding as the extension period was open label. The results from the NMA and associated treatment rankings are presented in Table 7.

The treatment which was the most effective at reducing symptoms as measured by the PASI score was risankizumab followed by guselkumab, brodalumab, ixekizumab and secukinumab. Apremilast was the least effective treatment (as shown by the rankings in Table 7). The estimated percentage of patients achieving clear skin (PASI100) was greatest with anti-IL23 inhibitors (53 to 59%) and anti-IL17 inhibitors (41 to 53%) and lowest with apremilast (3.7%).

Table 6: Summary of NMA evidence for PASI after 12 weeks of treatment

Drug	Treatment effect vs placebo (95% CrI) - PASI 75	PASI 75 Ranking	Treatment effect vs placebo (95% CrI) - PASI 90	PASI 90 Ranking	Treatment effect vs placebo (95% CrI) - PASI 100	PASI 100 Ranking
Biologics						
Anti-IL17						
Secukinumab	0.76 (0.74 to 0.79)	4	0.59 (0.56 to 0.62)	4	0.29 (0.36 to 0.32)	4
Ixekizumab	0.85 (0.83 to 0.87)	1	0.70 (0.67 to 0.72)	1	0.38 (0.36 to 0.41)	2
Brodalumab	0.79 (0.77 to 0.81)	3	0.67 (0.65 to 0.70)	2	0.40 (0.38 to 0.43)	1
Anti-IL23						
Guselkumab	0.75 (0.72 to 0.78)	6	0.54 (0.50 to 0.58)	6	0.21 (0.18 to 0.25)	5
Tildrakizumab	0.57 (0.53 to 0.62)	10	0.35 (0.31 to 0.39)	9	0.12 (0.10 to 0.15)	8
Risankizumab	0.80 (0.75 to 0.84)	2	0.62 (0.58 to 0.67)	3	0.31 (0.27 to 0.34)	3
Anti-IL23/12						
Ustekinumab	0.63 (0.60 to 0.66)	8	0.42 (0.40 to 0.45)	7	0.16 (0.14 to 0.17)	6
Anti-TNF alpha						
Etanercept	0.44 (0.42 to 0.47)	11	0.21 (0.19 to 0.23)	11	0.05 (0.04 to 0.06)	9
Infliximab	0.75 (0.72 to 0.79)	5	0.57 (0.51 to 0.63)	5	NR	-
Adalimumab	0.63 (0.60 to 0.66)	7	0.37 (0.34 to 0.40)	8	0.13 (0.11 to 0.15)	7
Certolizumab	0.61 (0.55 to 0.67)	9	0.34 (0.29 to 0.40)	10	NR	-
All comparisons are versus placebo, results are the treatment effect relative to placebo (proportion); rankings - the lower the value the better the drug at relieving symptoms Data taken from Warren 2020[5]						
Abbreviations: CrI credible interval; NR not reported						

Table 7: Summary of NMA evidence for PASI after one year of treatment

Drug	RR vs. placebo (95% CrI) - PASI 75	% with PASI 75	PASI 75 Ranking	RR vs placebo (95% CI) - PASI 90	% with PASI 90	PASI 90 Ranking	RR vs placebo (95% CI) - PASI 100	% with PASI 100	PASI 100 Ranking
Biologics									
Anti-IL17									
Secukinumab	14.11 (4.9 to 51.81)	81.9	5	34.36 (10.03 to 144.13)	66.0	5	124.07 (30.49 to 593.47)	40.6	5
Ixekizumab	14.63 (4.96 to 56.27)	85.0	4	36.66 (10.33 to 162.71)	70.5	4	138.93 (32.36 to 720.46)	45.6	4
Brodalumab	15.34 (5.03 to 62.62)	89.1	3	39.95 (10.67 to 193.72)	76.8	3	162.50 (34.9 to 941.62)	53.3	3
Anti-IL23									
Guselkumab	15.34 (5.05 to 62.07)	89.1	2	39.97 (10.73 to 189.43)	76.8	2	162.79 (35.45 to 905.8)	53.3	2
Risankizumab	15.76 (5.08 to 66.67)	91.5	1	42.09 (10.9 to 213.49)	80.9	1	179.82 (36.9 to 1104.12)	58.9	1
Anti-IL-23/12									
Ustekinumab	12.25 (4.6 to 40.65)	71.2	7	27.22 (8.85 to 101.5)	52.4	7	84.74 (23.74 to 359)	27.8	7
Anti-TNF alpha									
Etanercept	9.87 (4.19 to 27.5)	57.5	11	19.6 (7.49 to 59.56)	37.8	11	51.26 (17.54 to 170.53)	16.9	11
Infliximab	12.68 (4.7 to 42.63)	74.3	6	28.84 (9.22 to 110.12)	56.0	6	92.94 (25.58 to 407.83)	30.9	6
Adalimumab	11.81 (4.55 to 37.44)	68.9	9	25.72 (8.69 to 90.91)	49.7	9	77.46 (22.82 to 309.02)	25.6	9
Certolizumab pegol 200	10.64 (4.33 to 32.21)	62.8	10	21.97 (7.92 to 75.13)	43.1	10	61.2 (19.11 to 242.78)	20.6	10
Certolizumab pegol 400	12.09 (4.6 to 39.59)	71.1	8	26.75 (8.82 to 99.6)	52.2	8	82.71 (23.47 to 357.4)	27.6	8
Small molecules									
Apremilast	4.43 (2.54 to 8.99)	26.2	12	6.52 (3.43 to 14.47)	12.8	12	11.09 (5.16 to 27.72)	3.7	12
Placebo									
Placebo	NA	5.8	13	NA	1.9	13	NA	0.3	13

All comparisons are versus placebo; rankings - the lower the value the better the drug at relieving symptoms
NOTE: Data were not reported for Tildrakizumab
% with PASI are the estimated percentages with each PASI response predicted from the NMA

Drug	RR vs. placebo (95% CrI) - PASI 75	% with PASI 75	PASI 75 Ranking	RR vs placebo (95% CI) - PASI 90	% with PASI 90	PASI 90 Ranking	RR vs placebo (95% CI) - PASI 100	% with PASI 100	PASI 100 Ranking
Data taken from Yasmeen 2020[7]									
Abbreviations: CrI credible interval; NA not applicable; NR not reported; RR risk ratio									

A Cochrane Review published in 2020 evaluated conventional systemic agents (acitretin, ciclosporin, fumaric acid esters, methotrexate), small molecules (apremilast, tofacitinib, ponesimod), anti-TNF alpha (etanercept, infliximab, adalimumab, certolizumab), anti-IL12/23 (ustekinumab), anti-IL17 (secukinumab, ixekizumab, brodalumab), anti-IL23 (guselkumab, tildrakizumab) and other biologics (alefacept and itolizumab).[3] This included phase 2, 3 and 4 RCTs in adults with moderate to severe plaque psoriasis or psoriatic arthritis whose skin had been clinically diagnosed with moderate to severe psoriasis. A total of 140 trials were included which compared systemic and biologics to each other, or to placebo. Frequentist NMA compared PASI 75 and PASI 90 outcomes after 8 to 24 weeks of treatment between individual drugs and between drug classes. Trial quality was assessed using the Cochrane tool and 41 (29%) were judged as low risk of bias, 42 (30%) at unclear risk of bias and 57 (41%) at high risk of bias.

PASI 90 was reported by 95 trials. The results showed that the most effective treatment for improving PASI 90 after 8 to 24 weeks of treatment was infliximab followed by ixekizumab risankizumab, bimekizumab, guselkumab, secukinumab and brodalumab. Results for PASI 90 by individual drug showing absolute effects (risk of PASI 90 per 1000 people) are shown in Table 8. For PASI 75, infliximab was the most effective treatment, followed by ixekizumab, secukinumab, brodalumab, and guselkumab (Table 9).

NMAs were also performed for drug classes and the results are shown in Table 10. These showed that anti-IL17 treatments had a greater chance of achieving a PASI 90 response compared to placebo with a risk ratio (RR) of 29.33 (95% CI 23.38 to 36.79). All biologic treatments (anti-IL12/23, anti-IL23 and anti-TNF alpha) were superior to small molecule and conventional systemic treatments. Results for PASI 75 also showed that anti-IL17 treatments were the most effective at improving symptoms (RR 13.50, 95% CI 11.76 to 15.50).

Table 8: PASI 90 results by individual drug after 8 to 24 weeks

Drug	Number of studies	Number of patients	RR vs. placebo (95% CI)	Absolute risk (95% CI)	With placebo – success[§]	With treatment – success (95% CI)[§]	Ranking	Level of evidence (GRADE)
Conventional systemic agents								
Methotrexate	3	318	2.06 (0.53 to 7.97)	20 per 1000 (-9 to 132)	19 per 1000 (16 to 22)	39 per 1000 (7 to 154)	11	Low
Fumeric acid esters	1	704	4.47 (2.01 to 9.95)	66 per 1000 (19 to 170)	19 per 1000 (16 to 22)	85 per 1000 (35 to 192)	14	Very low
Biologics								
Anti-IL17								
Secukinumab	8	2895	27.47 (15.87 to 47.71)	503 per 1000 (283 to 887)	19 per 1000 (16 to 22)	522 per 1000 (299 to 909)	5	High
Ixekizumab	4	3268	53.85 (15.34 to 189.1)	1004 per 1000 (272 to 3573)	19 per 1000 (16 to 22)	1000 per 1000 (288 to 1000)[#]	2	Moderate
Brodalumab	5	4109	26.33 (16.77 to 41.33)	481 per 1000 (300 to 766)	19 per 1000 (16 to 22)	500 per 1000 (316 to 788)	6	Moderate
Anti-IL23								
Guselkumab	5	1767	27.79 (16.23 to 47.60)	509 per 1000 (289 to 885)	19 per 1000 (16 to 22)	528 per 1000 (305 to 907)	4	Moderate
Tildrakizumab	3	1903	17.26 (8.27 to 36.05)	309 per 1000 (138 to 666)	19 per 1000 (16 to 22)	328 per 1000 (154 to 688)	9	High
Risankizumab	4	1476	24.00 (13.04 to 44.18)	437 per 1000 (229 to 820)	19 per 1000 (16 to 22)	456 per 1000 (245 to 842)	3	High
Anti-IL23/12								
Ustekinumab	9	4231	20.02 (13.01 to 30.81)	361 per 1000 (228 to 556)	19 per 1000 (16 to 22)	380 per 1000 (244 to 578)	8	High
Anti-TNF alpha								
Etanercept	14	5650	11.68 (8.14 to 16.75)	203 per 1000 (136 to 299)	19 per 1000 (16 to 22)	222 per 1000 (152 to 321)	12	Moderate
Infliximab	5	1651	27.71 (12.52 to 61.30)	507 per 1000 (219 to 1146)	19 per 1000 (16 to 22)	526 per 1000 (235 to 1000)[#]	1	Moderate

Drug	Number of studies	Number of patients	RR vs. placebo (95% CI)	Absolute risk (95% CI)	With placebo – success[§]	With treatment – success (95% CI)[§]	Ranking	Level of evidence (GRADE)
Adalimumab	9	3421	13.13 (8.01 to 21.53)	230 per 1000 (133 to 390)	19 per 1000 (16 to 22)	249 per 1000 (149 to 412)	7	Moderate
Certolizumab	4	1026	18.54 (7.42 to 46.32)	333 per 1000 (122 to 861)	19 per 1000 (16 to 22)	352 (138 to 883)	10	Moderate
Small molecules[*]								
Apremilast [second-line only)	5	2029	6.94 (3.37 to 14.30)	113 per 1000 (45 to 253)	19 per 1000 (16 to 22)	132 (61 to 275)	13	Moderate
Tofacitinib	5	3092	7.81 (4.54 to 13.46)	129 per 1000 (67 to 237)	19 per 1000 (16 to 22)	148 per 1000 (83 to 259)	NA	Moderate
TYK2	1	267	13.99 (1.99 to 98.10)	247 per 1000 (19 to 1845)	19 per 1000 (16 to 22)	266 per 1000 (35 to 1000)[#]	NA	Very low

GRADE Working Group grades of evidence:
High certainty: Very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: Moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: Very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
[§] Own calculations; [#] capped at 1000;[*] Includes apremilast, tofacitinib and ponesimod
Data taken from analyses 1.1, 1.3-1.6, and 1.9 of Sbidian 2020[3]. Absolute risks calculated with GRADE profiler, i.e. upper ranges over 1000 given there. Absolute risk on placebo based on control risk (calculated to be 1.9% across the placebo arms of included trials).

CI confidence interval; NA not applicable; RR risk ratio. Smaller rankings indicate a greater increase in proportion achieving PASI 90

Table 9: PASI 75 results by individual drug after 8 to 24 weeks

Drug	Number of studies	Number of patients	RR vs. placebo (95% CI)	Absolute risk (range)	With placebo – success[§]	With treatment – success (95% CI)[§]	Level of evidence (GRADE)
Conventional systemic agents							
Methotrexate	2	283	2.36 (1.19 to 4.68)	83 per 1000 (12 to 224)	61 per 1000 (57 to 66)	144 per 1000 (69 to 290)	Low
Fumeric acid esters	1	704	2.56 (1.68 to 3.89)	95 per 1000 (41 to 176)	61 per 1000 (57 to 66)	156 per 1000 (98 to 242)	Very low
Biologics							
Anti-IL17							
Secukinumab	8	2905	15.22 (11.03 to 21.01)	867 per 1000 (612 to 1221)	61 per 1000 (57 to 66)	928 per 1000 (669 to 1000)[#]	High
Ixekizumab	4	3268	17.44 (10.45 to 29.10)	1003 per 1000 (576 to 1714)	61 per 1000 (57 to 66)	1000 per 1000 (633 to 1000)[#]	Moderate
Brodalumab	5	4109	12.80 (8.46 to 19.36)	720 per 1000 (455 to 1120)	61 per 1000 (57 to 66)	781 per 1000 (502 to 1000)[#]	Moderate
Anti-IL23							
Guselkumab	5	1767	12.65 (9.24 to 17.31)	711 per 1000 (503 to 995)	61 per 1000 (57 to 66)	772 per 1000 (560 to 1000)[#]	Moderate
Tildrakizumab	3	1904	11.24 (7.33 to 17.23)	625 per 1000 (386 to 990)	61 per 1000 (57 to 66)	686 per 1000 (443 to 1000)[#]	High
Risankizumab	4	1476	11.36 (7.95 to 16.21)	632 per 1000 (424 to 928)	61 per 1000 (57 to 66)	693 per 1000 (481 to 994)	High
Anti-IL23/12							
Ustekinumab	10	4553	11.71 (8.78 to 15.63)	653 per 1000 (475 to 892)	61 per 1000 (57 to 66)	714 per 1000 (532 to 958)	High
Anti-TNF alpha							
Etanercept	15	5762	8.56 (7.07 to 10.36)	461 per 1000 (370 to 571)	61 per 1000 (57 to 66)	522 per 1000 (427 to 637)	Moderate
Infliximab	6	1678	18.87 (8.53 to 41.75)	1090 per 1000 (459 to 2486)	61 per 1000 (57 to 66)	1000 per 1000 (516 to 1000)[#]	Moderate
Adalimumab	10	3485	8.25 (6.03 to 11.29)	442 per 1000 (307 to 628)	61 per 1000 (57 to 66)	503 per 1000 (364 to 694)	Moderate
Certolizumab	4	1026	9.45 (5.90 to	515 per 1000 (299 to 861)	61 per 1000 (57	576 per 1000	Moderate

Drug	Number of studies	Number of patients	RR vs. placebo (95% CI)	Absolute risk (range)	With placebo – success[§]	With treatment – success (95% CI)[§]	Level of evidence (GRADE)
			15.12)		to 66)	(356 to 927)	
Small molecules							
Apremilast	6	2229	3.86 (2.59 to 5.74)	174 per 1000 (97 to 289)	61 per 1000 (57 to 66)	235 per 1000 (154 to 355)	Moderate
Tofacitinib	7	3122	6.14 (4.31 to 8.73)	314 per 1000 (202 to 472)	61 per 1000 (57 to 66)	375 per 1000 (259 to 538)	Moderate
TYK2	1	267	7.77 (2.59 to 23.36)	413 per 1000 (97 to 1364)	61 per 1000 (57 to 66)	474 per 1000 (154 to 1000)[#]	Very low

GRADE Working Group grades of evidence:
High certainty: Very confident that the true effect lies close to that of the estimate of the effect; *Moderate certainty:* Moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; *Low certainty*: Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect; *Very low certainty*: Very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[§] Own calculations; [#] capped at 1000; CI confidence interval; RR risk ratio
Data taken from analyses 3.1, 3.3-3.6, and 3.9 of Sbidian 2020[3]. Absolute risks calculated with GRADE profiler, i.e. upper ranges over 1000 given there. Absolute risk on placebo based on control risk (calculated to be 6.1% across the placebo arms of included trials).

Table 10: Results by drug class after 8 to 24 weeks of treatment

Drug	RR vs placebo (95% CI) – PASI 75	PASI 75 Ranking	RR vs placebo (95% CI) – PASI 90	PASI 90 Ranking
Conventional systemic agents	4.28 (3.58 to 5.12)	6	4.65 (3.38 to 6.39)	6
Biologics	-	-	-	-
Anti-IL17	13.50 (11.76 to 15.50)	1	29.33 (23.38 to 36.79)	1
Anti-IL23	11.68 (10.12 to 13.49)	2	23.38 (18.49 to 29.56)	2
Anti-IL12/23	11.12 (9.64 to 12.83)	3	19.34 (15.28 to 24.48)	3
Anti-TNF alpha	8.59 (7.66 to 9.64)	4	13.33 (10.95 to 16.21)	4
Small molecules	5.73 (4.76 to 6.90)	5	9.01 (6.58 to 12.33)	5
All comparisons are vs. placebo; rankings - the lower the value the better the drug at relieving symptoms Data taken from Sbidian 2020[3]				
CI confidence interval; GRADE Grading of Recommendations, Assessment, Development and Evaluations; RR risk ratio				

3.5 FAQ 3: WILL IT HELP MAINTAIN REMISSION OF MY DISEASE?

Will my disease return?

Disease remission and relapse rates were not reported in the identified reviews. Psoriasis is a chronic disease for which there is no cure. European consensus on the treatment goals for moderate to severe psoriasis suggest that the aim of treatment should be to control the disease (as measured using the change in PASI score) and to try and improve patient quality of life (as measured using a scale such as the Dermatology Life Quality Index [DLQI]).[8-10] Patient friendly websites and leaflets confirm that there is currently no cure for psoriasis, but various treatments including biologics and other conventional therapies like fumaric acid esters and methotrexate can help to induce remission and maintain the remission of the disease.[1, 2] Once patients stop treatment the disease will likely return.

The German guideline[4] provides some information regarding potential relapse following treatment with ciclosporin:

- After short-term therapy (induction therapy), relapse rates (defined as loss of ≥50% of the therapy-induced improvement) are higher and the time to relapse shorter when comparing fast reduction to slow reduction of treatment dose. For example, reducing ciclosporin by 1 mg per kg body weight every week for four weeks, followed by a reduction by 0.5-1 mg per kg body weight every other week showed a median time to relapse of 119.5 days after a 12-week induction therapy.[4]
- Long-term treatments with ciclosporin should only be considered in exceptional circumstances due to the increased risk of side effects, including the higher risk of cutaneous malignancy (especially in patients with high (>1000 J/cm2) cumulative dose of PUVA therapy) and cases of lymphomas. According to two studies, lower relapse rates and better effectiveness, respectively, are reported for patients treated continuously compared to patients receiving intermittent medication for relapses after initial induction therapy.[4] The authors refer to a previous guideline which suggested reducing the effective dose after induction therapy by 50 mg every four weeks. In case of relapse or deterioration of affected areas the dose should be increased by 50 mg and this maintenance dose should be given for up to two years when drug withdrawal should be attempted.[4]

3.6 FAQ 4. HOW WILL THE TREATMENT IMPACT ON MY QUALITY OF LIFE?

How will the treatment affect my quality of life?

The Dermatology Life Quality Index (DLQI) is a simple tool used to measure the quality of life of patients with various skin problems including psoriasis. The tool consists of 10 questions which ask how much your psoriasis has affected your life over the last week.[2] Most of the questions ask you to select one of five possible responses each of which corresponds to a score (see Appendix 2). The questions cover skin sensation (itchy, sore, etc); embarrassment due to the appearance; interference with daily life, social activities, and clothing; difficulties with social and sexual relationships.

The scores are added together to give a total score out of a maximum of 30 and a minimum of 0, the higher the score the greater impairment in quality of life:[2]

- Score 0 –1 = no effect at all on patient's life
- Score 2–5 = small effect on patient's life
- Score 6 –10 = moderate effect on patient's life
- Score 11 –20 = very large effect on patient's life
- Score 21 –30 = extremely large effect on patient's life

Evidence for health related quality of life (HRQoL) outcomes was available in the systematic review and NMA by Warren 2020.[5] This included phase III randomised controlled trials (RCTs) evaluating biologic treatments in adults with moderate to severe psoriasis and included outcomes measured at ≤12 weeks. The literature was searched up to December 2018 and 32 trials of 11 biologics were included in the analysis. There was no quality assessment of the included trials. The analysis used DLQI score as a binary outcome where DLQI (0,1) represents patients with a score of 0 or 1 (no effect on quality of life) compared to a score ≥ 2 (small to large effect on quality of life). NMA results after 12 weeks of treatment are shown in Table 11. This shows that the treatment with the greatest impact on HRQoL as shown by the ranking was ixekizumab, followed by brodalumab and secukinumab which are all IL-17 inhibitors. The least effective treatment was the anti-TNF alpha treatment adalimumab, but it was still more effective than placebo. In terms of drug classes, anti-IL17 inhibitors showed the greatest improvement on HRQoL followed by anti-IL23 then anti-TNF alpha.

Table 11: NMA results for DLQI after 12 weeks of biologic therapy

Drug	Relative treatment effect vs placebo (95% CrI) - DLQI (0,1)	Ranking
Anti-IL17		
Secukinumab	0.53 (0.50 to 0.57)	3
Ixekizumab	0.57 (0.53 to 0.61)	1
Brodalumab	0.55 (0.52 to 0.58)	2
Anti-IL23		
Guselkumab	NR	NR
Tildrakizumab	0.35 (0.30 to 0.39)	6
Risankizumab	NR	NR
Anti-IL23/12		
Ustekinumab	0.45 (0.42 to 0.47)	4
Anti-TNF alpha		
Etanercept	0.30 (0.27 to 0.33)	7
Infliximab	NR	NR
Adalimumab	0.18 (0.10 to 0.26)	8
Certolizumab	0.41 (0.32 to 0.50)	5
All comparisons are vs. placebo, results are the relative effect (proportion); rankings - the lower the value the better the HRQoL Data taken from Warren 2020[5]		
CrI credible interval; DLQI Dermatology Life Quality Index; NMA network meta-analysis; NR not reported		

Further evidence is provided by a Cochrane Review published in 2020 which evaluated conventional systemic agents (acitretin, ciclosporin, fumaric acid esters, methotrexate), small molecules (apremilast, tofacitinib, ponesimod), anti-TNF alpha (etanercept, infliximab, adalimumab, certolizumab), anti-IL12/23 (ustekinumab), anti-IL17 (secukinumab, ixekizumab, brodalumab), anti-IL23 (guselkumab, tildrakizumab) and other biologics (alefacept and itolizumab).[3] This included phase 2, 3 and 4 RCTs in adults with moderate to severe plaque psoriasis or psoriatic arthritis whose skin had been clinically diagnosed with moderate to severe psoriasis. A total of 140 trials were included which compared treatments to each other, or to placebo. Different HRQoL scales were used including the DLQI, SkinDex, Psoriasis Disability Index and Psoriasis Symptom inventory. A frequentist NMA model analysed the standardised mean difference (SMD) of the change from baseline to up to 24 weeks. Trial quality was assessed using the Cochrane tool and 41 (29%) were judged as low risk of bias, 42 (30%) at unclear risk of bias and 57 (41%) at high risk of bias.

From the 140 included trials, 53 were included in the NMA of HRQol. Information on quality of life was poorly reported and was missing for almost half of the patients (46.1%) included in the NMA.

Results for individual drugs showed that, compared to placebo, the greatest improvement in HRQoL was seen with risankizumab, followed by ixekizumab, ustekinumb, tildrakizumab and infliximab. Three treatments, brodalimumab, apremilast and fumaric acid were no better than placebo.

Results for drug classes showed that anti-IL23 inhibitors had the greatest improvement in quality of life compared to placebo with a standardised mean difference (SMD) in HRQoL score of -1.41 (95% CI -1.64 to -1.18). Results are shown in Table 12 and show that other conventional systemic agents were the least effective in terms of improving HRQoL.

Table 12: HRQoL results by drug class after 8 to 24 weeks of treatment

Drug	SMD versus placebo (95% CI)	HRQoL Ranking
Conventional systemic agents (fumaric acid and methotrexate	-0.64 (-1.04 to -0.24)	6
Biologics	-	-
Anti-IL17	-1.29 (-1.60 to -0.99)	2
Anti-IL23	-1.41 (-1.64 to -1.18)	1
Anti-IL23/12	-1.29 (-1.57 to -1.01)	3
Anti-TNF alpha	-1.06 (-1.22 to -0.91)	4
Small molecules (includes apremilast, tofacitinib and ponesimod)	-0.73 (-0.99 to -0.47)	5
All comparisons are vs. placebo. Rankings: The lower the value the better the HRQoL Data taken from Sbidian 2017[3]		
Abbreviations: CI confidence interval; SMD standardised mean difference		

3.7 FAQ 5. WHAT ARE THE RISKS AND SIDE EFFECTS?

What side effects might I experience from my treatment?

Due to the chronic nature of psoriasis, treatments usually need to be used over long periods of time to control the disease. This means it is important to consider the potential adverse effects of the treatments and the risks of toxicity due to the build-up of drug levels in the body over time.[11]

One Cochrane systematic review[3] evaluated the occurrence of adverse events and carried out a meta-analysis comparing different treatments with placebo and against each other. This review searched for studies published up to January 2019 (see Table 13) and performed both direct and network meta-analyses. Adverse events were reported by 93 trials. Apart from anti-IL23 inhibitors, all drugs increased the risk of an adverse event compared to placebo. On an individual drug level, the safest drug with the lowest risk of an adverse event was tildrakizumab (RR 0.86, 95% CI 0.77 to 0.96). The least safe drugs which increased the risk of an adverse event compared to placebo were: apremilast (RR 1.24, 95% CI 1.13 to 1.37) and fumeric acid esters (RR 1.27, 95% CI 1.16 to 1.39). The safest drug class was anti-IL23 inhibitors, followed by placebo, anti-IL12/23 inhibitors, anti-TNF alpha inhibitors, anti-IL17 inhibitors and conventional systemic treatments. Details of adverse events are shown in Table 13.

Table 13: Pooled risk of adverse events by drug treatment compared to placebo from eight to 24 weeks after randomisation

Drug	Number of studies	Number of patients	RR vs. placebo (95% CI)	Ranking	Level of evidence (GRADE)
Conventional systemic agents					
Methotrexate	3	319	1.07 (0.99 to 1.17)	9	Moderate
Fumeric acid esters	1	704	1.27 (1.16 to 1.39)	19	Very low
Biologics					
Anti-IL17					
Secukinumab	7	2707	1.12 (0.74 to 1.70)	13	Moderate
Ixekizumab	4	3268	1.17 (1.09 to 1.26)	15	Moderate
Brodalumab	5	4109	1.12 (1.04 to 1.20)	12	Moderate
Anti-IL23					
Guselkumab	5	1767	0.99 (0.90 to 1.08)	2	Moderate
Tildrakizumab	3	1904	0.86 (0.77 to 0.96)	1	Moderate
Risankizumab	4	1476	1.00 (0.89 to 1.11)	4	Moderate
Anti-IL23/12					
Ustekinumab	10	4553	1.07 (1.02 to 1.13)	8	Moderate
Anti-TNF alpha					
Etanercept	11	4225	1.10 (1.04 to 1.16)	10	Moderate
Infliximab	4	1267	1.10 (1.02 to 1.16)	11	Moderate
Adalimumab	9	3338	1.03 (0.96 to 1.10)	7	Moderate
Certolizumab	4	1026	1.01 (0.90 to 1.14)	5	Low
Small molecules*					
Apremilast [second-line only)	6	2290	1.24 (1.13 to 1.37)	18	Low

GRADE Working Group grades of evidence:
High certainty: Very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: Moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: Very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
* Includes apremilast, tofacitinib and ponesimod
Smaller rankings indicate a greater reduction in SAE. Not all treatments in the NMA are in this table so not all rankings are present.
Data taken from Sbidian 2017[3]

CI confidence interval; GRADE NA not applicable; RR risk ratio

In addition, a narrative systematic review reported on the types of adverse effects (common, cumulative, and serious events) associated with conventional systemic treatments (methotrexate, fumaric acid esters and apremilast). Literature searches were carried out in Embase and PubMed in November 2018; the quality of the included studies was not assessed. Adverse events for biologic and small molecule treatments were described in patient information leaflets from websites.[2, 11]

Conventional systemic agents

Methotrexate is an oral treatment and common side effects can involve gastrointestinal symptoms including nausea, vomiting and abdominal discomfort. Other common adverse events lasting longer than just the first few days of treatment include fatigue, headache, and general tiredness. Over time treatment can also cause problems with liver toxicity.

Fumeric acid esters are also administered as an oral treatment. Common side effects associated with treatment include gastrointestinal complaints such as abdominal pain and flushing. Problems with white blood cell counts are also common.[11]

Biologics

Biologic treatments are usually administered by subcutaneous injection or infusion. Common side effects of biologic treatments included local injection/infusion site reactions (i.e. redness, swelling, itching, pain). However, these are usually mild and resolve over three to five days. Other common side effects of biologics can include abdominal pain, headache, nausea, and tiredness.[1] As biologics act to suppress psoriasis by damping down the immune system, they can be associated with a higher risk of infection. Commonly this can include upper respiratory infections (e.g. sinusitis, colds, etc.), viral and fungal infections. Other common adverse events include headache, nausea and fatigue.[1]

Details of individual types of commonly experienced adverse events are reported in Appendix 3.

Are there any serious risks associated with my treatment?

In some circumstances, serious adverse events can occur with drugs used to treat moderate to severe psoriasis and these can be considered severe enough to stop the use of treatment (see Appendix 3).[11]

One Cochrane systematic review[3] evaluated the occurrence of serious adverse events and carried out a meta-analysis comparing different treatments with placebo and against each other. This review searched for studies published up to January 2019 and performed both direct and network meta-analyses. Serious adverse events (SAE) were reported by 101 trials comprising 91.8% of all participants. Overall, there were no major differences between any of the conventional and biologic treatments compared with placebo. However, the number of serious adverse events was very low, and the trials had short follow-up periods of between eight and 24 weeks. The review authors advised a cautious interpretation and the GRADE levels of evidence ranged from very low to moderate (see Table 14).

Table 14: Pooled risk of serious adverse events by drug treatment compared to placebo from 8 to 24 weeks after randomisation

Drug	Number of studies	Number of patients	RR vs. placebo (95% CI)	Absolute risk (range)	Ranking	Level of evidence (GRADE)
Conventional systemic agents						
Methotrexate	3	319	0.43 (0.20 to 0.95)	7 per 1000 (3 to 16)	1	Moderate
Fumeric acid esters	1	704	0.98 (0.50 to 1.94)	17 per 1000 (9 to 33)	10	Very low
Biologics						
Anti-IL17						
Secukinumab	8	2904	1.12 (0.74 to 1.70)	19 per 1000 (13 to 29)	20	Moderate
Ixekizumab	4	3268	1.09 (0.69 to 1.73)	16 per 1000 (10 to 26)	17	Moderate
Brodalumab	5	4109	1.04 (0.62 to 1.73)	18 per 1000 (11 to 29)	15	Moderate
Anti-IL23						
Guselkumab	5	1767	0.98 (0.54 to 1.79)	17 per 1000 (9 to 30)	11	Moderate
Tildrakizumab	3	1904	0.84 (0.39 to 1.83)	14 per 1000 (7 to 31)	6	Moderate
Risankizumab	4	1476	0.60 (0.37 to 0.96)	10 per 1000 (6 to 16)	3	Moderate
Anti-IL23/12						
Ustekinumab	10	4553	0.89 (0.63 to 1.27)	15 per 1000 (11 to 22)	8	Moderate
Anti-TNF alpha						
Etanercept	13	4265	0.89 (0.61 to 1.31)	15 per 1000 (10 to 22)	9	Moderate
Infliximab	6	1678	1.11 (0.59 to 2.07)	19 per 1000 (10 to 35)	16	Moderate
Adalimumab	10	3485	0.98 (0.65 to 1.49)	17 per 1000 (11 to 25)	12	Moderate
Certolizumab	4	1026	0.74 (0.31 to 1.75)	13 per 1000 (5 to 30)	4	Low
Small molecules*						
Apremilast [second-line only)	6	2290	0.86 (0.48 to 1.51)	15 per 1000 (8 to 26)	7	Low

GRADE Working Group grades of evidence:
High certainty: Very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: Moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: Very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Drug	Number of studies	Number of patients	RR vs. placebo (95% CI)	Absolute risk (range)	Ranking	Level of evidence (GRADE)
* Includes apremilast, tofacitinib and ponesimod Data taken from Sbidian 2017[3] Absolute risk on placebo 17 per 1000 Smaller rankings indicate a greater reduction in SAE. Not all treatments in the NMA are in this table, as they were not within the scope of this report, so not all rankings are present.						
CI confidence interval; NA not applicable; NMA = network meta-analysis; RR risk ratio; SAE = serious adverse event.						

The risk of a serious adverse event was lowest with methotrexate (RR 0.43, 95% CI 0.20 to 0.95) and risankizumab (RR 0.60, 95% CI 0.37 to 0.96) and highest with secukinumab (RR 1.12, 95% CI 0.74 to 1.70). For drug classes, the risk of a serious adverse event was the lowest with conventional systemic treatments, followed by in order of ranking: anti-IL23 inhibitors, anti-Il12/23 inhibitors, anti-TNF alpha inhibitors, placebo, and anti-IL17 inhibitors. However, these findings are only over a relatively short follow-up period and do not reflect longer term use.

Conventional systemic agents

Despite a favourable short term toxicity profile, methotrexate treatment requires close monitoring over longer treatment durations.[11] High doses of methotrexate and the build-up of drug levels in the body over long periods of use can cause damage to the liver, lungs, kidneys and bone marrow. [11] Gastrointestinal symptoms may also be affiliated with long-term therapy, including nausea, vomiting, and abdominal discomfort. Low-dose methotrexate has rarely been found to cause significant liver damage, but patients usually require regular blood tests to monitor effects on their liver.[1, 11] Due to the long-term accumulation of methotrexate in the body, it is not suitable for patients who have an increased risk of liver toxicity including those with diabetes, obesity, a history of alcohol consumption, and those with a family history of liver disease. Women of childbearing age are also not advised to undergo treatment as there is a risk that methotrexate can adversely affect the development of the unborn embryo/foetus (i.e. the drug is considered teratogenic) and is contraindicated in pregnancy.[11]

Although rare, fumaric acid esters have been associated with the development of issues with a reduction in the levels of white blood cells including lymphopenia.[11] Long-term used may also be associated with leucopenia, and raised levels of liver enzymes.[11] Due to the risk of developing leucopenia, it is recommended that leucocyte and lymphocyte counts are monitored and treatment is stropped if necessary.[11]

Biologics

Serious, but rare effects of biologic treatments can include serious allergic responses involving difficulties breathing, facial swelling and rash. These is also some suggestion that biologic treatments may rarely cause cancers including lymphomas and non-melanoma skin cancers, through their effects on damping down the immune response.[1] However, the evidence for this is not always strong. Infections which are relatively common side effects of biologics may also develop into more serious infections and so any minor infections or procedures which may increase a patient's risk of infection need to be closely monitored.[1] Data on the safety of biologic drugs in pregnant women in general is limited and so their use in usually not advised.

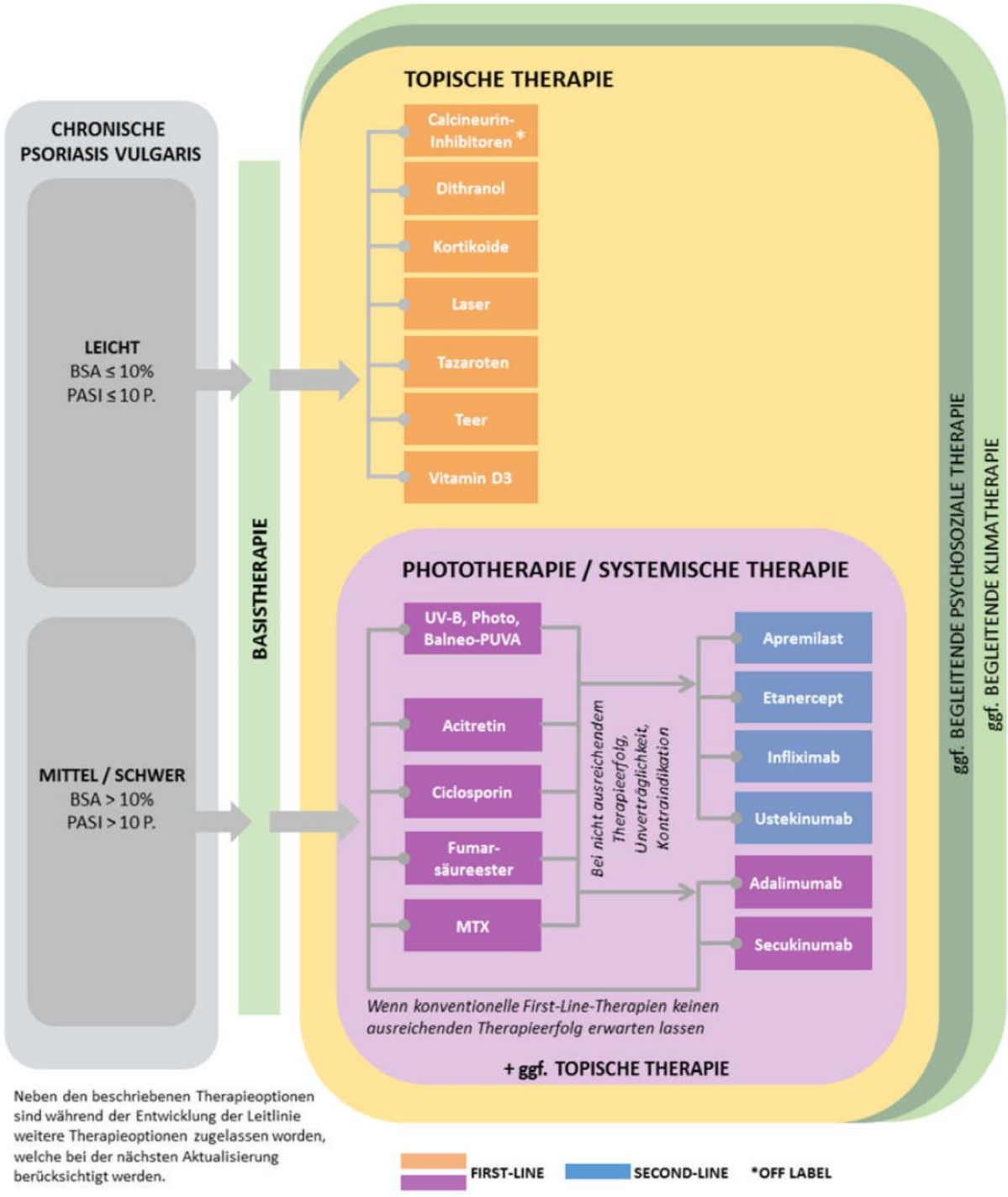
Details of individual types of serious adverse events are reported in Appendix 3.

4. DISCUSSION

4.1 SUMMARY OF GUIDELINES

German guidelines on the treatment of psoriasis including moderate to severe psoriasis were identified from 2017.[4] A summary of the currently recommended treatments for first and second-line are shown in Figure 2.

Figure 2: Summary of treatment pathway (S3-Leitlinie 013-001 Therapie der Psoriasis vulgaris guidelines 2017)



The guideline reported on the effectiveness, safety, and practicality of some of the treatments of interest to this review. No information was available on: certolizumab, brodalumab; ixekizumab; secukinumab; guselkumab; risankizumab; and tildrakizumab. A summary of the types and strength of evidence to support the different treatments of interest in this guideline is reported in Table 15.

Table 15: Summary of evidence for different moderate to severe psoriasis treatment types from S3-Leitlinie 013-001 Therapie der Psoriasis vulgaris guidelines 2017

Treatment	Effectiveness	Quality of evidence (PASI 75 vs. placebo)	Safety / Compatibility for induction therapy*	Safety /compatibility with maintenance therapy *	Practicality for patient	Practicality for physician
Conventional systemic agents						
Methotrexate	+	⊕⊕◯◯	+	++	+++	++
Fumeric acid	+*	⊕⊕◯◯	+	++	++	++
Biologics						
Anti-IL17						
Secukinumab	++++	⊕⊕⊕⊕	++	++	+++	++
Ixekizumab	No information in guideline					
Brodalumab	No information in guideline					
Anti-IL23						
Guselkumab	No information in guideline					
Tildrakizumab	No information in guideline					
Risankizumab	No information in guideline					
Anti-IL23/12						
Ustekinumab	+++	⊕⊕⊕◯	++	++	++++	+++
Anti-TNF alpha						
Etanercept	++*	⊕⊕⊕⊕	++	++	+++	++
Infliximab	++++	⊕⊕◯◯	+	++	+++	+/-
Adalimumab	+++*	⊕⊕⊕◯	++	++	+++	++
Certolizumab	No information in guideline					
Small molecules						
Apremilast	+	⊕⊕⊕◯	++	++	+++	+++
+ - to ++++ - assessment of the effectiveness considering PASI 75 results (placebo and head-to-head studies) as well as expert assessment * Considering expert judgment						
PASI Psoriasis Area Severity Index						

4.2 Summary of SDM

A decision aid (see Appendix 4) was identified on the website of the British Association of Dermatologists (BAD).[1] The aim of this was to aid patient and clinician decision making on biologic treatments for psoriasis; moderate to severe psoriasis was not specifically mentioned. This includes the following biologic treatments of interest to this review: adalimumab; certolizumab, etanercept; infliximab; ustekinumab; brodalumab; ixekizumab;

secukinumab; guselkumab; risankizumab; and tildrakizumab. The following FAQ style questions are used:

- Do I need to inject the treatment?
- For how long has this treatment been around?
- Roughly what proportion of people become clear or nearly clear (PASI90) after three to four months?
- What is the likelihood of staying on this treatment past one year?
- Roughly what proportion of people stop their treatment in the first three to four months due to unwanted effects?
- Roughly what proportion of people get a serious infection in the first three to four months?
- What are some of the conditions that would make your doctor hesitant about giving you the treatment?
- What if I have psoriatic arthritis?

Other SDM tools were also identified including one published in 2012,[15] but these may not be relevant to current clinical practice because of their age and are not discussed further.

4.3 Overall summary of results

The report focuses on evidence from systematic reviews, including several systematic reviews with meta-analyses and MTC. In addition, information has been taken from two patient friendly websites[1, 2] and a German guideline.[4]

A summary of the findings for the different treatment types (conventional systemic agents, biologic treatments, and small molecules) for FAQ 2 to 5 is shown in Table 16.

Details per individual drug within each of the treatment types are reported in Appendix 5.

Table 16: Summary of evidence for different moderate to severe psoriasis treatment types

Type of treatment	FAQ 2. Will it help my symptoms? (Based on PASI scores)	FAQ 3. Will it help maintain remission of my disease?	FAQ 4. How will the treatment impact on my quality of life? (DLQI compared to placebo)	FAQ 5. What are the risks and side effects?
Conventional systemic treatments*	PASI 90 data after 16wks of treatment suggested that conventional systemic treatments were inferior to all biologic treatments (RR versus placebo 4.65, 95% CI: 3.38 to 6.39).	No evidence	DLQI data after 12 to 16 wks of treatment suggested that conventional systemic treatments were inferior to all biologic treatments and small molecules (SMD -0.64, 95% CI: -1.04 to -0.24).[3]	***AE:*** All conventional treatments increased the risk of AE compared to placebo, the greatest increase in AE was with fumeric acid esters (RR 1.27, 95% CI 1.16 to 1.39; Note: based on very low-level evidence from one trial). ***SAE*:** Risk of SAE was lowest with methotrexate (RR 0.43, 95% CI 0.20 to 0.95) (Note: based on very low evidence).
Biologics	All biologic treatments (anti-IL12/23, anti-IL23 and anti-TNF alpha) after 12 to 16 wks treatment were superior to small molecule and conventional systemic agents. Considering different types of biologics, anti-IL17 inhibitors had a greater chance of achieving a PASI 90 response versus placebo (RR 29.33, 95% CI 23.38 to 36.79), when compared to other classes of biologics.	No evidence	Overall, biologics were superior to conventional systemic agents and small molecules. Considering types of biologics, anti-IL23 inhibitors had the greatest improvement compared to placebo (SMD -1.41, 95% CI -1.64 to -1.18). Rankings of other biologics (highest to lowest) were anti-IL17; anti-IL23/12; and anti-TNF-alpha	***AE:*** Apart from anti-IL23 inhibitors, all drugs increased the risk compared to placebo. The safest drug (lowest risk of AE) was tildrakizumab (RR 0.86, 95% CI 0.77 to 0.96). Safest drug class was anti-IL23 inhibitors, followed by placebo, anti-IL12/23 inhibitors, anti-TNF alpha inhibitors, and anti-IL17 inhibitors. ***SAE*:** Risk was lowest with risankizumab (RR 0.60, 95% CI 0.37 to 0.96) and highest with secukinumab (RR 1.12, 95% CI 0.74 to 1.70). For drug classes, the risk of SAE with biologics was higher than

Type of treatment	FAQ 2. Will it help my symptoms? (Based on PASI scores)	FAQ 3. Will it help maintain remission of my disease?	FAQ 4. How will the treatment impact on my quality of life? (DLQI compared to placebo)	FAQ 5. What are the risks and side effects?
				conventional systemic treatments. The ranking (safest to least safe) in biologics was: anti-IL23 inhibitors, anti-Il12/23 inhibitors, other biologics, anti-TNF alpha inhibitors, placebo, and anti-IL17 inhibitors.
Small molecules (including apremilast)	PASI 90 data suggested small molecules were inferior to biologic treatments, but superior to conventional treatments (RR versus placebo was 9.01, 95% CI: 6.58 to 12.33)		DLQI data after 12 to 16 wks of treatment suggested that small molecules were inferior to all biologic treatments and conventional systemic treatments (SMD versus placebo -0.73, 95% CI: -0.99 to -0.47).[3]	***AE:*** In comparison with other drug classes, the least safe drugs which increased the risk of AE compared to placebo were small molecules - apremilast (RR 1.24, 95% CI 1.13 to 1.37) ***SAE*:** The risk of SAE based on low level evidence was RR 0.86 (95% CI: 0.48 to 1.51), which was comparable to the other drugs.
Notes	Data taken from SR and NMA[3] unless otherwise stated; Trial quality was assessed using the Cochrane tool and 41 (29%) were judged as low risk of bias, 42 (30%) at unclear risk of bias and 57 (41%) at high risk of bias; outcomes were long term (after 1yr). PASI measures redness, thickness, and scale on a five-point scale across four regions of the body, the head, upper extremities, lower extremities, and trunk.	Psoriasis is a chronic condition which has no cure. The disease will return. There is currently no cure for psoriasis, but various treatments including biologics and other conventional therapies like	Data taken from SR and NMA[5] unless otherwise stated; there was no quality assessment; outcomes measured after 12wks treatment; quality rating based on lack of data and caution expressed by SR authors. DLQI measures HRQoL using 10 questions (how much your psoriasis has affected your life over the last week) giving a score from zero to 30 with a higher score indicating a worse quality of life.[2] Infliximab was not assessed.	Data taken from SR and NMA[3] and follow-up from 8 to 24 weeks after randomisation. Strength of evidence is based on GRADE assessment and based on majority of studies in the drug class, where a results is based on a different grade of evidence this has been noted.[5]

Type of treatment	FAQ 2. Will it help my symptoms? (Based on PASI scores)	FAQ 3. Will it help maintain remission of my disease?	FAQ 4. How will the treatment impact on my quality of life? (DLQI compared to placebo)	FAQ 5. What are the risks and side effects?
		fumaric acid esters and methotrexate can help to induce remission and maintain the remission of the disease. The goal of treatment is to maintain remission and HRQoL for as long as possible, as measured using PASI and HRQoL scores.		

Very low-quality evidence | Low quality evidence | Moderate quality evidence | High quality evidence

* including methotrexate and fumaric acid esters

GRADE Working Group grades of evidence:

High certainty: Very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: Moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: Very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

AE adverse event; CI confidence interval; Crl credible interval; DLQI Dermatology Life Quality Index; FAQ frequently asked question; GRADE Grading of Recommendations, Assessment, Development and Evaluations; HRQoL health related quality of life; NMA network meta analysis; PASI Psoriasis Area and Severity Index score; RR relative risk; SAE serious adverse event; SMD standardised mean difference; wk week; yr year

4.4 STRENGTHS, LIMITATIONS AND UNCERTAINTIES

Many recent published systematic reviews were identified in this topic area, many of which included meta-analyses and NMA comparing the treatments of interest to this SDM review. The most recent, highest quality and most comprehensive reviews have been selected for inclusion and it was not necessary to search for primary studies. We have relied on Cochrane reviews for many of the findings and have included the authors GRADE assessments where possible, to indicate the level of supporting evidence. For those outcomes with GRADE assessments, evidence within the Cochrane reviews was judged as 'moderate' level (i.e. the authors reported that they were 'moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different'). However, in some areas supporting evidence was judged to be very low to low. This included evidence on serious adverse events associated with fumeric acid esters (very low), certolizumab (low), and apremilast (low).

We were unable to identify any evidence for FAQ 3 (will it help maintain remission of my disease?), specifically to address the question – Will my disease return? However, psoriasis is a chronic disease for which there is no cure and current treatment goals are to control the disease and maintain patient quality of life.[1, 2, 8, 9]

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APPENDIX 1: SEARCH STRATEGIES

SR/Guidelines searches

Database	Dates	Results
CDSR & CDSR Protocols	2015 – 2020/08/Iss8	23
DARE	2015 – 2015/03	3
HTA	2015 – 2018/03	19
INAHTA	2015 –2020/08/18	53
KSR Evidence	2015 –2020/08/14	583
Epistemonikos	2015- 2020/08/19	771
NHS Evidence	2015-2020/08/18	455
NICE	up to 2020/08/18	39
GIN	2015- 2020/08/18	5
ECRI	up to 2020/08/18	13
Total		**1964**

SDM database searches

Database	Dates	Results
Embase	2015-2020/08/14	184
MEDLINE & PreMedline	2015-2020/08/14	148
CENTRAL	2015-2020/08/Iss8	7
Total		**339**

SR/Guidelines searches

Cochrane Database of Systematic Reviews (CDSR) (Wiley) up to 2020/08/Iss8
Searched: 17.8.20

#1 MeSH descriptor: [Psoriasis] explode all trees 3274
#2 (Psoria* or antipsoria* or acropustulos*):ti,ab,kw 8635
#3 Pustulos* NEAR/3 (palm* or sole* or Plantaris or Palmoplantar*):ti,ab,kw 129
#4 #1 or #2 or #3 with Cochrane Library publication date Between Jan 2015 and Dec 2020 5296

CDSR retrieved 18 records
CDSR Protocols retrieved 5 records

Database of Abstracts of Reviews of Effects (DARE) (CRD): up to 2015/03
Health Technology Assessment (HTA) database (CRD): up to 2018/03
http://www.crd.york.ac.uk/CRDWeb/
Searched: 18.8.20
(Note: both resources are now archive only and are no longer added to)

1 MeSH DESCRIPTOR Psoriasis EXPLODE ALL TREES 250
2 ((Psoria* or antipsoria* or acropustulos*)) 321

3 (Pustulos*) AND (palm* or sole* or Plantaris or Palmoplantar*) 2
4 #1 OR #2 OR #3 321
5 (#4) IN DARE FROM 2015 TO 2020 3
6 (#4) IN HTA FROM 2015 TO 2020 19

INAHTA up to 2020/08/18
https://database.inahta.org/
Searched: 18.8.20

"Psoriasis"[mhe]) OR (Psoria* or antipsoria* or acropustulos*) FROM 2015 TO 2020

Search retrieved 53 records

KSR Evidence: up to 2020/08/14
Searched: 17.8.20
Filtered by: PUBLICATION DATE 2020, 2019, 2018, 2017, 2016, 2015

1 (Psoria* or antipsoria* or acropustulos*) in All text 611 results
2 Pustulos* in All text 13 results
3 (palm* or sole* or Plantaris or Palmoplantar*) in All text 1693 results
4 #2 and #3 in All text 3 results
5 #1 or #4 in All text 583 results

NICE Evidence Search (Internet): up to 2020/08/18
https://www.evidence.nhs.uk/
Searched: 18.8.20

Search terms	**Results (Guidance or SR): 01/01/2015-18/08/2020**
Psoria* or antipsoria* or acropustulos*	**455**

National Institute for Health and Care Excellence (NICE): up to 2020/08/18
https://www.nice.org.uk/
Searched 18.8.20

Guidelines

Keywords	**Hits**
psoria* OR antipsoria* OR acropustulos*	39
Pustulos* AND (palm* OR sole* OR Plantaris OR Palmoplantar*)	0/1 (duplicate)
Total	**39**

Guidelines International Network (GIN) Library (Internet): up to 2020/08/18
http://www.g-i-n.net
Searched: 18.8.20

2015+

Search terms	Results
'psoria* OR antipsoria* OR acropustulos*'	**5**

ECRI Institute Guidelines Trust (Internet): up to 12020/08/18
https://guidelines.ecri.org/
Searched: 18.8.20

Search terms	Results
'psoria* OR antipsoria* OR acropustulos*'	**13**

Epistemonikos: up to 2020/08/19
https://www.epistemonikos.org/
Searched: 19.8.20

Retrieved 771 (search found 779 but only exported 771)
(advanced_title_en:((Psoria* OR antipsoria* OR acropustulos*) OR (Pustulos* AND (palm* OR sole* OR Plantaris OR Palmoplantar*))) OR advanced_abstract_en:((Psoria* OR antipsoria* OR acropustulos*) OR (Pustulos* AND (palm* OR sole* OR Plantaris OR Palmoplantar*)))) [Filters: protocol=no, classification=systematic-review, cochrane=missing, min_year=2015, max_year=2020]

SDM Searches

EMBASE (Ovid) 1974-2020/08/14
Searched: 17.8.20
1 exp psoriasis/ (87256)
2 (Psoria$ or antipsoria$ or Acropustulos$).ti,ab,ot,hw. (94702)
3 (Pustulos$ adj3 (palm$ or sole$ or Plantaris or Palmoplantar$)).ti,ab,ot,hw. (2256)
4 or/1-3 (95929)
5 shared decision making/ (7055)
6 ((share$ or sharing$ or inform$) adj3 (decision$ or deciding$ or choice$)).ti,ab. (50771)
7 sdm.ti,ab. (3347)
8 or/5-7 (54727)
9 4 and 8 (258)
10 limit 9 to yr="2015 -Current" (184)

MEDLINE (Ovid) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily: 1946-2020/08/14
Searched: 17.8.20

1 exp Psoriasis/ (40078)
2 (Psoria$ or antipsoria$ or Acropustulos$).ti,ab,ot,hw. (54939)
3 (Pustulos$ adj3 (palm$ or sole$ or Plantaris or Palmoplantar$)).ti,ab,ot,hw. (857)
4 or/1-3 (55210)
5 exp Decision Making/ (202539)
6 ((share$ or sharing$ or inform$) adj3 (decision$ or deciding$ or choice$)).ti,ab,ot. (37130)
7 sdm.ti,ab. (2590)
8 or/5-7 (230720)
9 4 and 8 (232)
10 limit 9 to yr="2015 -Current" (148)

Cochrane Central Register of Controlled Trials (CENTRAL): up to 2020/08/Iss8
Searched: 17.8.20

#1 MeSH descriptor: [Psoriasis] explode all trees 3274
#2 (Psoria* or antipsoria* or acropustulos*):ti,ab,kw 8635
#3 Pustulos* NEAR/3 (palm* or sole* or Plantaris or Palmoplantar*):ti,ab,kw 129
#4 #1 or #2 or #3 with Cochrane Library publication date Between Jan 2015 and Dec 2020 5296
#5 MeSH descriptor: [Decision Making] explode all trees 3842
#6 ((share* or sharing* or inform*) near/3 (decision* or deciding* or choice*)):ti,ab,kw 4219
#7 sdm:ti,ab,kw 380
#8 #5 or #6 or #7 7668
#9 #4 and #8 7

APPENDIX 2: COMMON, CUMULATIVE AND SERIOUS ADVERSE EVENTS ASSOCIATED WITH TREATMENTS FOR MODERATE TO SEVERE PSORIASIS

Table 17: Summary of DLQI

Question	Possible responses	Score
1. Over the last week, how itchy, sore, painful, or stinging has your skin been?	Very much A lot A little Not at all	3 2 1 0
2. Over the last week, how embarrassed or self-conscious have you been because of your skin?	Very much A lot A little Not at all	3 2 1 0
3. Over the last week, how much has your skin interfered with you going shopping or looking after your home or garden?	Very much A lot A little Not at all Not relevant	3 2 1 0 0
4. Over the last week, how much has your skin influenced the clothes you wear?	Very much A lot A little Not at all Not relevant	3 2 1 0 0
5. Over the last week, how much has your skin affected any social or leisure activities?	Very much A lot A little Not at all Not relevant	3 2 1 0 0
6. Over the last week, how much has your skin made it difficult for you to do any sport?	Very much A lot A little Not at all Not relevant	3 2 1 0 0
7. Over the last week, has your skin prevented you from working or studying?	Yes No Not relevant	3 0 0
If “No", over the last week how much has your skin been a problem at work or studying?	A lot A little Not at all	2 1 0
8. Over the last week, how much has your skin created problems with your partner or any of your close friends or relatives?	Very much A lot A little Not at all Not relevant	3 2 1 0 0
9. Over the last week, how much has your skin caused any sexual difficulties?	Very much A lot A little Not at all Not relevant	3 2 1 0 0

Question	Possible responses	Score
10. Over the last week, how much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all Not relevant	3 2 1 0 0
Reference[2]		

APPENDIX 3: COMMON, CUMULATIVE AND SERIOUS ADVERSE EVENTS ASSOCIATED WITH TREATMENTS FOR MODERATE TO SEVERE PSORIASIS

Table 18: Common adverse effects, cumulative and serious effects of treatments for moderate to severe psoriasis in adults

Drug	Common adverse effects[#]	Cumulative adverse effects due to build-up of drug in the body[#]	Serious adverse events[#]
Conventional systemic agents			
Methotrexate	• Fatigue [≥1% to <10%] • Headache [≥0.1% to >1%] • Malaise (general feeling of unwellness) • Increased risk of infection [≥0.1% to >1%] • Nausea, vomiting and abdominal discomfort [≥1% to <10%] • Reversible hair loss [≥1% to <10%]	• Liver damage (usually associated with alcohol use – alcohol should be avoided): increased transaminase [≥1% to <10%]; liver fibrosis or liver cirrhosis [≥0,01% to <0,1%]	• Problems with bone marrow [≥0,01% to <0,1%] • Lung problems [<0,01%] • Kidney problems [≥0,01% to <0,1%] • May effect developing embryo or foetus in pregnant women
Fumeric acid esters	• Gastrointestinal problems (commonly abdominal pain) [60%] • Flushing of skin • Abnormal white blood cell counts [≥10%]	• Kidney damage • Reduction in number of white blood cells [≥1% to <10%]	• Blood problems (e.g. failure to produce blood cells that help to fight infections) • Progressive multifocal leukoencephalopathy (PML) – a rare infection of the brain • Osteomalacia syndrome [<0.01%]
Biologics			
Anti-IL17			
Secukinumab	• Reactions at the injection site (e.g. redness, rash, swelling, itching, or bruising) • Upper respiratory infections (e.g. sinus infections) • Headaches • Diarrhoea • Nausea	-	• Increased risk of serious infections • Inflammatory bowel disease (including Crohn's disease and ulcerative colitis • Severe allergic reactions (e.g. severe rash, swollen face, difficulty breathing) • Blood problems (e.g. failure to produce blood cells that help to fight infections)

Drug	Common adverse effects[#]	Cumulative adverse effects due to build-up of drug in the body[#]	Serious adverse events[#]
	• Fatigue		
Ixekizumab	• Reactions at the injection site (e.g. redness, rash, swelling, itching, or bruising) • Upper respiratory infections (e.g. sinus infections) • Sore throat • Nausea	-	• Increased risk of serious infections • Inflammatory bowel disease (including Crohn's disease and ulcerative colitis) can rarely occur • Severe allergic reactions (e.g. severe rash, swollen face, difficulty breathing) • Blood problems (e.g. failure to produce blood cells that help to fight infections
Brodalumab	• Reactions at the injection site (e.g. redness, rash, swelling, itching, or bruising) • Infections (e.g. influenza and fungal infections) • Sore throat • Muscle aches and pains • Headaches • Diarrhoea • Nausea • Fatigue	-	• Increased risk of serious infections • Inflammatory bowel disease (including Crohn's disease and ulcerative colitis) can rarely occur • Blood problems (e.g. failure to produce blood cells that help to fight infections)
Anti-IL23			
Guselkumab	• Reactions at the injection site (e.g. redness, rash, swelling, itching, or bruising) • Upper respiratory infections (e.g. sinus infections) • Fungal infections • Headaches • Diarrhoea • Nausea	-	• Increased risk of serious infections • Severe allergic reactions (e.g. severe rash, swollen face, difficulty breathing)

Drug	Common adverse effects[#]	Cumulative adverse effects due to build-up of drug in the body[#]	Serious adverse events[#]
Tildrakizumab	• Reactions at the injection site (e.g. pain, redness, rash, swelling, itching, or bruising) • Upper respiratory infections (e.g. sinus infections). • Headaches • Diarrhoea • Nausea • Back pain	-	• Increased risk of serious infections • Severe allergic reactions (e.g. severe rash, swollen face, difficulty breathing)
Risankizumab	• Reactions at the injection site (e.g. redness, rash, swelling, itching, or bruising) • Upper respiratory infections (e.g. sinus infections) • Fungal infections • Headaches • Fatigue • Skin itching	-	• Increased risk of serious infections including tuberculosis • Severe allergic reactions (e.g. severe rash, swollen face, difficulty breathing)
Anti-IL23/12			
Ustekinumab	• Reactions at the injection site (e.g. redness, rash, swelling, itching, or bruising) • Upper respiratory infections (e.g. sinus infections) [2.9% to 7.1%] • Headaches [4.6% to 5.5%] • Dizziness • Rash • Diarrhoea • Fatigue	-	• Increased risk of serious infections especially tuberculosis • Blood problems (e.g. failure to produce new blood cells causing easy bruising, bleeding, and fever) • Severe allergic reactions (e.g. severe rash, swollen face, difficulty breathing) • Cancer (e.g. rare reports of lymphoma, but the risk of cancer is unclear at present)

Drug	Common adverse effects[#]	Cumulative adverse effects due to build-up of drug in the body[#]	Serious adverse events[#]
	• Arthralgia [2.4% to 3.4%]		
Anti-TNF alpha			
Etanercept	• Reactions at the injection site (e.g. redness, rash, swelling, itching, or bruising) • Upper respiratory infections (e.g. sinus infections) • Headaches • Muscle aches • Fatigue • Mild skin rashes	-	• Increased risk of serious infections especially tuberculosis • Worsening heart failure (not usually given to patients with heart failure) • Blood problems (e.g. failure to produce new blood cells causing easy bruising, bleeding, and fever) • Severe allergic reactions (e.g. severe rash, swollen face, difficulty breathing) • Nervous system diseases (e.g. rare reports of numbness, tingling, vision problems, weakness in arms and/or legs, dizziness) • Cancer (e.g. rare reports of lymphoma, but the risk of cancer is unclear at present)
Infliximab	• Infusion reactions (e.g. hives, itching, rash) [≥1% to <10%] • Viral infections (e.g. influenza, colds, cold sores, headache, inflammation of the sinuses, nausea, and abdominal pain)	-	• Increased risk of serious infections especially tuberculosis • Worsening heart failure (not usually given to patients with heart failure) • Blood problems (e.g. failure to produce blood cells that help fight to infections or stop bleeding) • Severe allergic reactions (e.g. severe rash, swollen face, difficulty breathing) • Nervous system diseases (e.g. rare reports of numbness, tingling, vision problems, weakness in arms and/or legs, dizziness) • Cancer (low unquantifiable risk) • Liver inflammation • Lupus-like reactions (e.g. rash and joint pains)

Drug	Common adverse effects[#]	Cumulative adverse effects due to build-up of drug in the body[#]	Serious adverse events[#]
Adalimumab	• Reactions at the injection site (e.g. redness, rash, swelling, itching, or bruising) [20%] • Upper respiratory infections (e.g. sinus infections) • Headaches • Rash • Nausea	-	• Increased risk of serious infections • Heart problems • Blood problems (e.g. failure to produce blood cells that help fight to infections or stop bleeding) • Severe allergic reactions (e.g. severe rash, swollen face, difficulty breathing) [≥0,01% to <0,1%] • Nervous system diseases (e.g. rare reports of numbness, tingling, vision problems, weakness in arms and/or legs, dizziness) • Lupus-like reactions (e.g. rash and joint pains) • Cancer (e.g. rare reports of lymphoma, non-melanoma skin cancer) [<0,01%]
Certolizumab	• Reactions at the injection site (e.g. redness, rash, swelling, itching, or bruising) • Bacterial and viral infections • Headaches • Raised blood pressure • Nausea • Rash • Liver inflammation	-	• Increased risk of serious infections (including tuberculosis) • Heart problems • Blood problems (e.g. failure to produce blood cells that help fight to infections or stop bleeding) • Nervous system diseases (e.g. rare reports of numbness, tingling, vision problems, weakness in arms and/or legs, dizziness) • Severe allergic reactions (e.g. severe rash, swollen face, difficulty breathing) • Cancer (e.g. rare reports of lymphoma, Merkel cell carcinoma, non-melanoma skin cancer) • Hair loss (rare)
Small molecules*			
Apremilast [second line only	• Skin problems (dryness, itching, peeling of palms of hands and soles of feet)	• Bone problems (e.g. excessive bone growth) • Liver damage	• Depression • Suicidal thoughts [≥0.1% to >1%]

Drug	Common adverse effects[#]	Cumulative adverse effects due to build-up of drug in the body[#]	Serious adverse events[#]
	• Alopecia (hair loss) • Dryness of mucous membranes • Joint pain • Muscle pain • Diarrhoea [approx. 20%] • Weight loss [15%]		• May effect developing embryo or foetus in pregnant women
[#] Where information available, classified based on German guideline as ≥10% (sehr häufig, very frequent), ≥1% to <10% (häufig, frequent), ≥0.1% to >1% (gelegentlich, occasional), ≥0,01% to <0,1% (selten, rare), <0,01% (sehr selten, very rare)[4] [*] includes apremilast, tofacitinib and TYK2 References[1, 11] Effect sizes taken from S3 German Guidelines[4]			
TNF tumour necrosis factor			

Table 19: Summary of adverse events across different treatments – categories of frequency and severity taken from EUROGUIDERM guideline for the systemic treatment of psoriasis vulgaris

Drug	Very frequent adverse events	Frequent adverse events	Occasional adverse events	Rare adverse events	Very rare adverse events
Conventional systemic agents					
Methotrexate	Nausea, malaise, hair loss	Elevated transaminases, bone marrow suppression, gastrointestinal ulcers	Fever, chills, depression, infections	Nephrotoxicity, liver fibrosis, and cirrhosis	Interstitial pneumonia, alveolitis
Fumeric acid esters	Diarrhoea, flush, mild leukopenia and lymphopenia (appr. 50 % of patients)	Abdominal cramps, flatulence, severe lymphocytopenia (appr. 3 % of patients), transient eosinophilia	Nausea, dizziness, headache, fatigue, proteinuria, increase in serum creatinine, increase in liver enzymes	Nausea, dizziness, headache, fatigue, proteinuria, increase in serum creatinine, increase in liver enzymes	None

Drug	Very frequent adverse events	Frequent adverse events	Occasional adverse events	Rare adverse events	Very rare adverse events
Biologics					
Anti-IL17					
Secukinumab	NR*	NR*	NR*	Neutropenia	NR*
Ixekizumab	Injection site reactions, upper airway infections	Oropharyngeal pain, nausea, tinea infections, mucocutaneous herpes simplex	NR	NR	NR
Brodalumab	NR	Influenza, tinea infections (including tinea pedis, tinea versicolor, tinea cruris), neutropenia, headache, orophageal pain, diarrhea, nausea, arthralgia, myalgia, fatigue and injection site reactions	NR	NR	Suicidal thoughts
Anti-IL23					
Guselkumab	NR	Upper respiratory tract infections, gastroenteritis, herpes, headache, diarrhoea, urticaria and arthralgias	NR	NR	NR
Tildrakizumab	NR	NR	NR	NR	NR
Risankizumab	NR	Upper respiratory tract infections, Including nasopharyngitis, rhinitis, pharyngitis, sinusitis, and tonsillitis; injection site reactions	NR	NR	NR

Drug	Very frequent adverse events	Frequent adverse events	Occasional adverse events	Rare adverse events	Very rare adverse events
Anti-IL23/12					
Ustekinumab	NR	NR	NR	NR	NR
Anti-TNF alpha					
Etanercept	Injection-site reaction	Infections	Tuberculosis, reactivation of latent tuberculosis, heart failure	Allergic reactions, adverse reactions of the haematologic system, demyelinating diseases	Autoantibodies, drug-induced lupus, malignancies
Infliximab	Injection-site reaction	Infections	Tuberculosis, reactivation of latent tuberculosis, heart failure	Allergic reactions, adverse reactions of the haematologic system, demyelinating diseases	Autoantibodies, drug-induced lupus, malignancies
Adalimumab	Injection-site reaction	Infections	Tuberculosis, reactivation of latent tuberculosis, heart failure	Allergic reactions, adverse reactions of the haematologic system, demyelinating diseases	Autoantibodies, drug-induced lupus, malignancies
Certolizumab	Injection-site reaction	Infections	Tuberculosis, reactivation of latent tuberculosis, heart failure	Allergic reactions, adverse reactions of the haematologic system, demyelinating diseases	Autoantibodies, drug-induced lupus, malignancies
Small molecules*					
Apremilast [second line only	NR**	NR**	NR**	NR**	NR**

Information taken from reference[12]

*In the placebo-controlled period of clinical studies in plaque psoriasis infections were reported in 28.7% of patients treated with secukinumab and 18.9% of patients with placebo. Most cases of infection were mild or moderate upper respiratory tract infections. Higher rates of fungal infections, primarily non-serious skin and mucosal candida infections are observed.

**The most commonly reported adverse reactions in Phase III clinical studies have been gastrointestinal (GI) disorders including diarrhoea (15.7%) and nausea (13.9%). These GI adverse reactions were mostly mild to moderate in severity, with 0.3% of diarrhoea and 0.3% of nausea reported as being severe. A total of 0.1% of patients treated with apremilast discontinued due to adverse reaction of weight decreased. Some patients may experience psychiatric symptoms with apremilast, including depression and suicidal thoughts. Stop treatment if patients have new psychiatric symptoms or if existing symptoms worsen.

Abbreviations: NR not reported; TNF tumour necrosis factor

APPENDIX 4: SDM TOOL FOR BIOLOGIC TREATMENTS FOR PSORIASIS FROM BRITISH ASSOCIATION OF DERMATOLOGISTS (BAD)

Taken from[1]: https://www.bad.org.uk/healthcare-professionals/psoriasis

© BRITISH ASSOICATION OF DERMATOLOGISTS – DECISION AID FOR BIOLOGICAL THERAPY FOR PSORIASIS

This is a decision aid to help clinicians and patients decide their treatment choice and not a comprehensive data source or replacement for the individual drug Summary of Product Characteristics. Please use in conjunction with the published guidelines, pathway algorithm and discussions in the online supporting information document (File S2, Appendix D).

	How do I take it?		How effective is it?		How common are the side effects?		Is there anything else to consider?	
Questions you might want to ask	How often do I need to inject the treatment?*	For how long has this treatment been around?†	Roughly what proportion of people becomes clear or nearly clear (PASI90) after 3-4 months?‡	What is the likelihood of staying on this treatment past 1 year?§	Roughly what proportion of people stops their treatment in the first 3-4 months due to unwanted effects?‡	Roughly what proportion of people gets a serious infection in the first 3-4 months?**	What are *some* of the conditions that would make your doctor hesitant about giving you the treatment?††	What if I have psoriatic arthritis?
TNF								
Adalimumab	1 injection under the skin, every other week	Since 2008	 41%	77-81% chance	2%	< 1%	Moderate or severe heart failure, multiple sclerosis (or other conditions affecting the nerves)	Recommended treatment for psoriatic arthritis
Certolizumab pegol	1 or 2 injections under the skin, every 2 weeks	Since 2019	 41-48%	Not known at present	2%	< 1%	Moderate or severe heart failure, multiple sclerosis (or other conditions affecting the nerves)	Recommended treatment for psoriatic arthritis
Etanercept	1 injection under the skin, once or twice a week	Since 2004	 23%	67-73% chance	2%	< 1%	Moderate or severe heart failure, multiple sclerosis (or other conditions affecting the nerves)	Recommended treatment for psoriatic arthritis
Infliximab	1 injection in the vein,‡‡ every 8 weeks	Since 2006	 53%	54-74% chance	5%	Not known at present	Moderate or severe heart failure, multiple sclerosis (or other conditions affecting the nerves)	Recommended treatment for psoriatic arthritis
IL12/23								
Ustekinumab	1 injection under the skin, every 12 weeks	Since 2009	 46%	86-92% chance	 1%	< 1%	No particular condition	Recommended treatment for psoriatic arthritis only when TNF inhibitors have failed

* Only licensed maintenance doses are featured; see File S1: Table S1 for information on initiation dosing schedules
† First approval of the drug for moderate to severe plaque psoriasis
‡ The evidence is drawn from clinical trials including a mixed biologic-naïve and experienced population; figures quoted are based on anticipated absolute effects derived from network meta-analyses of licensed biologic doses
§ The evidence is drawn from a real-world UK biologic-naïve population; it may not apply to biologic choice for subsequent lines of treatment
** The evidence is drawn from clinical trials including a mixed biologic-naïve and experienced population; figures quoted are based on Peto odds ratio analyses of all biologic doses
†† Please refer to individual drugs' summary of product characteristics for a more comprehensive list (www.medicines.org.uk)
‡‡ Requires attendance to hospital

	How do I take it?		How effective is it?		How common are the side effects?		Is there anything else to consider?	
Questions you might want to ask	How often do I need to inject the treatment?*	For how long has this treatment been around?†	Roughly what proportion of people becomes clear or nearly clear (PASI90) after 3-4 months?‡	What is the likelihood of staying on this treatment past 1 year?§	Roughly what proportion of people stops their treatment in the first 3-4 months due to unwanted effects?‡	Roughly what proportion of people gets a serious infection in the first 3-4 months?**	What are *some* of the conditions that would make your doctor hesitant about giving you the treatment?††	What if I have psoriatic arthritis?
IL17								
Brodalumab	1 injection under the skin, every 2 weeks	Since 2018	 73%	Not known at present	2%	< 1%	Inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis), recurrent candida infection (i.e. thrush)	This treatment is not licensed§§ for psoriatic arthritis
Ixekizumab	1 injection under the skin, every 4 weeks	Since 2016	 72%	Not known at present	3%	< 1%	Inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis), recurrent candida infection (i.e. thrush)	Recommended treatment for psoriatic arthritis
Secukinumab	2 injections under the skin, every month	Since 2015	 60%	Not known at present	2%	< 1%	Inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis), recurrent candida infection (i.e. thrush)	Recommended treatment for psoriatic arthritis
IL23								
Guselkumab	1 injection under the skin, every 8 weeks	Since 2018	 68%	Not known at present	2%	< 1%	No particular condition	This treatment is not licensed§§ for psoriatic arthritis
Risankizumab	2 injections under the skin, every 12 weeks	Since 2019	 74%	Not known at present	1%	< 1%	No particular condition	This treatment is not licensed§§ for psoriatic arthritis
Tildrakizumab	1 or 2 injections under the skin, every 12 weeks	Since 2019	 39%	Not known at present	2%	< 1%	No particular condition	This treatment is not licensed§§ for psoriatic arthritis
Placebo								
No active treatment	Does not apply	Does not apply	 2%	Does not apply	 2%	 < 1%	Does not apply	Does not apply

NICE eligibility criteria, infliximab: PASI ≥20, DLQI >18; other biologic therapies: PASI ≥10, DLQI >10

§§ A treatment that is not licensed for a particular condition means it has not been awarded a Market Authorisation from the U.K. Medicines Healthcare Products Regulatory Agency (MHRA) for that condition. Once awarded, the licensed treatment can be marketed and sold in the U.K.

APPENDIX 5: SUMMARY OF FINDINGS FOR EACH INDIVIDUAL DRUG TO TREAT MODERATE TO SEVERE PSORIASIS

Table 20: Summary of findings for individual drugs used to treat moderate to severe psoriasis

Ranking of treatment	FAQ 2. Will it help my symptoms? (Based on PASI scores reported as RR with 95% CI versus placebo after 1yr of treatment)	FAQ 3. Will it help maintain remission of my disease?	FAQ 4. How will the treatment impact on my quality of life? (HRQoL relative treatment effect with 95% CrI after 12wks of treatment)	FAQ 5. What are the risks and side effects?	
				Occurrence of AE reported as RR with 95% CI	Occurrence of SAE reported as RR with 95% CI
Highest (best performing)	**Risankizumab** *PASI 100*: 179.82 (36.9 to 1104.12) *PASI 90:* 42.09 (10.9 to 213.49)	No evidence	**Ixekizumab** 0.57 (0.53 to 0.61)	**Tildrakizumab** 0.86 (0.77 to 0.96)	**Methotrexate** 0.43 (0.20 to 0.95)
	Guselkumab *PASI 100*: 162.79 (35.45 to 905.8) *PASI 90:* 39.97 (10.73 to 189.43)	No evidence	**Brodalumab** 0.55 (0.52 to 0.58)	**Guselkumab** 0.99 (0.90 to 1.08)	**Risankizumab** 0.60 (0.37 to 0.96)
	Brodalumab *PASI 100*: 162.50 (34.9 to 941.62) *PASI 90:* 39.95 (10.67 to 193.72)	No evidence	**Secukinumab** 0.53 (0.50 to 0.57)	**Risankizumab** 1.00 (0.89 to 1.11)	**Certolizumab** 0.74 (0.31 to 1.75)
	Ixekizumab *PASI 100*: 138.93 (32.36 to 720.46) *PASI 90:* 36.66 (10.33 to 162.71)	No evidence	**Ustekinumab** 0.45 (0.42 to 0.47)	**Certolizumab** 1.01 (0.90 to 1.14)	**Tildrakizumab** 0.84 (0.39 to 1.83)
	Secukinumab *PASI 100*: 124.07 (30.49 to 593.47) *PASI 90:* 34.36 (10.03 to 144.13)	No evidence	**Certolizumab** 0.41 (0.32 to 0.50)	**Adalimumab** 1.03 (0.96 to 1.10)	**Apremilast** 0.86 (0.48 to 1.51)
	Infliximab *PASI 100*: 92.94 (25.58 to 407.83) *PASI 90:* 28.84 (9.22 to 110.12)	No evidence	**Tildrakizumab** 0.35 (0.30 to 0.39)	**Ustekinumab** 1.07 (1.02 to 1.13)	**Ustekinumab** 0.89 (0.63 to 1.27)
	Ustekinumab *PASI 100*: 84.74 (23.74 to 359)	No evidence	**Etanercept** 0.30 (0.27 to 0.33)	**Methotrexate** 1.07 (0.99 to 1.17)	**Etanercept** 0.89 (0.61 to 1.31)

Ranking of treatment	FAQ 2. Will it help my symptoms? (Based on PASI scores reported as RR with 95% CI versus placebo after 1yr of treatment)	FAQ 3. Will it help maintain remission of my disease?	FAQ 4. How will the treatment impact on my quality of life? (HRQoL relative treatment effect with 95% CrI after 12wks of treatment)	FAQ 5. What are the risks and side effects?	
				Occurrence of AE reported as RR with 95% CI	Occurrence of SAE reported as RR with 95% CI
Lowest (worst performing)	*PASI 90:* 27.22 (8.85 to 101.5)				
	Certolizumab pegol 400 *PASI 100*: 82.71 (23.47 to 357.4) *PASI 90:* 26.75 (8.82 to 99.6)	No evidence	**Adalimumab** 0.18 (0.10 to 0.26)	**Etanercept** 1.10 (1.04 to 1.16)	**Fumeric acid esters** 0.98 (0.50 to 1.94)
	Adalimumab *PASI 100*: 77.46 (22.82 to 309.02) *PASI 90:* 25.72 (8.69 to 90.91)	No evidence	**Conventional systemic treatments (including methotrexate and fumaric acid esters)** DLQI data 12 to 16wks of treatment suggested that conventional systemic treatments were inferior to all biologic treatments.[3]	**Infliximab** 1.10 (1.02 to 1.16)	**Guselkumab** 0.98 (0.54 to 1.79)
	Certolizumab pegol 200 *PASI 100*: 61.2 (19.11 to 242.78) *PASI 90:* 21.97 (7.92 to 75.13)	No evidence	**Small molecules (including apremilast)** DLQI data after 12 to 16wks treatment suggested inferior to all biologic treatments and conventional systemic treatments.[3]	**Brodalumab** 1.12 (1.04 to 1.20)	**Adalimumab** 0.98 (0.65 to 1.49)
	Etanercept *PASI 100*: 51.26 (17.54 to 170.53) *PASI 90:* 19.6 (7.49 to 59.56)	No evidence		**Secukinumab** 1.12 (0.74 to 1.70)	**Brodalumab** 1.04 (0.62 to 1.73)
	Apremilast *PASI 100*: 11.09 (5.16 to 27.72) *PASI 90:* 6.52 (3.43 to 14.47)	No evidence		**Ixekizumab** 1.17 (1.09 to 1.26)	**Infliximab** 1.11 (0.59 to 2.07)

Ranking of treatment	FAQ 2. Will it help my symptoms? (Based on PASI scores reported as RR with 95% CI versus placebo after 1yr of treatment)	FAQ 3. Will it help maintain remission of my disease?	FAQ 4. How will the treatment impact on my quality of life? (HRQoL relative treatment effect with 95% CrI after 12wks of treatment)	FAQ 5. What are the risks and side effects?	
				Occurrence of AE reported as RR with 95% CI	Occurrence of SAE reported as RR with 95% CI
	Conventional systemic treatments (including methotrexate and fumaric acid esters) PASI 90 data after 16wks of treatment suggested that conventional systemic treatments were inferior to all biologic treatments.[3]	No evidence		**Apremilast** 1.24 (1.13 to 1.37) Fumeric acid esters 1.27 (1.16 to 1.39)	**Ixekizumab** 1.09 (0.69 to 1.73) 1.12 (0.74 to 1.70)
	Notes: Data from SR and NMA[7] unless otherwise stated; majority of trials considered low risk of bias – used to grade evidence as moderate; outcomes were long term (after 1yr). PASI measures redness, thickness, and scale on a five-point scale across four regions of the body, the head, upper extremities, lower extremities, and trunk. PASI 100 corresponds to 100% clearance of skin and PASI 90 as 90% clearance. Tildrakizumab was not assessed.	*Notes*: Psoriasis is a chronic condition which has no cure. The disease will return. The goal of treatment is to maintain remission and HRQoL for as long as possible, as measured using PASI and HRQoL scores.	*Notes*: Data from SR and NMA[5] unless otherwise stated; no quality assessment; outcomes measured after 12wks treatment; evidence graded as low based on lack of data and caution advised.[5] DLQI is simple tool to measure HRQoL uses 10 questions (how much your psoriasis has affected your life over the last week).[2] Infliximab, risankizumab, and guselkumab were not assessed.	*Notes*: Data taken from SR and NMA[3] and follow-up from 8 to 24 weeks after randomisation. Strength of evidence is based on GRADE assessment.[5]	*Notes*: Data taken from SR and NMA[3] and follow-up from 8 to 24 weeks after randomisation. Strength of evidence is based on GRADE assessment.[5]

Ranking of treatment	FAQ 2. Will it help my symptoms? (Based on PASI scores reported as RR with 95% CI versus placebo after 1yr of treatment)	FAQ 3. Will it help maintain remission of my disease?	FAQ 4. How will the treatment impact on my quality of life? (HRQoL relative treatment effect with 95% CrI after 12wks of treatment)	FAQ 5. What are the risks and side effects?	
				Occurrence of AE reported as RR with 95% CI	Occurrence of SAE reported as RR with 95% CI

Very low-quality evidence | Low quality evidence | Moderate quality evidence | High quality evidence

GRADE Working Group grades of evidence:

High certainty: Very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: Moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: Very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Abbreviations: AE adverse event; CI confidence interval; CrI credible interval; DLQI Dermatology Life Quality Index; FAQ frequently asked question; GRADE Grading of Recommendations, Assessment, Development and Evaluations; HRQoL health related quality of life; NMA network meta analysis; PASI Psoriasis Area and Severity Index score; RR relative risk; SAE serious adverse event; SMD standardised mean difference; wk week; yr year