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Methods report: Update of the German S3 guideline for the treatment of psoriasis vulgaris

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1 Abstract

Background: This report describes the methods and processes used to develop the 2017 update of the German evidence- and consensus-based (S3) guideline for the treatment of psoriasis vulgaris (Deutsche S3-Leitlinie zur Therapie der Psoriasis vulgaris – Update 2017, AWMF Registry No. 013/001).

Methods: The methods used to search for, assess and grade the evidence on the systemic treatment of psoriasis followed the recommendations given in the Cochrane Handbook for Systematic Reviews, as well as those of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group and the German Association of Scientific Medical Societies (AWMF). The nominal group technique was used during the guideline consensus conference to generate draft recommendations, discuss alternatives and reach final consensus.

Results: The systematic literature search considered studies published up to and including 1 December 2016 and identified 1655 records. After two screening phases, 15 records reporting 12 new studies that satisfied the inclusion criteria remained. In total, evidence from 76 studies was graded, producing 56 individual GRADE summary of findings (SoF) tables. Draft recommendations were prepared by experts for all consensus-based recommendations. All draft recommendations were discussed and voted on in two consensus conferences attended by the experts from the guideline development group.

Conclusion: The field of psoriasis therapy is in constant transition. A lack of head-to-head trials makes direct comparisons challenging. Continuous updating will be necessary to respond to the further changes expected in the field. Updates on newly approved medications such as ixekizumab are expected to take place before the present guideline expires on 31 December 2020.

2 Guideline Development Group

Title	Surname	First Name	Affiliation	Nominating organization
Expert panel				
Dr. med.	Amelunxen	Lasse	Fachklinik Bad Bentheim	DDG
Prof. Dr. med.	Augustin	Matthias	Universitätsklinikum Hamburg-Eppendorf, Institut für Versorgungsforschung in der Dermatologie und bei Pflegeberufen	DDG
Prof. Dr. med.	Boehncke	Wolf-Henning	Service de Dermatologie et Vénéréologie, Hôpitaux Universitaires de Genève	DDG
Prof. Dr. med.	Härle	Peter	Katholisches Klinikum Mainz, Zentrum für Rheumatologische Akutdiagnostik, Klinik für Rheumatologie, Klinische Immunologie und Physikalische Therapie	DGRh
Prof. Dr. med.	Mrowietz	Ulrich	Psoriasis-Zentrum, Klinik für Dermatologie, Venerologie, Allergologie, Universitätsklinikum Schleswig-Holstein, Campus Kiel	DDG
Prof. Dr. med.	Ockenfels	Hans-Michael	Haut- und Allergieklinik, Klinikum Hanau	BVDD
Dr. med.	Philipp	Sandra	Psoriasisstudienzentrum, Klinik für Dermatologie, Venerologie und Allergologie, Charité – Universitätsmedizin Berlin	DDG
Prof. Dr. med.	Reich	Kristian	Dermatologikum Hamburg	DDG
PD Dr. med.	Rosenbach	Thomas	Office-based dermatologist, Osnabrück	BVDD
Dr. med.	Schlaeger	Martin	Office-based dermatologist, Oldenburg	BVDD
Prof. Dr. med.	Schmid-Ott	Gerhard	Berolina Klinik, Löhne	DGPPR
Dr. med.	Sebastian	Michael	Office-based dermatologist, Mahlow	BVDD
Dr. med.	von Kiedrowski	Ralph	Office-based dermatologist, Selters	BVDD
PD Dr. med.	Weberschock	Tobias	Klinik für Dermatologie, Venerologie und Allergologie, Universitätsklinikum Frankfurt, Frankfurt/Main und Arbeitsgruppe EbM Frankfurt, Institut für Allgemeinmedizin, Goethe-Universität Frankfurt, Frankfurt/Main	DDG
Patient representatives				
	Klaus	Joachim	Deutscher Psoriasis Bund e.V.	DPB
	Koza	Joachim	Deutscher Psoriasis Bund e.V.	DPB
	Hoffstadt	Bernd	Selbsthilfegemeinschaft Haut e.V.	SGH
Methodologists and coordinating research team				
Dr.	Dressler	Corinna	dEBM	n/a
	Gaskins	Matthew	dEBM	n/a
Prof. Dr. med.	Nast	Alexander	dEBM	n/a
Independent co-chair				
Prof. Dr. med.	Rzany	Berthold	Office-based dermatologist, Berlin	n/a

Notes: BVDD = Berufsverband der Deutschen Dermatologen (Professional Association of German Dermatologists); DDG = Deutsche Dermatologische Gesellschaft (German Society of Dermatology); dEBM = Division of Evidence-Based Medicine; DGPPR = Deutsche Gesellschaft für klinische Psychotherapie und Psychosomatische Rehabilitation (German Association for Clinical Psychotherapy and Psychosomatics); DGRh = Deutsche Gesellschaft für Rheumatologie (German Society of Rheumatology); DPB = Deutscher Psoriasis Bund (German Psoriasis Alliance); SGH = Selbsthilfegemeinschaft Haut (Skin Self-help Association)

3 Introduction

This report describes the methods and processes used to develop the 2017 update of the German evidence- and consensus-based (S3) guideline for the treatment of psoriasis vulgaris (Deutsche S3-Leitlinie zur Therapie der Psoriasis vulgaris – Update 2017, AWMF Registry No. 013/001). The guideline has been published in the Journal of the German Society of Dermatology (Journal der Deutschen Dermatologischen Gesellschaft). When citing the guideline, please use one or more of the references below depending on the language version and parts of the guideline you are referring to:

- Nast A, Amelunxen L, Augustin M et al. S3-Leitlinie zur Therapie der Psoriasis vulgaris Update – Kurzfassung Teil 1 – Systemische Therapie. J Dtsch Dermatol Ges 2018; 16(5): 645–70.
- Nast A, Amelunxen L, Augustin M et al. S3 Guideline for the treatment of psoriasis vulgaris, update – Short version part 1 – Systemic treatment. J Dtsch Dermatol Ges 2018; 16(5): 645–69.
- Nast A, Amelunxen L, Augustin M et al. S3-Leitlinie zur Therapie der Psoriasis vulgaris Update – Kurzfassung Teil 2 – Besondere Patientengruppen und spezielle Behandlungssituationen. J Dtsch Dermatol Ges 2018; 16(6): 806–14.
- Nast, A., et al. (2018). S3 Guideline for the treatment of psoriasis vulgaris, update – Short version part 2 – Special patient populations and treatment situations. J Dtsch Dermatol Ges 2018; 16(6): 806–14.

Researchers at the Division of Evidence-Based Medicine (dEBM) at Charité – Universitätsmedizin Berlin identified, reviewed and evaluated the evidence underpinning the guideline and coordinated the process of guideline development. The methods used to do so followed the recommendations given in the Cochrane Handbook for Systematic Reviews [1], as well as those of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group [2] and the German Association of Scientific Medical Societies (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften; AWMF) [3]. The criteria contained within the Appraisal of Guidelines Research & Evaluation II (AGREE II) Instrument and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist were taken into consideration when writing this report [4].

The nominal group technique was used during the guideline consensus conference to generate draft recommendations, discuss alternatives and reach a final consensus [5]. The development of the guideline was funded by the German Society of Dermatology (DDG).

4 Methods and processes

4.1 Nomination of experts

Experts were nominated to the guideline development group by national societies in Germany for dermatology, pharmaceutical medicine, psychotherapy and psychosomatic rehabilitation and rheumatology. A list of the experts is given in Section 2.

To be nominated, an individual had to satisfy at least one of the following criteria:

- Extensive clinical experience in the treatment of psoriasis
- Relevant publications in the field of psoriasis
- Relevant experience in evidence-based medicine

Additionally, patient representatives were recruited by the national societies and the dEBM from national self-help organizations to be full voting members of the group.

The dEBM was chosen as the coordinating research centre due to its experience in developing guidelines, including the 2015 update of the European S3 guideline on the systemic treatment of psoriasis vulgaris [6] and the 2006 and 2011 versions of the German S3 guideline for the treatment of psoriasis vulgaris.

4.2 Managing conflicts of interest

All members of the guideline development group completed and returned conflict of interest forms before the kick-off meeting of the group in April 2016. The forms were developed by the AWMF specifically for use in the development of clinical practice guidelines [3].

An external co-chair (Bertold Rzany, BR) without any conflicts of interest evaluated the completed forms. Potential conflicts of interests were classified as minimal, moderate or severe, as recommended by the AWMF in its algorithm for managing conflicts of interest [3]. The head of the dEBM (Alexander Nast, AN), who co-chaired the group throughout the guideline development process, and the external co-chair also completed conflict of interest forms. These were evaluated externally by the president of the German Society of Dermatology. These and the conflict of interest declarations of the group members can be found in Appendix B.

The overview of conflicts of interest was presented and discussed in a pre-kick-off online meeting of the group in January 2016 by the external co-chair. The group agreed unanimously to follow the AWMF requirements that:

(a) the group be facilitated during its meetings by a member without relevant conflicts of interest (BR);

(b) teams of experts working on a set of chapters be headed by a working group leader with no relevant conflicts of interest;

(c) experts abstain from voting on recommendations in which they have conflicts of interest that have been rated as moderate; and

(d) experts with severe conflicts of interest not be permitted to take part in the group.

The external co-chair monitored that these requirements were adhered to during the subsequent guideline development process and consensus conferences.

During the consensus conferences, the members of the guideline development group were reminded before each vote to abstain if they had a relevant conflict of interest. Abstentions were noted in each case by a show of hands, and the dEBM team made note of the names in each case in the conference protocols. These can be viewed at the dEBM upon request.

4.3 Kick-off meeting

The kick-off meeting of the guideline development group took place in Hamburg, Germany, in April 2016. The participants discussed and agreed upon the structure and content of the guideline, as well as the relevant interventions, comparators and key outcomes to be assessed.

Structure of the guideline

The group agreed to retain the structure of the 2011 version of the guideline while adding chapters on secukinumab and apremilast, as well as on special treatment situations and patient populations. The group decided that the latter set of chapters would cover the following topics:

- Tuberculosis screening
- HIV
- Malignancies including lymphoma and skin cancer
- Hepatitis and other hepatological dysfunctions
- Neurological disease
- Ischemic heart disease and congestive heart failure
- Diabetes
- Kidney failure and renal impairment
- Pregnancy
- Psoriatic arthritis
- Vaccination
- Irritable bowel disease

The group decided to include only consensus-based recommendations in these chapters.

Additionally, the group voted unanimously against adding a chapter on ixekizumab based on the observation that data and experience with this newer agent were still insufficient to develop evidence- or consensus-based recommendations. However, the majority of participants agreed that it should be covered as soon as possible by means of a fast update.

Methods to assess evidence

The group agreed that the methods set out by the GRADE Working Group should be followed in the chapters on systemic therapy to rate the quality of evidence and decide upon the strength of individual recommendations. The group also decided to retain and not update the chapters on UV and topical treatments from the 2011 version of the guideline as it was felt that only minor developments had taken place in these areas.

Outcomes to be assessed

The group agreed that the outcomes to be assessed in the 2017 update of the guideline would be a 90% reduction in Psoriasis Area Severity Index (PASI) score from baseline (PASI 90), a 75% reduction in PASI score from baseline (PASI 75), a Dermatology Life Quality Index score of 0 or 1 (DLQI 0/1) and withdrawal due to adverse events. The group also decided to limit its recommendations to induction treatment, which it defined as any systemic treatment lasting at least 8 weeks and up to 16 weeks.

4.4 Systematic literature review

In accordance with input from the guideline development group, the research questions were developed using the Population, Intervention, Comparator, Outcome (PICO) format. In order to update the German Psoriasis guideline from 2012, the research team drew upon work conducted for the European S3 guideline for the treatment of psoriasis vulgaris from 2015 [6] and the European S3 guideline on the systemic treatment of pvulgaris – Update apremilast and secukinumab from 2017 [7]. Because the methods used for the current guideline had to mirror those described in the methods report for these two publications [8], a separate protocol was not written in this case. For the same reason, parts of this and the following section may be similar or identical to sections in the earlier methods report. Researchers at the dEBM team coordinated the development of all three guidelines and conducted the systematic review and GRADE assessment.

Searches for the European S3 guideline were conducted in December 2013 (auto alerts until October 2014). For the present update of the guideline, the searches were conducted in February 2016 (auto alerts until July 2016). Combining the two search strategies and incorporating recently added MeSH terms, the research team used the following four databases: Embase Ovid (1980 to 2016 September 29), MEDLINE Ovid (1946 to September week 3 2016), MEDLINE(R) In-Process & Other Non-Indexed Citations Ovid (September 29, 2016) and the Cochrane Central Register of Controlled Trials (CENTRAL).

The search was limited to the years 2014 to 2016 and the Scottish Intercollegiate Guidelines Network (SIGN) filter for randomized controlled trials was applied (see Appendix A for example search strategy) [9].

The search did not include existing guidelines or systematic reviews because the 2017 version of this guideline is an update. As noted above, the earlier versions of the guideline were developed by researchers at the dEBM, who conducted the searches for primary data, the data analyses and the evaluation with GRADE [6, 7, 10, 11]. As a result, it was possible to add additional, more recent primary data as part of the present update.

4.4.1 Screening and data extraction

Two researchers (CD, MG) independently screened the titles and abstracts of all records using the inclusion and exclusion criteria given in Table 1. Differences in opinion were not discussed at this stage, and all records identified as meeting the inclusion criteria were obtained in full text. In cases where no abstract was available, full-text publications were sought unless it was clear from the title that the publication should be excluded.

Table 1: Inclusion and exclusion criteria

Patients	Patients with moderate to severe psoriasis vulgaris
	Adults (≥ 18 years, depending on definition used in each study)
	At least 10 patients per study arm
Intervention	**Include:**
	Acitretin
	Adalimumab
	Apremilast (all doses, administered at least twice)
	Ciclosporin
	Cisclosporin and diet
	Combination treatment with 2 systemic medications or 1 systemic and 1 topical medication
	Etanercept
	Fumaric acid esters
	Infliximab
	Methotrexate
	Secukinumab (≥ 150mg, administered at least twice)
	Ustekinumab
	Exclude:
	Biosimilars
Comparison treatment	Placebo or one of the other included interventions
Study end points	PASI 75 and PASI 90
	DLQI 0/1
	Withdrawal due to AE
	Time period: induction treatment (16 weeks if possible; otherwise: at least 8 weeks but no more than 16 weeks)
	Additional endpoints: Time until onset of action, patients with at least one adverse event, patients with at least one serious adverse event
	Exclusion:
	Long-term and maintenance treatment (> 16 weeks)
Study design	**Include:**
	RCTs (cross-over, parallel, cluster, factorial, pragmatic)
	Exclude:
	Observational studies

Full-text publications were subsequently screened independently by the same two researchers. In case of exclusion, the reason was recorded. Disagreements on the inclusion of full-text publications were resolved by discussion. The references of included studies were not screened for further relevant studies.

Data for the items listed in Table 2 were first extracted by one researcher (CD) using a standardized data extraction sheet in Microsoft Excel 2013 and subsequently checked for accuracy by the second researcher (MG). Engauge Digitizer (Version 9.8) was used to extract data from figures. All studies that had been included in the systematic review underpinning the European S3 guideline from 2015 or in the 2017 update were re-screened against the inclusion and exclusion criteria and additional data items were extracted in accordance with the research questions relevant to the current guideline (see Table 2). Discrepancies and differences of opinion were resolved by discussion.

Table 2: Items for data extraction

GENERAL INFORMATION	First author	Surname of first author
	Year	Year of print publication
	Trial name	Trial name and/or clinicaltrials.gov identifier
	Intervention	For each study arm: drug generic name with Latin abbreviations for dosing regimens; placebo if placebo; intervention duration
STUDY CHARACTERISTICS	No. randomized	Number (n) of pts. randomized per study arm
	Study duration	Maximum duration of controlled phase of treatment plus duration of any extension and/or follow up in weeks [w]
	Max. treat. duration	Maximum duration of controlled treatment phase in weeks [w]
	Extension duration	Duration of any extension and/or follow up in weeks [w]
	Concurrent treatment	Which (if any) concurrent systemic/topical treatments allowed
	Washout phase	Duration of washout phase for any systemic or topical treatments in months [m], weeks [w] or days [d]
STUDY INCLUSION CRITERIA	Minimum PASI	Minimum PASI value to take part in trial
	Age	Age range for participating in trial
	Previous treatment required?	Any topical / systemic treatment pts required to have taken before beginning of study
BASELINE CHARACTERISTICS	Age	Mean/median (range/SD) age of pts. in each study arm at baseline
	PASI	Mean (SD/range) PASI of pts. in each study arm at baseline
	DLQI	Mean (SD/range) of DLQI of pts. in each study arm at baseline
	Female	Percentage (%) of pts. in each study arm who were female

WITHDRAWALS	AE in induction therapy	Number of patients who left the study due to adverse events.
COCHRANE RISK OF BIAS	Seven separate categories	Each of the following seven categories to be assessed as having high, low or unclear risk of bias: sequence generation, allocation concealment, blinding of patients, blinding of personnel and outcome, incomplete outcome data, selective outcome reporting, other sources of bias
INDUCTION: PASI RESPONSE	Time of assessment	Time at which outcome assessment was performed in weeks [w]
	PASI 75	For each study arm: proportion of patients who achieved a 75% reduction in the Psoriasis Area and Severity Index
	PASI 90	For each study arm: proportion of patients who achieved a 90% reduction in the Psoriasis Area and Severity Index
INDUCTION: DLQI	Time of assessment	Time when outcome assessment was performed in weeks [w]
	DLQI 0 or 1	Proportion of pts. with Dermatology Quality of Life Index 0 or 1
INDUCTION: ADVERSE EVENTS	Time of assessment	Time when outcome assessment was performed in weeks [w]
	No. of pts. with ≥ 1 AE	Proportion of patients with at least 1 adverse event
	No. of pts. with at ≥ 1 AE	Proportion of patients with at least 1 serious adverse event

Notes: AE = adverse event; DLQI = Dermatology Quality of Life Index; No. = number; max. = maximum; pts. = patients; SD = standard deviation; treat. = treatment; [d] = day(s); [w] = week(s); [m] = month(s)

4.4.2 Statistical analyses

Risk ratios and mean differences with corresponding 95% confidence intervals were calculated using Review Manager 5.3.4 [12]. Data were entered into Review Manager in the form in which they had been reported in the included publications. No imputation was performed. Care was taken not to double count participants in the comparator arms of multi-arm studies. For dichotomous outcomes, the total number of events and patients in the comparator arms was split evenly across each subgroup.

The decision to pool data was driven by the research question. A Mantel-Haentzel random-effects model was chosen because the difference between the studies suggested that no common effect was being assessed (DerSimionian-Laird [13]). Heterogeneity was assessed using the I^2 statistic. Data were pooled, and in cases where the I^2 statistic was larger than 35%, the quality of evidence rating was downgraded due to concerns about inconsistency. Additionally, time until onset of action was presented separately for each of the interventions. The methods used for this have been reported elsewhere [14].

4.4.3 Risk of bias assessment

Both researchers (CD, MG) independently assessed the risk of bias in the included studies using the Cochrane Risk of Bias Assessment tool [1]. This involved making separate critical assessments for each of the following domains: *random sequence generation*, *allocation concealment*, *blinding of patients*, *blinding of personnel and outcomes*, *incomplete outcome*

data, *selective outcome reporting*, and *other sources of bias*. The risk of bias for each domain was rated as “unclear”, “low” or “high” and recorded in the data extraction sheet. Differences of opinion were resolved by discussion.

4.4.4 Assessing the quality of evidence

Using the approach developed by the GRADE Working Group, the quality of evidence was rated as *high*, *moderate, low* or *very low* based on an assessment of whether there were limitations or concerns that could be considered *very serious*, *serious* or *not serious* in each of the following five areas: risk of bias, inconsistency, indirectness, imprecision and publication bias. A summary of this approach and definitions for the quality of evidence grades are given in Table 3 (adapted from Bashem et al. 2001 [15]).

Table 3: Summary of the GRADE approach to assessing the quality of the evidence by outcome for RCTs [15]

Study design	Initial quality of body of evidence	Criteria that may lead to rating down quality of evidence	Quality of body of evidence	
RCT	High	Risk of bias Inconsistency Indirectness Imprecision Publication bias	High (++++)	We are very confident that the true effect lies close to that of the estimate of effect.
			Moderate (+++)	We are 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 (++)	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
			Very low (+)	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

1. Risk of Bias: The Cochrane Risk of Bias Tool was used to assess limitations at the study level. Weights assigned in the meta-analysis were considered when deciding the overall risk of bias when dealing with more than one study. The researchers downgraded to serious or very serious depending on the overall risk of bias. In cases where placebo data had been imputed for a comparison after 24 weeks, the researchers downgraded by two points.

2. Inconsistency [16]: Inconsistency could only be assessed in cases where results from more than one study had been pooled. The researchers downgraded when the confidence intervals did not overlap or if the I^2 was large ($I^2 > 35\%$).

3. Indirectness [17]: In this category, the researchers assessed whether there was a difference between the patients recruited for a study and those to whom the recommendation

in question was meant to apply. The former was assessed by considering the inclusion criteria and baseline characteristics reported in the included publications.

4. Imprecision [18]: For dichotomous outcomes, imprecision was evaluated based on whether the confidence interval crossed the line of no effect, the threshold for minimal important difference (MID), or both. The MID for risk ratios was set at ± 0.25 of the line of no effect. Therefore, if the confidence interval crossed the line of no effect and the MID, the researchers downgraded to serious due to “uncertain(ty) whether there is any difference”. If only the MID was crossed, we downgraded due to “statistically significant difference of uncertain clinical importance”. Another reason to downgrade would have been a very wide confidence interval.

5. Publication bias [19]: It is possible to downgrade in this category if publication bias is detected. Due to the small number of studies, however, funnel plots could not be used as a formal method to assess this bias. No other methods were used and the default option of ‘not detected’ was chosen.

The reasons for downgrading by one or two levels are stated in the explanatory footnotes of each GRADE Summary of Findings (SoF) table. All SoF tables can be found in Appendix C.

4.4.5 Systematic literature search results

The searches were conducted on 30 September 2016. These yielded a total of 1655 records after entries from the year 2013 had been removed by hand. After removal of duplicate entries, 1189 records remained, of which 146 were included during the screening phase for titles and abstracts. A total of 26 records were deemed eligible during the full-text screening. Data were extracted from 15 records reporting 12 new studies. Altogether 255 records were received via the autoalert function, which was active until 1 December 2016. A total of four of these (two new studies and two records reporting additional outcomes of already included studies) were deemed eligible. Initially, 87 studies were included in the meta-analysis and 52 GRADE SoF tables were developed (i.e., one for each comparison). However, at this stage the expert group decided that only licensed doses should be included, which led to the exclusion of a further 11 studies. This yielded a total of 75 publications reporting 76 studies and 56 GRADE SoF tables. The study selection process is documented in Figure 1.

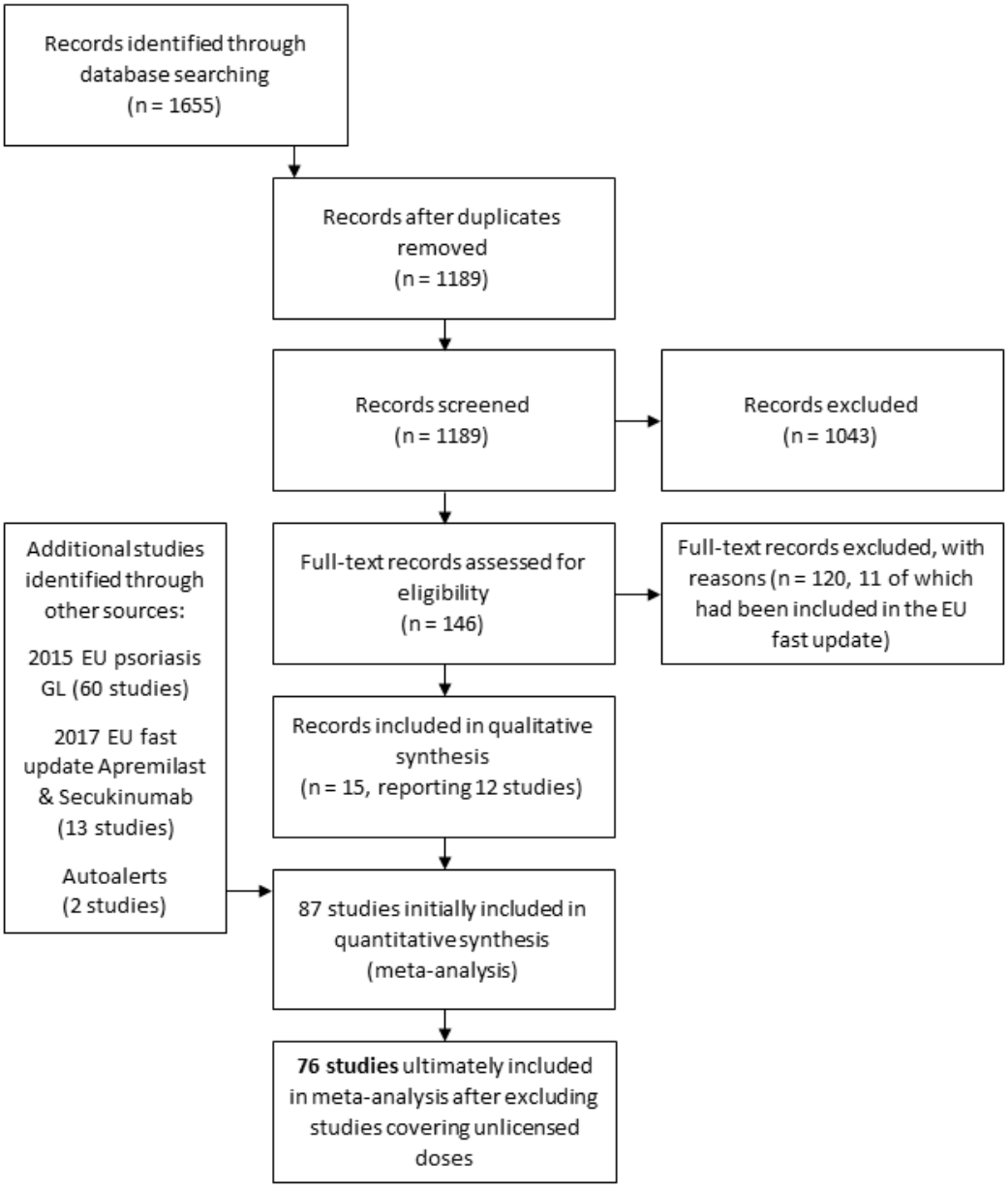

Figure 1: Study selection process

All SoF tables can be found in Appendix C. Each row in the table reports one outcome and the quality of evidence. The relative effects are presented as risk ratios and 95% confidence intervals alongside the absolute effect, which refers to how many more or fewer patients achieve the outcome when compared to the control group. A short text in each chapter of the main guideline document summarises the findings. A list of excluded studies can be viewed at the dEBM upon request.

4.5 Consensus conference

The consensus conference took place at Charité – Universitätsmedizin Berlin on 13 February 2017. The conference was co-chaired by BR and AN, both of whom are AWMF-certified

moderators of consensus conferences. At the start of the consensus conference, the moderator (BR) made an opening statement clarifying the roles of the group members, the structure of the day and the procedures to be used. He also presented an overview of the conflicts of interest in the group as collated from the conflict of interest declarations provided in advance by all group members. These were discussed in detail by the group followed by round-robin feedback to determine whether any conflicts of interest had been missed or needed to be clarified. Participants were asked to abstain from voting on any recommendations for which a potential conflict of interest was present. All consensus conference participants agreed to this process.

The moderator used the nominal group technique to ensure that the presentation and discussion of evidence, the drafting of recommendations and the voting procedures would remain structured and controlled. The steps, all of which were led by the moderator, were as follows:

a) presentation of the evidence on efficacy and safety prepared by the dEBM researchers (where available);

b) presentation of the draft recommendation prepared by the section authors;

c) round-robin feedback from the group;

d) open discussion considering efficacy, safety, clinical experience, patient preference, practicability and cost followed by an initial vote by a show of hands;

e) further discussion and generation of alternative wording suggestions for recommendation; and

f) final vote by show of hands.

As noted above, the members of the group were reminded by the moderator before each vote to abstain if they had a relevant conflict of interest. Abstentions were noted in each case by a show of hands, and the dEBM team made note of the names in each case in the conference protocols.

In general, the goal of each round of discussion was to obtain a strong consensus (≥ 95%) among group members. It was agreed that in cases where this could not be obtained even after renewed presentation of the evidence and extended discussion, voting would take place and the lower level of consensus would be recorded alongside the recommendation. Levels of consensus were formally defined a priori and presented at the beginning of the consensus conference as follows:

- Strong consensus (“Starker Konsens”): ≥ 95% of participants
- Consensus (“Konsens”): 75% to 94% of participants

- Simple majority (“Mehrheitliche Zustimmung”): 51% to 74% of participants
- No consensus (“Kein Konsens”): 50% of participants or fewer

All members of the group were entitled to one vote per recommendation. The member of the dEBM research team who had prepared the GRADE SoF tables (CD) was also entitled to one vote per recommendation in all cases where the recommendation drew upon this evidence. Standardized wording and symbols were used to formulate the recommendations (Table).

Table 4: Standardized wording and symbols for recommendations

Wording in German (plus English translation)	**Symbols**
wird empfohlen (“is recommended”)*	⇑⇑
kann empfohlen werden (“can be recommended”)*	⇑
kann erwogen werden (“can be considered”)*	⇒
kann nicht empfohlen werden (“cannot be recommended”)*	⇓

* English translations in parentheses remain close to the original German wording and are for illustrative purposes only. More idiomatic translations would be: “is strongly recommended”, “is recommended”, “can be considered”, and “is not recommended”

A second, shorter consensus conference was held on 12 April 2017 by teleconference and video screen sharing to cover material that the group had been unable to cover in the day-long conference on 13 February 2017. Abstentions were noted in each case by an electronic show of hands, and the dEBM team made note of the names in each case in the conference protocols.

5 Funding

The development of the guideline was funded exclusively through a grant from the DDG. The members of the guideline development group received no payments for their work other than compensation for travel expenses. The guideline development group worked independently and the DDG had no influence on the recommendations of the guideline.

6 External review and approval from professional societies

The guideline underwent an extensive external review and, alongside this methods report, was available online for comments and suggested amendments from 27 July 2017 through 25 August 2017. The external review was open to anyone interested in commenting on the guideline. Additionally, approval of the guideline was sought from all involved professional societies.

In total, the dEBM received and evaluated 269 comments. A document summarizing all comments and how they were managed can be viewed at the dEBM upon request.

7 Dissemination, implementation and evaluation

The success of a guideline depends on whether it is accepted and used in clinical practice. To this end, the present guideline will be produced in a short and long version available on the dEBM psoriasis website and the AWMF homepage, as well as in print and online in the JDDG. It will also continue to be publicized and discussed in seminars and other events of the Professional Association of German Dermatologists (Berufsverband der Deutschen Dermatologen; BVDD) and DDG. Furthermore, all of the experts involved in the development of the guideline were encouraged to give talks and present the results and recommendations of the guideline at conferences.

Measuring the impact of a guideline is difficult given that treatment decisions are made on a case-by-case basis and take many individual factors into account. There is therefore no practical, universally applicable test to determine whether optimal treatment decisions have been made in everyday clinical practice. It is, however, possible to explore whether changes in certain aspects of practice, such as prescribing behaviour, have taken place over time and are associated with the publication of a guideline. An analysis of such changes and of doctors' awareness of the psoriasis S3 guideline is planned as part of the dEBM's continuing guideline development work.

8 Updating the guideline

Clinical practice guidelines should ideally be updated at regular intervals to account for changes in technologies and evidence, as well as policy and infrastructure. While conventional treatments for psoriasis vulgaris are unlikely to change substantially in the near future, advances in systemic treatments using biologics will probably require a partial or full update within several years.

With this in mind, the guideline development group decided that the psoriasis S3 guideline can be considered valid until 31 December 2020. The update will be prepared and coordinated by the dEBM in Berlin. Fast updates on newly approved medications, for example ixekizumab, will be undertaken in the interim.

9 Limitations

Trials registries and sources of grey literature were not searched, and authors were not contacted due to limited resources. Information bias may have occurred because supplementary material and study protocols were viewed only when these were available through the journal websites.

10 Acknowledgements

We would like to thank the DDG for funding the development of the guideline.

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Appendix A: Literature search strategy (MEDLINE Ovid)

1. exp Psoriasis/
2. psoriasis.mp.
3. 1 or 2
4. exp Methotrexate/
5. "methotrexat*".ab,ti.
6. MTX.ab,ti.
7. exp Cyclosporine/
8. "c#clospor*".ab,ti.
9. CSA.ab,ti.
10. exp Fumarates/
11. "fumar*".ab,ti.
12. "monomethylfumar*".ab,ti.
13. "dimethylfumar*".ab,ti.
14. FAE.ab,ti.
15. DMF.ab,ti.
16. MMF.ab,ti.
17. exp Acitretin/
18. acitretin.ab,ti.
19. infliximab.ab,ti.
20. etanercept.ab,ti.
21. ustekinumab.ab,ti.
22. adalimumab.ab,ti.
23. Randomized Controlled Trials as Topic/
24. randomized controlled trial/
25. Random Allocation/
26. Double-Blind Method/
27. Single Blind Method/
28. clinical trial/
29. clinical trial, phase I.pt.
30. clinical trial, phase II.pt.
31. clinical trial, phase III.pt.
32. clinical trial, phase IV.pt.
33. controlled clinical trial.pt.
34. randomized controlled trial.pt.
35. multicenter study.pt.
36. clinical trial.pt.
37. exp Clinical Trials as topic/
38. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37
39. (clinical adj trial$).tw.
40. ((singl$ or doubl$ or treb$ or tribl$) adj (blind$3 or mask$3)).tw.
41. Placebos/

42. placebo$.tw.
43. randomly allocated.tw.
44. (allocated adj2 random$).tw.
45. 39 or 40 or 41 or 42 or 43 or 44
46. 38 or 45
47. case report.tw.
48. letter/
49. historical article/
50. 47 or 48 or 49
51. 46 not 50
52. infliximab.mp.
53. etanercept.mp.
54. ustekinumab.mp.
55. adalimumab.mp.
56. secukinumab.mp.
57. apremilast.mp.
58. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 52 or 53 or 54 or 55 or 56 or 57
59. 3 and 51 and 58

Appendix B: Declarations of Interest

		Leitlinienkoordinator: Alexander Nast **Leitlinie: S3 – Leitlinie zur Therapie der Psoriasis vulgaris: Update 2017** **Registernr:**				
		Dr. med. Lasse Amelunxen	Prof. Dr. med. Matthias Augustin	Prof. Dr. med. Wolf-Henning Boehncke	Dr. Corinna Dressler	Matthew Gaskins
1	Berater- bzw. Gutachtertätigkeit oder bezahlte Mitarbeit in einem wissenschaftlichen Beirat eines Unternehmens der Gesundheitswirtschaft (z.B. Arzneimittelindustrie, Medizinproduktindustrie), eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	nein	Berater bzw. Gutachter für die Firmen AbbVie, Almirall, Amgen, Boehringer Ingelheim, Celgene, Lilly, Janssen, Leo, Medac, Novartis	Ja: Abbvie, Allmirall, Biogen, BMS, Celgene, Lilly, Novartis, Sun Pharmaceuticals	nein	nein
2	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften im Auftrag eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	nein	Erhalten von AbbVie, Almirall, Amgen, Boehringer Ingelheim, Celgene, Lilly, Janssen, Leo, Medac, Novartis	Ja: Abbvie, Allmirall, Biogen, BMS, Celgene, Leo, Lilly, Novartis	nein	nein
3	Finanzielle Zuwendungen (Drittmittel) für Forschungsvorhaben oder direkte Finanzierung von Mitarbeitern der Einrichtung von Seiten eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	nein	Erhalten von AbbVie, Almirall, Amgen, Boehringer Ingelheim, Celgene, Lilly, Janssen, Leo, Medac, Novartis	Ja: Pfizer	nein	nein
4	Eigentümerinteresse an Arzneimitteln/Medizinprodukten (z. B. Patent, Urheberrecht, Verkaufslizenz)	nein	nein	nein	nein	nein
5	Besitz von Geschäftsanteilen, Aktien, Fonds mit Beteiligung von Unternehmen der Gesundheitswirtschaft	nein	nein	nein	nein	nein
6	Persönliche Beziehungen zu einem Vertretungsberechtigten eines Unternehmens Gesundheitswirtschaft	nein	nein	nein	nein	nein
7	Mitglied von in Zusammenhang mit der Leitlinienentwicklung relevanten Fachgesellschaften/Berufsverbänden, Mandatsträger im Rahmen der Leitlinienentwicklung	Mitglied in der DDG	Mitglied im DDG und im BVDD	Mitglied in der DDG		nein
8	Politische, akademische (z.B. Zugehörigkeit zu bestimmten „Schulen“), wissenschaftliche oder persönliche Interessen, die mögliche Konflikte begründen könnten	nein	nein	nein		nein
9	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre	Fachklinik Bad Bentheim	Universitätsklinikum Hamburg-Eppendorf, Institut für Versorgungs-forschung in der Dermatologie und bei Pflegeberufen	Hôpitaux Univeristaires de Genève, Service de Dermatologie et Vénéréologie	Charité – Universitäts-medizin Berlin, Klinik für Dermatologie, Venerologie und Allergologie, Division of Evidence Based Medicine	Charité – Universitäts-medizin Berlin, Klinik für Dermatologie, Venerologie und Allergologie, Division of Evidence Based Medicine
10	Bewertung der Relevanz der Interessenkonflikte	keine	moderat	moderat	keine	keine

		Prof. Dr. med. Peter Härle	Bernd Hoffstadt	Joachim Klaus	Joachim Koza
1	Berater- bzw. Gutachtertätigkeit oder bezahlte Mitarbeit in einem wissenschaftlichen Beirat eines Unternehmens der Gesundheitswirtschaft (z.B. Arzneimittelindustrie, Medizinproduktindustrie), eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	Nein	nein	nein	nein
2	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften im Auftrag eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	Nein	nein	nein	nein
3	Finanzielle Zuwendungen (Drittmittel) für Forschungsvorhaben oder direkte Finanzierung von Mitarbeitern der Einrichtung von Seiten eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	Nein	nein	nein	nein
4	Eigentümerinteresse an Arzneimitteln/Medizinprodukten (z. B. Patent, Urheberrecht, Verkaufslizenz)	Nein	nein	nein	nein
5	Besitz von Geschäftsanteilen, Aktien, Fonds mit Beteiligung von Unternehmen der Gesundheitswirtschaft	Nein	nein	nein	nein
6	Persönliche Beziehungen zu einem Vertretungsberechtigten eines Unternehmens Gesundheitswirtschaft	Nein	nein	nein	nein
7	Mitglied von in Zusammenhang mit der Leitlinienentwicklung relevanten Fachgesellschaften/Berufsverbänden, Mandatsträger im Rahmen der Leitlinienentwicklung	DGRh	nein	nein	nein
8	Politische, akademische (z.B. Zugehörigkeit zu bestimmten „Schulen“), wissenschaftliche oder persönliche Interessen, die mögliche Konflikte begründen könnten	Nein	nein	nein	nein
9	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre	Katholisches Klinikum Mainz	Umweltschutz-techniker Angestellter	Landwirt, Geschäftsführer	MdB Kai Wegner
10	Bewertung der Relevanz der Interessenkonflikte	gering	keine	keine	keine

		Prof. Dr. med. Ulrich Mrowietz	Prof. Dr. med. Alexander Nast	Prof. Dr. med. Hans Michael Ockenfels
1	Berater- bzw. Gutachtertätigkeit oder bezahlte Mitarbeit in einem wissenschaftlichen Beirat eines Unternehmens der Gesundheitswirtschaft (z.B. Arzneimittelindustrie, Medizinproduktindustrie), eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	AbbVie, Almirall, Amgen, Boehringer-Ingelheim, Celgene, Dr. Reddy's, Eli Lilly, Formycon, Forward Pharma, Janssen, LEO Pharma, Medac, Novartis, VBL, Xenoport	Tatigkeit mit Bezug zum Thema der Leitlinie: Keine Tätigkeit ohne Bezug zum Thema der Leitlinie Boehringer Ingelheim, Bayer	nein
2	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften im Auftrag eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	AbbVie, Almirall, Biogen, Boehringer-Ingelheim, Celgene, Eli Lilly, Janssen, LEO Pharma, Medac, MSD, Novartis	Tätigkeit mit Bezug zum Thema der Leitlinie: Novartis, Pfizer, Janssen Tätigkeit ohne Bezug zur Leitlinie: MEDA, Pierre Fabre, Bayer	nein
3	Finanzielle Zuwendungen (Drittmittel) für Forschungsvorhaben oder direkte Finanzierung von Mitarbeitern der Einrichtung von Seiten eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	AbbVie, Almirall, Celgene, Eli Lilly, Forward Pharma, Janssen, LEO Pharma, Novartis	Projekte mit Bezug zum Thema der Leitlinie: Pfizer, Lilly, Novartis Projekte ohne Bezug zum Thema der Leitlinei: Merz, MEDA, Dermira	nein
4	Eigentümerinteresse an Arzneimitteln/Medizinprodukten (z. B. Patent, Urheberrecht, Verkaufslizenz)	nein	nein	Erfindung eines Lasersystems zur Behandlung von Hautkrankheiten Patentnummer 10310913
5	Besitz von Geschäftsanteilen, Aktien, Fonds mit Beteiligung von Unternehmen der Gesundheitswirtschaft	nein	nein	nein
6	Persönliche Beziehungen zu einem Vertretungsberechtigten eines Unternehmens Gesundheitswirtschaft	nein	nein	nein
7	Mitglied von in Zusammenhang mit der Leitlinienentwicklung relevanten Fachgesellschaften/Berufsverbänden, Mandatsträger im Rahmen der Leitlinienentwicklung	Mitglied im Deutschen Psoriasisbund e.V., in der ADF, DDG und im BVDD	DDG, EDF, BDG, EADV	Mitglied im BVDD und in der DDG
8	Politische, akademische (z.B. Zugehörigkeit zu bestimmten „Schulen"), wissenschaftliche oder persönliche Interessen, die mögliche Konflikte begründen könnten	nein	keine	nein
9	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre	Universitätsklinikum Schleswig-Holstein, Campus Kiel	Charité – Universitätsmedizin Berlin, Klinik für Dermatologie, Venerologie und Allergologie, Division of Evidence Based Medicine	Klinikum Stadt Hanau, Abteilung für Haut- und Geschlechtskrankheiten, Allergologie
10	Bewertung der Relevanz der Interessenkonflikte	moderat	gering	gering

		Dr. med. Sandra Philipp	Prof. Dr. med. Kristian Reich	Priv.-Dozent Dr. med. Thomas Rosenbach	Prof. Dr. med. Berthold Rzany
1	Berater- bzw. Gutachtertätigkeit oder bezahlte Mitarbeit in einem wissenschaftlichen Beirat eines Unternehmens der Gesundheitswirtschaft (z.B. Arzneimittelindustrie, Medizinproduktindustrie), eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	Ja, für folgende Unternehmen (in alphabetischer Reihenfolge.) AbbVie, Almirall, Biogen, Boehringer-Ingelheim, Celgene, Eli Lilly, Janssen, Leo, MSD, Novartis, Pfizer	Abbvie, Amgen,Biogen, Boehringer Ingelheim Pharma, Celgene, Covagen, Forward Pharma, Janssen-Cilag, Leo, Lilly, Novartis, Pfizer, Regeneron,Takeda, UCB Pharma, Xenoport	Abbvie, Amgen, Astra Zeneca, Biogen Idec, Eli Lilly, Foamix, Janssen Cilag, Leo, Pfizer, Novartis, Regeneron, Sciderm	nein
2	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften im Auftrag eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	Ja, in alphabetischer Reihenfolge: AbbVie, Almirall, Amgen, Biogen, BMS GmbH, Boehringer Ingelheim, Celgene, Eli Lilly, Hexal, Janssen Cilag, Leo Pharma, MSD, Mundipharma, Novartis, Pfizer, UCB Pharma; Co-Autorenvertrag mit Thieme-Verlag	Abbvie, Biogen, Celgene, Covagen, Forward Pharma, GlaxoSmithKline, Janssen-Cilag,, Leo, Lilly, Medac, Merck Sharp & Dohme Corp., Novartis,UCB Pharma	Abbvie, Biogen Idec, Fortbildungskolleg, Janssen Cilag, Leo, Medical Training, Pfizer, Novartis,	nein
3	Finanzielle Zuwendungen (Drittmittel) für Forschungsvorhaben oder direkte Finanzierung von Mitarbeitern der Einrichtung von Seiten eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	Ja, Drittmittel für Arbeitsgruppe (in alphabetischer Reihenfolge): AbbVie, Almirall, Amgen, Biogen, Boehringer Ingelheim, Celgene, Dermira, Eli Lilly, GSK, Janssen Cilag, Leo Pharma, Maruho, Merck, Novartis, Pfizer, UCB Pharma und VBL Therapeutics	Abbvie, Amgen, Biogen,Boehringer Ingelheim Pharma, Celgene,Covagen,Forward Pharma, GlaxoSmithKline, Janssen-Cilag,,Leo, Lilly, Medac, Merck Sharp & Dohme Corp.,Novartis,Regeneron, Takeda, UCB Pharma	nein	nein
4	Eigentümerinteresse an Arzneimitteln/Medizinprodukten (z. B. Patent, Urheberrecht, Verkaufslizenz)	nein	nein	nein	nein
5	Besitz von Geschäftsanteilen, Aktien, Fonds mit Beteiligung von Unternehmen der Gesundheitswirtschaft	nein	nein	nein	nein
6	Persönliche Beziehungen zu einem Vertretungsberechtigten eines Unternehmens Gesundheitswirtschaft	nein	nein	nein	nein
7	Mitglied von in Zusammenhang mit der Leitlinienentwicklung relevanten Fachgesellschaften/Berufsverbänden, Mandatsträger im Rahmen der Leitlinienentwicklung	Mitglied in der DDG, der ADF und in der EADV, Mitglied im wissenschaftlichen Beirat des DPB, 2. Vorsitzende im Psonet Berlin-Brandenburg	Mitglied im DDG, in der EADV und in der ADF; Vorsitzender des wissenschaftlichen Beirats von PsoBest; Mitglied im wissenschaftlichen Beirat des DPB	Mitglied in der DDG, im BVDD und im DPB	Mitglied in der DDG
8	Politische, akademische (z.B. Zugehörigkeit zu bestimmten „Schulen“), wissenschaftliche oder persönliche Interessen, die mögliche Konflikte begründen könnten	nein	nein	nein	nein
9	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre	Charité – Universitätsmedizin Berlin, Klinik für Dermatologie, Venerologie und Allergologie, Psoriasisstudienzentrum	Niedergelassener Dermatologe im Dermatologikum Hamburg	Niedergelassener Dermatologe in Osnabrück	Privatpraxis Rzany & Hund, Berlin
10	Bewertung der Relevanz der Interessenkonflikte	moderat	moderat	moderat	keine

		Dr. med. Martin Schlaeger	Prof. Dr. med. Gerhard Schmid-Ott	Dr. med. Michael Sebastian
1	Berater- bzw. Gutachtertätigkeit oder bezahlte Mitarbeit in einem wissenschaftlichen Beirat eines Unternehmens der Gesundheitswirtschaft (z.B. Arzneimittelindustrie, Medizinproduktindustrie), eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	nein	nein	Lilly, Novartis, Celgene, Janssen-Cilag, Abbvie, Leo Pharma, Almirall, Hexal
2	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften im Auftrag eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	nein	4., aktualisierte Auflage „Schuppenflechte – Was Sie schon immer über Psoriasis wissen wollten“, Karger 2017	Lilly, Novartis, Celgene, Janssen-Cilag, Abbvie, Leo Pharma, Almirall, Hexal, Medac, Mundipharma
3	Finanzielle Zuwendungen (Drittmittel) für Forschungsvorhaben oder direkte Finanzierung von Mitarbeitern der Einrichtung von Seiten eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	nein	nein	nein
4	Eigentümerinteresse an Arzneimitteln/Medizinprodukten (z. B. Patent, Urheberrecht, Verkaufslizenz)	nein	nein	nein
5	Besitz von Geschäftsanteilen, Aktien, Fonds mit Beteiligung von Unternehmen der Gesundheitswirtschaft	nein	nein	nein
6	Persönliche Beziehungen zu einem Vertretungsberechtigten eines Unternehmens Gesundheitswirtschaft	nein	nein	nein
7	Mitglied von in Zusammenhang mit der Leitlinienentwicklung relevanten Fachgesellschaften/Berufsverbänden, Mandatsträger im Rahmen der Leitlinienentwicklung	nein	nein	nein
8	Politische, akademische (z.B. Zugehörigkeit zu bestimmten „Schulen“), wissenschaftliche oder persönliche Interessen, die mögliche Konflikte begründen könnten	nein	Zugehörigkeit zur Medizinischen Hochschule Hannover	nein
9	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre	Niedergelassener Dermatologe in Oldenburg	Berolina Klinik in Löhne bei Bad Oeynhausen	Niedergelassener Dermatologe in Mahlow
10	Bewertung der Relevanz der Interessenkonflikte	keine	keine	moderat

		Dr. med. Ralph von Kiedrowski	Priv.-Dozent Dr. med. Tobias Weberschock
1	Berater- bzw. Gutachtertätigkeit oder bezahlte Mitarbeit in einem wissenschaftlichen Beirat eines Unternehmens der Gesundheitswirtschaft (z.B. Arzneimittelindustrie, Medizinproduktindustrie), eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	AbbVie, Almirall Hermal, Biogen, Boehringer Ingelheim, Celgene, Hexal, Janssen-Cilag, Leo, Lilly, Medac, MSD, Novartis, Pfizer	Stiftung Warentest, Medizinische Dienst des Spitzenverbandes Bund der Krankenkassen, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
2	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften im Auftrag eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	AbbVie, Almirall Hermal, Biogen, Celgene, Janssen-Cilag, Leo, Lilly,Medac, MSD, Novartis, Pfizer, UCB	Durchführung der Frankfurter Fortbildungsreihe Evidenzbasierte Medizin seit 2005 mit Teilnahmemöglichkeit aller Interessierten
3	Finanzielle Zuwendungen (Drittmittel) für Forschungsvorhaben oder direkte Finanzierung von Mitarbeitern der Einrichtung von Seiten eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	AbbVie, Biogen, Celgene, CVDerm, Janssen-Cilag, Lilly,Medac, Novartis, Pfizer	
4	Eigentümerinteresse an Arzneimitteln/Medizinprodukten (z. B. Patent, Urheberrecht, Verkaufslizenz)	nein	nein
5	Besitz von Geschäftsanteilen, Aktien, Fonds mit Beteiligung von Unternehmen der Gesundheitswirtschaft	nein	nein
6	Persönliche Beziehungen zu einem Vertretungsberechtigten eines Unternehmens Gesundheitswirtschaft	nein	nein
7	Mitglied von in Zusammenhang mit der Leitlinienentwicklung relevanten Fachgesellschaften/Berufsverbänden, Mandatsträger im Rahmen der Leitlinienentwicklung	EADV, BVDD, DDG	Mitglied im Deutschen Netzwerk Evidenzbasierter Medizin, GIN; DDG
8	Politische, akademische (z.B. Zugehörigkeit zu bestimmten „Schulen“), wissenschaftliche oder persönliche Interessen, die mögliche Konflikte begründen könnten	nein	nein
9	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre	Niedergelassener Arzt in Selters Geschäftsführer, Ärztl. Direktor und Prüfarzt Company for Medical Study & Service Selters GmbH	Universitätsklinikum Frankfurt, Klinik für Dermatologie, Goethe Universität Frankfurt, Institut für Allgemeinmedizin
10	Bewertung der Relevanz der Interessenkonflikte	moderat	keine

Appendix C: GRADE Summary of Findings (SoF) tables

A total of 56 GRADE Summary of Findings tables were produced with the Software GRADEpro GDT. The following definitions and clarifications are valid for all of the tables:

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*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are 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: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

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

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Etanercept 50mg BIW compared to combination of etanercept 25mg BIW + acitretin 10mg BID for psoriasis

Bibliography: Lee 2016

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with combination of etanercept 25mg QW + acitretin	Risk difference with etanercept 25mg BIW
PASI 75 - induction	40 (1 RCT)	⨁⨁◯◯ LOW [a,b]	**RR 1.81** (0.65 to 5.06)	211 per 1.000	**171 more per 1.000** (74 fewer to 855 more)
Withdrawal due to AE - induction	41 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	**RR 2.86** (0.12 to 66.44)	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)

Explanations

a. Unclear methods of allocation concealment, no blinding of patients, no/unclear blinding of personnel

b. Confidence interval crosses line of no effect and minimal important difference (MID) thresholds: uncertain whether there is any difference

c. Wide confidence interval

Acitretin 25mg compared to acitretin 35mg for psoriasis

Bibliography: Dogra 2013

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with acitretin 35mg	Risk difference with acitretin 25mg
PASI 75 - induction	31 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	**RR 0.68** (0.36 to 1.28)	688 per 1.000	**220 fewer per 1.000** (440 fewer to 193 more)
Withdrawal due to AE - induction	40 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,d]	not estimable	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)

Explanations

a. High drop-out rates, no ITT; small study

b. Patients with low initial PASI

c. Confidence interval crosses line of no effect and minimal important difference thresholds: uncertain whether there is any difference

d. Effect not estimable, 0 events in both groups

Acitretin 25mg compared to acitretin 50mg for psoriasis

Bibliography: Dogra 2013

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with acitretin 50mg	Risk difference with acitretin 25mg
PASI 75 - induction	32 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	**RR 0.88** (0.44 to 1.78)	529 per 1.000	**64 fewer per 1.000** (296 fewer to 413 more)
Withdrawal due to AE - induction	41 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,d]	not estimable	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)

Explanations

a. High drop-out rates, no ITT; small study

b. Patients with low initial PASI

c. Confidence interval crosses line of no effect and minimal important difference thresholds: uncertain whether there is any difference

d. Effect not estimable, 0 events in both groups

Acitretin 35mg compared to acitretin 50mg for psoriasis

Bibliography: Dogra 2013

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with acitretin 50mg	Risk difference with acitretin 35mg
PASI 75 - induction	33 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	**RR 1.30** (0.74 to 2.27)	529 per 1.000	**159 more per 1.000** (138 fewer to 672 more)
Withdrawal due to AE - induction	41 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,d]	not estimable	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)

Explanations

a. High drop-out rates, no ITT; small study

b. Patients with low initial PASI

c. Confidence interval crosses line of no effect and minimal important difference thresholds: uncertain whether there is any difference

d. Effect not estimable, 0 events in both groups

Acitretin 0.4mg/kg QD compared to combination of acitretin 0.4mg/kg QD + etanercept 25mg QW for psoriasis

Bibliography: Gisondi 2008, Lee 2016

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with combination of acitretin 0.4mg/kg QD + etanercept 25mg QW	Risk difference with acitretin 0.4mg/kg QD
PASI 75 - induction	75 (2 RCTs)	⨁◯◯◯ VERY LOW [a,b,c]	**RR 0.56** (0.18 to 1.76)	189 per 1.000	**83 fewer per 1.000** (155 fewer to 144 more)

Acitretin 0.4mg/kg QD compared to combination of acitretin 0.4mg/kg QD + etanercept 25mg QW for psoriasis

Bibliography: Gisondi 2008, Lee 2016

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with combination of acitretin 0.4mg/kg QD + etanercept 25mg QW	Risk difference with acitretin 0.4mg/kg QD
Withdrawal due to AE - induction	77 (2 RCTs)	⨁◯◯◯ VERY LOW [a,b,c]	**RR 3.15** (0.14 to 72.88)	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)

Explanations

a. Unclear methods of allocation concealment, no blinding of patients, unclear blinding of personnel

b. Gisondi et al. 2008: patients with low initial PASI

c. Confidence interval crosses line of no effect and minimal important difference thresholds: uncertain whether there is any difference

Acitretin compared to combination of acitretin + top. calcipotriol 50µg/g BID for psoriasis

Bibliography: Rim 2003, van de Kerkhof 1998

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with combination of acitretin + top. calcipotriol 50µg/g BID	Risk difference with acitretin
Withdrawal due to AE - induction	135 (2 RCTs)	⨁⨁◯◯ LOW [a,b]	**RR 1.86** (0.85 to 4.05)	118 per 1.000	**102 more per 1.000** (18 fewer to 361 more)

Acitretin compared to combination of acitretin + top. calcipotriol 50µg/g BID for psoriasis

Bibliography: Rim 2003, van de Kerkhof 1998

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with combination of acitretin + top. calcipotriol 50µg/g BID	Risk difference with acitretin
Pts. with at least 1 AE - induction	135 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	**RR 0.97** (0.91 to 1.05)	974 per 1.000	**29 fewer per 1.000** (88 fewer to 49 more)

Explanations

a. Unclear randomisation method, high drop-out rate

b. Confidence interval crosses line of no effect and minimal important difference thresholds: uncertain whether there is any difference

Acitretin 0.4mg/kg QD compared to etanercept (25mg QW or 50mg BIW) for psoriasis

Bibliography: Caprioni 2009, Gisondi 2008, Lee 2016

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with etanercept (25mg QW or 50mg BIW)	Risk difference with acitretin 0.4mg/kg QD
PASI 75 - induction 12w	141 (3 RCTs)	⨁⨁◯◯ LOW [a,b]	**RR 0.43** (0.25 to 0.76)	411 per 1.000	**234 fewer per 1.000** (308 fewer to 99 fewer)
Withdrawal due to AE - induction	142 (3 RCTs)	⨁◯◯◯ VERY LOW [a,b,c,d]	**RR 1.11** (0.07 to 16.47)	14 per 1.000	**2 more per 1.000** (13 fewer to 212 more)

Explanations

a. Unclear methods of allocation concealment, no blinding of patients, unclear blinding of personnel/no blinding

b. Gisondi et al. 2008: patients with low initial PASI

c. Confidence interval crosses line of no effect and minimal important difference thresholds: uncertain whether there is any difference

d. Wide confidence interval

Adalimumab (80/40mg) compared to combiantion of adalimumab + top. calcipotriol/betamethasone for psoriasis

Bibliography: Thaci 2010

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with combiantion of adalimumab + top. calcipotriol/betamethasone	Risk difference with Adalimumab (80/40mg)
PASI 75 - induction	730 (1 RCT)	⊕⊕⊕⊕ HIGH	**RR 1.09** (0.99 to 1.21)	648 per 1.000	**58 more per 1.000** (6 fewer to 136 more)
PASI 90 - induction	730 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	**RR 1.30** (1.10 to 1.53)	388 per 1.000	**116 more per 1.000** (39 more to 206 more)
Withdrawal due to AE - induction	730 (1 RCT)	⊕⊕⊕⊕ HIGH	**RR 0.34** (0.13 to 0.83)	49 per 1.000	**32 fewer per 1.000** (43 fewer to 8 fewer)
Pts. with at least 1 AE - induction	730 (1 RCT)	⊕⊕⊕⊕ HIGH	**RR 0.97** (0.86 to 1.10)	601 per 1.000	**18 fewer per 1.000** (84 fewer to 60 more)
Pts. with at least 1 SAE - induction	730 (1 RCT)	⊕⊕⊕◯ MODERATE [b]	**RR 0.94** (0.47 to 1.88)	44 per 1.000	**3 fewer per 1.000** (23 fewer to 38 more)

Explanations

a. Confidence interval crosses minimal important difference threshold: stat. sign. difference of uncertain clinical importance

b. Confidence interval crosses line of no effect and minimal important difference thresholds: uncertain whether there is any difference

Adalimumab compared to placebo for psoriasis

Bibliography: Asahina 2010, Cai 2016, Gordon 2015, Menter 2008, Saurat 2008,

Outcomes	№ of	Certainty of	Relative effect	Anticipated absolute effects

	participants (studies) Follow-up	the evidence (GRADE)	(95% CI)	Risk with placebo	Risk difference with adalimumab
PASI 75 - induction	2038 (6 RCTs)	⊕⊕◯◯ LOW [a,b]	**RR 7.87** (5.00 to 12.38)	79 per 1.000	**542 more per 1.000** (315 more to 897 more)
PASI 90 - induction	1941 (5 RCTs)	⊕⊕◯◯ LOW [b,c]	**RR 12.90** (5.17 to 32.14)	29 per 1.000	**340 more per 1.000** (119 more to 890 more)
DLQI 0 or 1	81 (1 RCT)	⊕⊕⊕◯ MODERATE [d]	**RR 6.82** (2.19 to 21.26)	71 per 1.000	**416 more per 1.000** (85 more to 1.447 more)
Withdrawal due to AE - induction	1555 (4 RCTs)	⊕⊕⊕◯ MODERATE [e]	**RR 0.99** (0.49 to 2.00)	22 per 1.000	**0 fewer per 1.000** (11 fewer to 22 more)
Pts. with at least 1 AE - induction	1979 (5 RCTs)	⊕⊕⊕◯ MODERATE [b]	**RR 1.06** (0.95 to 1.17)	559 per 1.000	**34 more per 1.000** (28 fewer to 95 more)
Pts. with at least 1 SAE - induction	1554 (4 RCTs)	⊕⊕⊕◯ MODERATE [e]	**RR 1.11** (0.51 to 2.41)	17 per 1.000	**2 more per 1.000** (8 fewer to 23 more)

Explanations

a. Statistical heterogeneity (I^2 = 52%)

b. Asahina 2010, Gordon 2015 higher bl mean PASI

c. Statistical heterogeneity (I^2= 68%)

d. Open-label

e. Confidence interval crosses line of no effect and minimal important difference thresholds: uncertain whether there is any difference

MTX compared to Adalimumab 80mg/40mg for psoriasis

Bibliography: Saurat 2008, Goldminz 2015

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Adalimumab 80mg/40mg	Risk difference with MTX
PASI 75 - induction	248 (2 RCTs)	⨁⨁⨁⨁ HIGH	**RR 0.44** (0.34 to 0.57)	780 per 1.000	**437 fewer per 1.000** (515 fewer to 336 fewer)
PASI 90 - induction	218 (1 RCT)	⨁⨁⨁⨁ HIGH	**RR 0.27** (0.16 to 0.44)	509 per 1.000	**372 fewer per 1.000** (428 fewer to 285 fewer)
Withdrawal due to AE - induction	248 (2 RCTs)	⨁⨁⨁◯ MODERATE [a]	**RR 5.89** (0.72 to 48.12)	8 per 1.000	**40 more per 1.000** (2 fewer to 383 more)
Pts. with at least 1 AE - induction	217 (1 RCT)	⨁⨁⨁⨁ HIGH	**RR 1.10** (0.95 to 1.27)	738 per 1.000	**74 more per 1.000** (37 fewer to 199 more)
Pts. with at least 1 SAE - induction	217 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	**RR 0.49** (0.04 to 5.28)	19 per 1.000	**10 fewer per 1.000** (18 fewer to 80 more)

Explanations

a. Confidence interval crosses line of no effect and minimal important difference thresholds: uncertain whether there is any difference

Apremilast compared to etanercept for psoriasis

Bibliography: Reich 2016 (NCT01690299)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with etanercept	Risk difference with Apremilast
PASI 75 - induction w12/16	166 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	**RR 0.80** (0.56 to 1.14)	482 per 1.000	**96 fewer per 1.000** (212 fewer to 67 more)
PASI 90 - induction w16 - 30mg BID	166 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	**RR 0.71** (0.36 to 1.38)	205 per 1.000	**59 fewer per 1.000** (131 fewer to 78 more)
DLQI 0 or 1 - induction w12/16 - 30mg BID	166 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	**RR 0.81** (0.51 to 1.31)	325 per 1.000	**62 fewer per 1.000** (159 fewer to 101 more)
Pts. with at least 1 AE - induction w12/16	166 (1 RCT)	⊕⊕⊕◯ MODERATE [b]	**RR 1.82** (1.10 to 3.03)	205 per 1.000	**168 more per 1.000** (20 more to 416 more)
Pts. with at least 1 SAE - induction w12/16	166 (1 RCT)	⊕⊕◯◯ LOW [a,c]	**RR 3.00** (0.32 to 28.25)	12 per 1.000	**24 more per 1.000** (8 fewer to 328 more)

Explanations

a. Confidence interval crosses line of no effect and minimal important difference threshold(s): uncertain whether there is any difference

b. Confidence interval crosses minimal important difference threshold: statistically significant difference of uncertain clinical importance

c. Wide confidence interval

Apremilast compared to placebo for psoriasis

Bibliography: Papp 2012 (NCT00773734), Papp 2015 & Papp 2015 abstract (NCT01194219), Paul 2015 & Papp 2015 abstract (NCT01232283), Reich 2016 (NCT01690299)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Apremilast
PASI 75 - induction w12/16	1598 (4 RCTs)	⨁⨁⨁⨁ HIGH	**RR 5.12** (3.66 to 7.14)	64 per 1.000	**265 more per 1.000** (171 more to 395 more)
PASI 90 - induction w12/16	1598 (4 RCTs)	⨁⨁⨁⨁ HIGH	**RR 7.18** (3.14 to 16.44)	12 per 1.000	**73 more per 1.000** (25 more to 183 more)
DLQI 0 or 1 - induction w12/16 - 30mg BID	1422 (3 RCTs)	⨁⨁⨁◯ MODERATE [a]	**RR 3.77** (1.40 to 10.16)	85 per 1.000	**237 more per 1.000** (34 more to 783 more)
Withdrawal due to AE - induction w12/16	1431 (3 RCTs)	⨁⨁⨁◯ MODERATE [b]	**RR 1.79** (1.03 to 3.09)	34 per 1.000	**27 more per 1.000** (1 more to 71 more)
Pts. with at least 1 AE - induction w12/16	1593 (4 RCTs)	⨁⨁⨁◯ MODERATE [b]	**RR 1.22** (1.13 to 1.33)	536 per 1.000	**118 more per 1.000** (70 more to 177 more)
Pts. with at least 1 SAE - induction w12/16	1535 (4 RCTs)	⨁⨁⨁◯ MODERATE [c]	**RR 0.79** (0.40 to 1.55)	24 per 1.000	**5 fewer per 1.000** (15 fewer to 13 more)

Explanations

a. Statistical heterogeneity (I^2 = 90%)

b. Statistical significant difference of uncertain clinical importance

c. Confidence interval crosses line of no effect and minimal important difference threshold(s): uncertain whether there is any difference.

CSA 2mg/kg QD + calcipotriol 50µg/g BID compared to CSA 2mg/kg QD for psoriasis

Bibliography: Grossman 1994

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with CSA 2mg/kg QD	Risk difference with CSA 2mg/kg QD + calcipotriol 50µg/g BID
Withdrawal due to AE - induction	69 (1 RCT)	⨁⨁◯◯ LOW [a,b]	**RR 0.49** (0.05 to 5.11)	59 per 1.000	**30 fewer per 1.000** (56 fewer to 242 more)

Explanations

a. Unclear randomisation methods

b. Confidence interval crosses line of no effect and minimal important difference thresholds: uncertain whether there is any difference

CSA 1.25mg/kg QD compared to CSA 2.5mg/kg QD for psoriasis

Bibliography: Meffert 1997

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with CSA 2.5mg/kg QD	Risk difference with CSA 1.25mg/kg QD
PASI 75 - induction	81 (1 RCT)	⨁⨁◯◯ LOW [a,b]	**RR 0.34** (0.12 to 0.97)	293 per 1.000	**193 fewer per 1.000** (258 fewer to 9 fewer)
Withdrawal due to AE - induction	85 (1 RCT)	⨁◯◯◯ VERY LOW [a,c]	not estimable	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)
Pts. with at least 1 AE - induction	81 (1 RCT)	⨁⨁⨁◯ MODERATE [a,b]	**RR 0.48** (0.30 to 0.76)	732 per 1.000	**380 fewer per 1.000** (512 fewer to 176 fewer)

Explanations

a. Unclear randomisation methods, no ITT

b. Confidence interval crosses minimal important difference threshold: stat. sign. difference of uncertain clinical importance

c. Effect not estimable, 0 events in both groups

CSA 1.25mg/kg QD compared to CSA 5mg/kg QD for psoriasis

Bibliography: Meffert 1997

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with CSA 5mg/kg QD	Risk difference with CSA 1.25mg/kg QD

CSA 1.25mg/kg QD compared to CSA 5mg/kg QD for psoriasis

Bibliography: Meffert 1997

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with CSA 5mg/kg QD	Risk difference with CSA 1.25mg/kg QD
PASI 75 - induction	34 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	**RR 0.39** (0.17 to 0.91)	667 per 1.000	**407 fewer per 1.000** (553 fewer to 60 fewer)

Explanations

a. Confidence interval crosses minimal important difference threshold: stat. sign. difference of uncertain clinical importance

CSA 2.5-3mg/kg QD compared to CSA 5mg/kg QD for psoriasis

Bibliography: Ellis 1991, Laburte 1994, Takahashi 2009, Yoon 2007

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with CSA 5mg/kg QD	Risk difference with CSA 2.5-3mg/kg QD
PASI 75 - induction	251 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	**RR 0.54** (0.44 to 0.66)	886 per 1.000	**408 fewer per 1.000** (496 fewer to 301 fewer)
Withdrawal due to AE - induction	45 (1 RCT)	⨁⨁⨁◯ MODERATE [b]	**RR 0.40** (0.04 to 4.10)	100 per 1.000	**60 fewer per 1.000** (96 fewer to 310 more)
Pts. with at least 1 AE - induction	30 (1 RCT)	⨁⨁◯◯ LOW [a,b]	**RR 1.09** (0.36 to 3.29)	286 per 1.000	**26 more per 1.000** (183 fewer to 654 more)

Explanations

a. Unclear randomisation methods, no blinding

b. Confidence interval crosses line of no effect and minimal important difference thresholds: uncertain whether there is any difference

CSA 2mg/kg QD + calcipotriol 50µg/g and betamethasone dipropionate 0.5mg/g compared to CSA 2mg/kg QD for psoriasis

Bibliography: Vena 2012

Outcomes	№ of	Certainty of the	Relative effect	Anticipated absolute effects

	participants (studies) Follow-up	evidence (GRADE)	(95% CI)	Risk with CSA 2mg/kg QD	Risk difference with CSA 2mg/kg QD + calcipotriol 50µg/g and betamethasone dipropionate 0.5mg/g
PASI 75 - induction	60 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	**RR 2.36** (1.45 to 3.86)	367 per 1.000	**499 more per 1.000** (165 more to 1.049 more)
PASI 90 - induction	60 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	**RR 3.00** (1.61 to 5.58)	267 per 1.000	**533 more per 1.000** (163 more to 1.221 more)
Withdrawal due to AE - induction	47 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	not estimable	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)
Pts. with at least 1 AE - induction	47 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	not estimable	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)
Pts. with at least 1 SAE - induction	47 (1 RCT)	⊕◯◯◯ VERY LOW [a,b]	not estimable	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)

Explanations
a. Open study
b. Effect not estimable, 0 events in both groups

CSA 3mg/kg QD compared to CSA 7.5mg/kg QD for psoriasis

Bibliography: Ellis 1991

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with CSA 7.5mg/kg QD	Risk difference with CSA 3mg/kg QD
Withdrawal due to AE - induction	40 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	**RR 0.60** (0.04 to 8.90)	67 per 1.000	**27 fewer per 1.000** (64 fewer to 527 more)

Explanations

a. Confidence interval crosses line of no effect and minimal important difference thresholds: uncertain whether there is any difference

CSA 5mg/kg QD compared to CSA 7.5mg/kg QD for psoriasis

Bibliography: Ellis 1991

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with CSA 7.5mg/kg QD	Risk difference with CSA 5mg/kg QD
Withdrawal due to AE - induction	35 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	**RR 1.50** (0.15 to 15.04)	67 per 1.000	**33 more per 1.000** (57 fewer to 936 more)

Explanations

a. Confidence interval crosses line of no effect and minimal important difference thresholds: uncertain whether there is any difference

CSA 100mg QD compared to CSA 50mg BID for psoriasis

Bibliography: . Shintani 2011

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with CSA 50mg BID	Risk difference with CSA 100mg QD
PASI 75 - induction	35 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	**RR 0.82** (0.40 to 1.71)	500 per 1.000	**90 fewer per 1.000** (300 fewer to 355 more)
PASI 90 - induction	35 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	**RR 0.79** (0.21 to 3.04)	222 per 1.000	**47 fewer per 1.000** (176 fewer to 453 more)
Withdrawal due to AE - induction	40 (1 RCT)	⨁◯◯◯ VERY LOW [a,c]	**RR 5.00** (0.26 to 98.00)	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)

Explanations

a. Unclear randomisation methods, no blinding, incomplete outcome data, small study size

b. Confidence interval crosses line of no effect and minimal important difference thresholds: uncertain whether there is any difference

c. Confidence interval crosses line of no effect and minimal important difference thresholds: uncertain whether there is any difference, very wide confidence interval

CSA 2.5mg low calorie diet compared to CSA 2.5mg without diet for psoriasis

Bibliography: Gisondi 2008

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with CSA 2.5mg without diet	Risk difference with CSA 2.5mg low calorie diet
PASI 75 - induction	61 (1 RCT)	⨁⨁⨁⨁ HIGH	**RR 3.10** (1.43 to 6.73)	194 per 1.000	**406 more per 1.000** (83 more to 1.109 more)

CSA fixed dose compared to CSA weight dependend dose for psoriasis

Bibliography: Thaci 2002

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with CSA weight dependend dose	Risk difference with CSA fixed dose
Withdrawal due to AE - induction	122 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	**RR 0.50** (0.05 to 5.37)	33 per 1.000	**16 fewer per 1.000** (31 fewer to 143 more)
Pts. with at least 1 drug-related AE - induction	122 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	**RR 0.76** (0.44 to 1.31)	344 per 1.000	**83 fewer per 1.000** (193 fewer to 107 more)

Explanations

a. No blinding, incomplete outcome data (no ITT)

b. Confidence interval crosses line of no effect and minimal important difference thresholds: uncertain whether there is any difference

CSA 2.5mg increased to 5mg compared to CSA 5mg decreased to 2.5mg for psoriasis

Bibliography: Yoon 2007

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with CSA 5mg decreased to 2.5mg	Risk difference with CSA 2.5mg increased to 5mg

CSA 2.5mg increased to 5mg compared to CSA 5mg decreased to 2.5mg for psoriasis

Bibliography: Yoon 2007

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with CSA 5mg decreased to 2.5mg	Risk difference with CSA 2.5mg increased to 5mg
PASI 75 - induction	61 (1 RCT)	⨁⨁◯◯ LOW [a,b]	**RR 0.69** (0.46 to 1.02)	750 per 1.000	**233 fewer per 1.000** (405 fewer to 15 more)
Pts. with at least 1 AE - induction	61 (1 RCT)	⨁⨁◯◯ LOW [a,b]	**RR 0.73** (0.28 to 1.91)	250 per 1.000	**68 fewer per 1.000** (180 fewer to 227 more)

Explanations

a. Unclear randomisation methods, no blinding

b. Confidence interval crosses line of no effect and minimal important difference thresholds: uncertain whether there is any difference

CSA 3mg/kg QD compared to MTX (7.5-22.5mg) for psoriasis

Bibliography: Heydendael 2003, Flytstrom 2008

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with MTX (7.5-22.5mg)	Risk difference with CSA 3mg/kg QD
PASI 75 - induction	153 (2 RCTs)	⨁◯◯◯ VERY LOW [a,b,c,d]	**RR 1.59** (0.78 to 3.26)	438 per 1.000	**258 more per 1.000** (96 fewer to 989 more)
PASI 90 - induction	153 (2 RCTs)	⨁◯◯◯ VERY LOW [a,d,e]	**RR 1.37** (0.44 to 4.28)	263 per 1.000	**97 more per 1.000** (147 fewer to 861 more)
Withdrawal due to AE - induction	153 (2 RCTs)	⨁◯◯◯ VERY LOW [a,c,f,g]	**RR 0.85** (0.01 to 97.31)	150 per 1.000	**23 fewer per 1.000** (149 fewer to 14.447 more)
Pts. with at least 1 AE - induction	153 (2 RCTs)	⨁◯◯◯ VERY LOW [a,c,h]	**RR 1.24** (1.07 to 1.43)	725 per 1.000	**174 more per 1.000** (51 more to 312 more)
Pts. with at least 1 SAE - induction	153 (2 RCTs)	⨁◯◯◯ VERY LOW [a,c,i]	not estimable	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)

Explanations

a. Unclear or no blinding, Flytström et al.: high drop-out rate

b. Statistical heterogeneity (I^2=76%) maybe due to methodological differences; subgroup results: CSA vs. 7.5 mg MTX: 2.39 [1.26-4.54] (Flytström et al. with high risk of bias); CSA vs. 15 mg MTX: 1.18 [0.87-1.61]

c. Inclusion of patients with mild psoriasis

d. Confidence interval crosses line of no effect and minimal important difference thresholds: uncertain whether there is any difference

e. Statistical heterogeneity (I^2=72%) maybe due to methodological differences

f. Statistical heterogeneity (I^2=86%) maybe due to methodological differences; subgroup results: CSA vs. 7.5 mg MTX: 10.69 [0.60-191.09] (Flytström et al. with high risk of bias); CSA vs. 15 mg MTX: 0.09 [0.01-0.63]

g. Confidence interval crosses line of no effect and minimal important difference thresholds: uncertain whether there is any difference; Wide confidence interval

h. Confidence interval crosses minimal important difference threshold: stat. sign. difference of uncertain clinical importance

i. Effect not estimable, 0 events in both groups

CSA compared to placebo for psoriasis

Bibliography: Ellis 1991, Meffert 1997

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with CSA
PASI 75 - induction	120 (1 RCT)	⨁⨁◯◯ LOW [a,b]	**RR 3.47** (0.82 to 14.69)	51 per 1.000	**127 more per 1.000** (9 fewer to 702 more)
Withdrawal due to AE - induction	85 (1 RCT)	⨁⨁⨁◯ MODERATE [b]	**RR 1.63** (0.28 to 9.45)	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)
Pts. with at least 1 AE - induction	120 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	**RR 5.00** (1.92 to 13.01)	103 per 1.000	**410 more per 1.000** (94 more to 1.232 more)

Explanations

a. Unclear randomisation methods, no ITT

b. Confidence interval crosses line of no effect and minimal important difference thresholds: uncertain whether there is any difference

Apremilast compared to etanercept for psoriasis

Bibliography: Reich 2016 (NCT01690299)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with etanercept	Risk difference with Apremilast

Apremilast compared to etanercept for psoriasis

Bibliography: Reich 2016 (NCT01690299)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with etanercept	Risk difference with Apremilast
PASI 75 - induction w12/16	166 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	**RR 0.80** (0.56 to 1.14)	482 per 1.000	**96 fewer per 1.000** (212 fewer to 67 more)
PASI 90 - induction w16 - 30mg BID	166 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	**RR 0.71** (0.36 to 1.38)	205 per 1.000	**59 fewer per 1.000** (131 fewer to 78 more)
DLQI 0 or 1 - induction w12/16 - 30mg BID	166 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	**RR 0.81** (0.51 to 1.31)	325 per 1.000	**62 fewer per 1.000** (159 fewer to 101 more)
Pts. with at least 1 AE - induction w12/16	166 (1 RCT)	⨁⨁⨁◯ MODERATE [b]	**RR 1.82** (1.10 to 3.03)	205 per 1.000	**168 more per 1.000** (20 more to 416 more)
Pts. with at least 1 SAE - induction w12/16	166 (1 RCT)	⨁⨁◯◯ LOW [a,c]	**RR 3.00** (0.32 to 28.25)	12 per 1.000	**24 more per 1.000** (8 fewer to 328 more)

Explanations

a. Confidence interval crosses line of no effect and minimal important difference threshold(s): uncertain whether there is any difference

b. Confidence interval crosses minimal important difference threshold: statistically significant difference of uncertain clinical importance

c. Wide confidence interval

Etanercept 50mg BIW / 50mg QW compared to combination etanercept 50mg BIW / 50mg QW + clobetasol propionate 0.05% BID (w11-12 + w23-24) for psoriasis

Bibliography: Lebwohl 2013

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with combination etanercept 50mg BIW / 50mg QW + clobetasol propionate 0.05% BID (w11-12 + w23-24)	Risk difference with etanercept 50mg BIW / 50mg QW
PASI 75 - induction	592 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	**RR 0.74** (0.64 to 0.85)	651 per 1.000	**169 fewer per 1.000** (234 fewer to 98 fewer)
PASI 90 - induction	592 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	**RR 0.65** (0.49 to 0.87)	298 per 1.000	**104 fewer per 1.000** (152 fewer to 39 fewer)

Explanations

a. Confidence interval crosses minimal important difference threshold: stat. sign. difference of uncertain clinical importance

Etanercept 50mg QW vs 50mg BIW

Bibliography: Leonardi 2003, Papp 2005, Sterry 201, Strohal 2013

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with etanercept

Etanercept 50mg QW vs 50mg BIW

Bibliography: Leonardi 2003, Papp 2005, Sterry 201, Strohal 2013

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with etanercept
PASI 75 - induction	4757 (12 RCTs)	⊕⊕⊕⊕ HIGH	**RR 9.12** (7.37 to 11.28)	47 per 1.000	**380 more per 1.000** (298 more to 481 more)
PASI 90 - induction	4708 (12 RCTs)	⊕⊕⊕⊕ HIGH	**RR 11.66** (7.92 to 17.17)	14 per 1.000	**150 more per 1.000** (98 more to 228 more)
DLQI 0 or 1	2159 (4 RCTs)	⊕⊕⊕⊕ HIGH	**RR 5.51** (4.22 to 7.20)	69 per 1.000	**312 more per 1.000** (223 more to 429 more)
Withdrawal due to AE - induction	4068 (10 RCTs)	⊕⊕⊕◯ MODERATE [a]	**RR 1.06** (0.63 to 1.77)	16 per 1.000	**1 more per 1.000** (6 fewer to 12 more)
Pts. with at least 1 AE - induction	2251 (6 RCTs)	⊕⊕⊕⊕ HIGH	**RR 1.11** (1.02 to 1.22)	458 per 1.000	**50 more per 1.000** (9 more to 101 more)
Pts. with at least 1 SAE - induction	2526 (8 RCTs)	⊕⊕⊕◯ MODERATE [a]	**RR 0.61** (0.32 to 1.17)	19 per 1.000	**7 fewer per 1.000** (13 fewer to 3 more)

Explanations

a. Confidence interval crosses line of no effect and minimal important difference thresholds: uncertain whether there is any difference

Etanercept 50mg BIW compared to combination of etanercept 25mg BIW + acitretin 10mg BID for psoriasis

Bibliography: Lee 2016

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with combination of etanercept 25mg QW + acitretin	Risk difference with etanercept 25mg BIW
PASI 75 - induction	40 (1 RCT)	⨁⨁◯◯ LOW [a,b]	**RR 1.81** (0.65 to 5.06)	211 per 1.000	**171 more per 1.000** (74 fewer to 855 more)
Withdrawal due to AE - induction	41 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	**RR 2.86** (0.12 to 66.44)	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)

Explanations

a. Unclear methods of allocation concealment, no blinding of patients, no/unclear blinding of personnel

b. Confidence interval crosses line of no effect and minimal important difference thresholds: uncertain whether there is any difference

c. Wide confidence interval

Etanercept compared to etanercept + fumarates oral for psoriasis

Bibliography: van Bezooijn 2016

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Etanercept + Fumarsäureester	Risk difference with Etanercept
PASI75	32 (1 RCT)	⨁⨁◯◯ LOW [a,b]	**RR 0.96** (0.58 to 1.60)	667 per 1.000	**27 fewer per 1.000** (280 fewer to 400 more)
Withdrawal due to AE	33 (1 RCT)	⨁⨁⨁◯ MODERATE [a,c]	not estimable	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)

Explanations

a. Open-label

b. Confidence interval crosses line of no effect and minimal important difference threshold(s): unclear whether there is any difference

c. 0 events in both groups

Etanercept 50mg BIW / 50mg QW compared to combination of etanercept 50mg BIW / 50mg QW + MTX 7.5-15mg for psoriasis

Bibliography: Gottlieb 2012

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with combination of etanercept 50mg BIW / 50mg QW + MTX 7.5-15mg	Risk difference with etanercept 50mg BIW / 50mg QW
PASI 75 - induction	478 (1 RCT)	⨁⨁◯◯ LOW [a,b]	**RR 0.77** (0.67 to 0.89)	703 per 1.000	**162 fewer per 1.000** (232 fewer to 77 fewer)
PASI 90 - induction	478 (1 RCT)	⨁⨁◯◯ LOW [a,b]	**RR 0.68** (0.51 to 0.91)	339 per 1.000	**108 fewer per 1.000** (166 fewer to 31 fewer)

Explanations

a. Unclear methods of allocation concealment

b. Confidence interval crosses minimal important difference threshold: stat. sign. difference of uncertain clinical importance

Etanercept 50mg BIW compared to infliximab 5mg/kg for psoriasis

Bibliography: DeVries 2013

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with infliximab 5mg/kg	Risk difference with etanercept 50mg BIW
PASI 75 - induction	48 (1 RCT)	⨁⨁⨁⨁ HIGH	**RR 0.29** (0.13 to 0.64)	760 per 1.000	**540 fewer per 1.000** (661 fewer to 274 fewer)

Etanercept compared to placebo for psoriasis

Bibliography:

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with etanercept
PASI 75 - induction	4757 (12 RCTs)	⊕⊕⊕⊕ HIGH	**RR 9.12** (7.37 to 11.28)	47 per 1.000	**380 more per 1.000** (298 more to 481 more)
PASI 90 - induction	4708 (12 RCTs)	⊕⊕⊕⊕ HIGH	**RR 11.66** (7.92 to 17.17)	14 per 1.000	**150 more per 1.000** (98 more to 228 more)
DLQI 0 or 1	2159 (4 RCTs)	⊕⊕⊕⊕ HIGH	**RR 5.51** (4.22 to 7.20)	69 per 1.000	**312 more per 1.000** (223 more to 429 more)
Withdrawal due to AE - induction	4068 (10 RCTs)	⊕⊕⊕◯ MODERATE [a]	**RR 1.06** (0.63 to 1.77)	16 per 1.000	**1 more per 1.000** (6 fewer to 12 more)
Pts. with at least 1 AE - induction	2251 (6 RCTs)	⊕⊕⊕⊕ HIGH	**RR 1.11** (1.02 to 1.22)	458 per 1.000	**50 more per 1.000** (9 more to 101 more)
Pts. with at least 1 SAE - induction	2526 (8 RCTs)	⊕⊕⊕◯ MODERATE [a]	**RR 0.61** (0.32 to 1.17)	19 per 1.000	**7 fewer per 1.000** (13 fewer to 3 more)

Explanations

a. Confidence interval crosses line of no effect and minimal important difference thresholds: uncertain whether there is any difference

Etanercept 50mg BIW compared to ustekimumab (45mg or 90mg) for psoriasis

Bibliography: Griffith 2010

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ustekimumab (45mg or 90mg)	Risk difference with etanercept 50mg BIW
PASI 75 - induction	903 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	**RR 0.80** (0.72 to 0.89)	714 per 1.000	**143 fewer per 1.000** (200 fewer to 79 fewer)
PASI 90 - induction	903 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	**RR 0.57** (0.45 to 0.71)	415 per 1.000	**179 fewer per 1.000** (229 fewer to 120 fewer)
Withdrawal due to AE - induction	903 (1 RCT)	⨁⨁◯◯ LOW [a,b]	**RR 1.55** (0.59 to 4.09)	14 per 1.000	**8 more per 1.000** (6 fewer to 44 more)
Pts. with at least 1 AE - induction	903 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	**RR 1.03** (0.94 to 1.13)	680 per 1.000	**20 more per 1.000** (41 fewer to 88 more)
Pts. with at least 1 SAE - induction	903 (1 RCT)	⨁⨁◯◯ LOW [a,b]	**RR 0.78** (0.24 to 2.56)	14 per 1.000	**3 fewer per 1.000** (11 fewer to 22 more)

Explanations

a. Unclear randomization methods/allocation concealment, unblinded patients

b. Confidence interval crosses line of no effect and minimal important difference thresholds: uncertain whether there is any difference

Secukinumab compared to etanercept for psoriasis

Bibliography: Langley 2014

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with etanercept	Risk difference with Secukinumab
PASI 75 - induction w12	646 (1 RCT)	⨁⨁⨁⨁ HIGH	**RR 1.75** (1.53 to 2.01)	440 per 1.000	**330 more per 1.000** (233 more to 444 more)
PASI 90 - induction w12	646 (1 RCT)	⨁⨁⨁⨁ HIGH	**RR 2.61** (2.06 to 3.31)	207 per 1.000	**334 more per 1.000** (220 more to 479 more)
DLQI 0 or 1 - induction w12	646 (1 RCT)	⨁⨁⨁⨁ HIGH	**RR 1.65** (1.38 to 1.97)	344 per 1.000	**223 more per 1.000** (131 more to 333 more)
Pts. with at least 1 AE - induction w12	649 (1 RCT)	⨁⨁⨁⨁ HIGH	**RR 0.96** (0.84 to 1.10)	576 per 1.000	**23 fewer per 1.000** (92 fewer to 58 more)
Pts. with at least 1 SAE - induction w12	649 (1 RCT)	⨁⨁⨁⨁ HIGH	**RR 1.00** (0.98 to 1.01)	9 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)
Withdrawal due to AE - induction w12	649 (1 RCT)	⨁⨁⨁⨁ HIGH	**RR 1.01** (0.99 to 1.03)	19 per 1.000	**0 fewer per 1.000** (0 fewer to 1 more)

Acitretin 0.4mg/kg QD compared to combination of acitretin 0.4mg/kg QD + etanercept 25mg QW for psoriasis

Bibliography: Gisondi 2008, Lee 2016

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with combination of acitretin 0.4mg/kg QD + etanercept 25mg QW	Risk difference with acitretin 0.4mg/kg QD
PASI 75 - induction	75 (2 RCTs)	⨁◯◯◯ VERY LOW [a,b,c]	**RR 0.56** (0.18 to 1.76)	189 per 1.000	**83 fewer per 1.000** (155 fewer to 144 more)
Withdrawal due to AE - induction	77 (2 RCTs)	⨁◯◯◯ VERY LOW [a,b,c]	**RR 3.15** (0.14 to 72.88)	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)

Explanations

a. Unclear methods of allocation concealment, no blinding of patients, unclear blinding of personnel

b. Gisondi et al. 2008: patients with low initial PASI

c. Confidence interval crosses line of no effect and minimal important difference thresholds: uncertain whether there is any difference

Acitretin 0.4mg/kg QD compared to etanercept (25mg QW or 50mg BIW) for psoriasis

Bibliography: Caprioni 2009, Gisondi 2008, Lee 2016

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with etanercept (25mg QW or 50mg BIW)	Risk difference with acitretin 0.4mg/kg QD

Acitretin 0.4mg/kg QD compared to etanercept (25mg QW or 50mg BIW) for psoriasis

Bibliography: Caprioni 2009, Gisondi 2008, Lee 2016

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with etanercept (25mg QW or 50mg BIW)	Risk difference with acitretin 0.4mg/kg QD
PASI 75 - induction 12w	141 (3 RCTs)	⨁⨁◯◯ LOW [a,b]	**RR 0.43** (0.25 to 0.76)	411 per 1.000	**234 fewer per 1.000** (308 fewer to 99 fewer)
Withdrawal due to AE - induction	142 (3 RCTs)	⨁◯◯◯ VERY LOW [a,b,c,d]	**RR 1.11** (0.07 to 16.47)	14 per 1.000	**2 more per 1.000** (13 fewer to 212 more)

Explanations

a. Unclear methods of allocation concealment, no blinding of patients, unclear blinding of personnel/no blinding

b. Gisondi et al. 2008: patients with low initial PASI

c. Confidence interval crosses line of no effect and minimal important difference thresholds: uncertain whether there is any difference

d. Wide confidence interval

Fumaric acid esters compared to combination of FAE + calcipotriol for psoriasis

Bibliography: Gollnick 2002

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with combination of FAE + calcipotriol	Risk difference with fumaric acid esters
Pts. with at least 1 AE - induction	134 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	**RR 0.96** (0.81 to 1.13)	824 per 1.000	**33 fewer per 1.000** (156 fewer to 107 more)
Pts. with at least 1 SAE - induction	134 (1 RCT)	⨁⨁◯◯ LOW [a,b]	**RR 0.34** (0.01 to 8.28)	15 per 1.000	**10 fewer per 1.000** (15 fewer to 107 more)

Explanations

a. Unclear randomisation methods

b. Confidence interval crosses line of no effect and minimal important difference thresholds: uncertain whether there is any difference

Fumaric acid esters compared to MTX for psoriasis

Bibliography: Fallah 2011

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with MTX	Risk difference with fumaric acid esters
PASI 75 - induction	51 (1 RCT)	⨁⨁◯◯ LOW [a,b]	**RR 0.80** (0.28 to 2.29)	240 per 1.000	**48 fewer per 1.000** (173 fewer to 310 more)
PASI 90 - induction	51 (1 RCT)	⨁⨁◯◯ LOW [a,b]	**RR 0.48** (0.05 to 4.98)	80 per 1.000	**42 fewer per 1.000** (76 fewer to 318 more)
Withdrawal due to AE - induction	54 (1 RCT)	⨁⨁◯◯ LOW [a,b]	**RR 0.20** (0.02 to 1.60)	185 per 1.000	**148 fewer per 1.000** (181 fewer to 111 more)
Pts. with at least 1 AE - induction	54 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	**RR 0.89** (0.77 to 1.03)	1.000 per 1.000	**110 fewer per 1.000** (230 fewer to 30 more)
Pts. with at least 1 SAE - induction	54 (1 RCT)	⨁◯◯◯ VERY LOW [a,c]	**RR 0.89** (0.77 to 1.03)	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)

Explanations

a. Open study, incomplete outcome data

b. Confidence interval crosses line of no effect and minimal important difference thresholds: uncertain whether there is any difference

c. Effect not estimable, 0 events in both groups

Fumaric acid esters compared to placebo for psoriasis

Bibliography: Mrowietz 2005, Altmeyer 1994, Nugteren-Huying 1990

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with fumaric acid esters
PASI 75 - induction	175 (1 RCT)	⨁⨁◯◯ LOW [a,b]	**RR 27.33** (3.85 to 194.15)	14 per 1.000	**376 more per 1.000** (41 more to 2.759 more)
Withdrawal due to AE - induction	138 (2 RCTs)	⨁⨁◯◯ LOW [a,c,d]	**RR 3.18** (0.71 to 14.23)	16 per 1.000	**35 more per 1.000** (5 fewer to 210 more)
Pts. with at least 1 AE - induction	99 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	**RR 4.72** (2.45 to 9.08)	160 per 1.000	**595 more per 1.000** (232 more to 1.293 more)

Explanations

a. Unclear randomisation methods, incomplete outcome data (results given in % only)

b. Wide confidence interval

c. No ITT, small study size

d. Confidence interval crosses line of no effect and minimal important difference thresholds: uncertain whether there is any difference

Etanercept 50mg BIW compared to infliximab 5mg/kg for psoriasis

Bibliography: DeVries 2013

Outcomes	№ of	Certainty of the	Relative effect	Anticipated absolute effects

	participants (studies) Follow-up	evidence (GRADE)	(95% CI)	Risk with infliximab 5mg/kg	Risk difference with etanercept 50mg BIW
PASI 75 - induction	48 (1 RCT)	⨁⨁⨁⨁ HIGH	**RR 0.29** (0.13 to 0.64)	760 per 1.000	**540 fewer per 1.000** (661 fewer to 274 fewer)

Infliximab compared to placebo for psoriasis

Bibliography: Chaudhari 2001, Gottlieb 2004, Menter 2007, Reich 2005, Torii 2010, Yang 2012

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with infliximab
PASI 75 - induction	1255 (6 RCTs)	⨁⨁◯◯ LOW [a,b]	**RR 19.67** (9.07 to 42.65)	29 per 1.000	**545 more per 1.000** (236 more to 1.216 more)
PASI 90 - induction	1233 (5 RCTs)	⨁⨁◯◯ LOW [c,d]	**RR 44.89** (16.92 to 119.12)	8 per 1.000	**329 more per 1.000** (119 more to 886 more)
Withdrawal due to AE - induction	877 (5 RCTs)	⨁⨁◯◯ LOW [c,e]	**RR 1.71** (0.72 to 4.05)	18 per 1.000	**13 more per 1.000** (5 fewer to 55 more)
Pts. with at least 1 AE - induction	704 (3 RCTs)	⨁⨁⨁◯ MODERATE [f]	**RR 1.28** (1.08 to 1.52)	531 per 1.000	**149 more per 1.000** (43 more to 276 more)
Pts. with at least 1 SAE - induction	704 (3 RCTs)	⨁⨁⨁◯ MODERATE [e]	**RR 1.11** (0.43 to 2.88)	22 per 1.000	**2 more per 1.000** (13 fewer to 42 more)

Explanations

a. Unclear randomization methods in 3 out of 6 studies

b. Moderate heterogeneity ($I^2 > 40\%$) may be due to different methodological quality of the included studies

c. Unclear randomization methods in 3 out of 5 studies

d. Very wide confidence interval

e. Confidence interval crosses line of no effect and minimal important difference thresholds: uncertain whether there is any difference

f. Confidence interval crosses minimal important difference threshold: stat. sign. difference of uncertain clinical importance

MTX 15-20mg QW compared to infliximab 5mg/kg for psoriasis

Bibliography: Barker 2011

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with infliximab 5mg/kg	Risk difference with MTX 15-20mg QW
PASI 75 - induction	868 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	**RR 0.54** (0.46 to 0.63)	778 per 1.000	**358 fewer per 1.000** (420 fewer to 288 fewer)
PASI 90 - induction	868 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	**RR 0.35** (0.26 to 0.46)	545 per 1.000	**354 fewer per 1.000** (403 fewer to 294 fewer)
DLQI 0 or 1	736 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	**RR 0.58** (0.47 to 0.70)	642 per 1.000	**270 fewer per 1.000** (340 fewer to 193 fewer)
Pts. with at least 1 AE - induction	860 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	**RR 1.00** (0.89 to 1.12)	644 per 1.000	**0 fewer per 1.000** (71 fewer to 77 more)
Pts. with at least 1 SAE - induction	860 (1 RCT)	⨁⨁◯◯ LOW [a,b]	**RR 0.34** (0.12 to 0.95)	55 per 1.000	**37 fewer per 1.000** (49 fewer to 3 fewer)

MTX 15-20mg QW compared to infliximab 5mg/kg for psoriasis

Bibliography: Barker 2011

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with infliximab 5mg/kg	Risk difference with MTX 15-20mg QW
Withdrawal due to AE - induction	868 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	**RR 0.30** (0.15 to 0.62)	123 per 1.000	**86 fewer per 1.000** (104 fewer to 47 fewer)

Explanations

a. Open study

b. Confidence interval crosses minimal important difference threshold: stat. sign. difference of uncertain clinical importance

Etanercept 50mg BIW / 50mg QW compared to combination of etanercept 50mg BIW / 50mg QW + MTX 7.5-15mg for psoriasis

Bibliography: Gottlieb 2012

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with combination of etanercept 50mg BIW / 50mg QW + MTX 7.5-15mg	Risk difference with etanercept 50mg BIW / 50mg QW
PASI 75 - induction	478 (1 RCT)	⨁⨁◯◯ LOW [a,b]	**RR 0.77** (0.67 to 0.89)	703 per 1.000	**162 fewer per 1.000** (232 fewer to 77 fewer)
PASI 90 - induction	478 (1 RCT)	⨁⨁◯◯ LOW [a,b]	**RR 0.68** (0.51 to 0.91)	339 per 1.000	**108 fewer per 1.000** (166 fewer to 31 fewer)

Explanations

a. Unclear methods of allocation concealment

b. Confidence interval crosses minimal important difference threshold: stat. sign. difference of uncertain clinical importance

Fumaric acid esters compared to MTX for psoriasis

Bibliography: Fallah 2011

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with MTX	Risk difference with fumaric acid esters
PASI 75 - induction	51 (1 RCT)	⨁⨁◯◯ LOW [a,b]	**RR 0.80** (0.28 to 2.29)	240 per 1.000	**48 fewer per 1.000** (173 fewer to 310 more)
PASI 90 - induction	51 (1 RCT)	⨁⨁◯◯ LOW [a,b]	**RR 0.48** (0.05 to 4.98)	80 per 1.000	**42 fewer per 1.000** (76 fewer to 318 more)
Withdrawal due to AE - induction	54 (1 RCT)	⨁⨁◯◯ LOW [a,b]	**RR 0.20** (0.02 to 1.60)	185 per 1.000	**148 fewer per 1.000** (181 fewer to 111 more)
Pts. with at least 1 AE - induction	54 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	**RR 0.89** (0.77 to 1.03)	1.000 per 1.000	**110 fewer per 1.000** (230 fewer to 30 more)
Pts. with at least 1 SAE - induction	54 (1 RCT)	⨁◯◯◯ VERY LOW [a,c]	**RR 0.89** (0.77 to 1.03)	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)

Explanations

a. Open study, incomplete outcome data

b. Confidence interval crosses line of no effect and minimal important difference thresholds: uncertain whether there is any difference

c. Effect not estimable, 0 events in both groups

MTX compared to Adalimumab 80mg/40mg for psoriasis

Bibliography: Saurat 2008, Goldminz 2015

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Adalimumab 80mg/40mg	Risk difference with MTX
PASI 75 - induction	248 (2 RCTs)	⨁⨁⨁⨁ HIGH	**RR 0.44** (0.34 to 0.57)	780 per 1.000	**437 fewer per 1.000** (515 fewer to 336 fewer)
PASI 90 - induction	218 (1 RCT)	⨁⨁⨁⨁ HIGH	**RR 0.27** (0.16 to 0.44)	509 per 1.000	**372 fewer per 1.000** (428 fewer to 285 fewer)
Withdrawal due to AE - induction	248 (2 RCTs)	⨁⨁⨁◯ MODERATE [a]	**RR 5.89** (0.72 to 48.12)	8 per 1.000	**40 more per 1.000** (2 fewer to 383 more)
Pts. with at least 1 AE - induction	217 (1 RCT)	⨁⨁⨁⨁ HIGH	**RR 1.10** (0.95 to 1.27)	738 per 1.000	**74 more per 1.000** (37 fewer to 199 more)
Pts. with at least 1 SAE - induction	217 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	**RR 0.49** (0.04 to 5.28)	19 per 1.000	**10 fewer per 1.000** (18 fewer to 80 more)

Explanations

a. Confidence interval crosses line of no effect and minimal important difference thresholds: uncertain whether there is any difference

MTX 15-20mg QW compared to infliximab 5mg/kg for psoriasis

Bibliography: Barker 2011

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with infliximab 5mg/kg	Risk difference with MTX 15-20mg QW
PASI 75 - induction	868 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	**RR 0.54** (0.46 to 0.63)	778 per 1.000	**358 fewer per 1.000** (420 fewer to 288 fewer)
PASI 90 - induction	868 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	**RR 0.35** (0.26 to 0.46)	545 per 1.000	**354 fewer per 1.000** (403 fewer to 294 fewer)
DLQI 0 or 1	736 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	**RR 0.58** (0.47 to 0.70)	642 per 1.000	**270 fewer per 1.000** (340 fewer to 193 fewer)
Pts. with at least 1 AE - induction	860 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	**RR 1.00** (0.89 to 1.12)	644 per 1.000	**0 fewer per 1.000** (71 fewer to 77 more)
Pts. with at least 1 SAE - induction	860 (1 RCT)	⨁⨁◯◯ LOW [a,b]	**RR 0.34** (0.12 to 0.95)	55 per 1.000	**37 fewer per 1.000** (49 fewer to 3 fewer)

MTX 15-20mg QW compared to infliximab 5mg/kg for psoriasis

Bibliography: Barker 2011

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with infliximab 5mg/kg	Risk difference with MTX 15-20mg QW
Withdrawal due to AE - induction	868 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	**RR 0.30** (0.15 to 0.62)	123 per 1.000	**86 fewer per 1.000** (104 fewer to 47 fewer)

Explanations

a. Open study

b. Confidence interval crosses minimal important difference threshold: stat. sign. difference of uncertain clinical importance

MTX 15mg compared to MTX 7.5mg for psoriasis

Bibliography: Chládek 2002

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with MTX 7.5mg	Risk difference with MTX 15mg
Withdrawal due to AE - induction	24 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	**RR 3.00** (0.33 to 27.23)	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)

Explanations

a. Unclear randomization methods, no blinding, small study size

b. Effect not estimable, 0 events in both groups

MTX compared to placebo for psoriasis

Bibliography: Saurat 2008, Warren 2016

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with MTX
PASI 75 - induction	283 (2 RCTs)	⨁⨁◯◯ LOW [a,b]	**RR 2.43** (1.16 to 5.10)	157 per 1.000	**224 more per 1.000** (25 more to 642 more)
PASI 90 - induction	283 (2 RCTs)	⨁◯◯◯ VERY LOW [a,b,c]	**RR 2.66** (0.25 to 27.81)	72 per 1.000	**120 more per 1.000** (54 fewer to 1.938 more)
Withdrawal due to AE - induction	163 (1 RCT)	⨁⨁⨁◯ MODERATE [d]	**RR 2.89** (0.36 to 23.41)	19 per 1.000	**36 more per 1.000** (12 fewer to 423 more)
Pts. with at least 1 AE - induction	163 (1 RCT)	⨁⨁⨁⨁ HIGH	**RR 1.02** (0.87 to 1.20)	792 per 1.000	**16 more per 1.000** (103 fewer to 158 more)
Pts. with at least 1 SAE - induction	163 (1 RCT)	⨁⨁⨁◯ MODERATE [d]	**RR 0.48** (0.03 to 7.55)	19 per 1.000	**10 fewer per 1.000** (18 fewer to 124 more)

Explanations

a. Warren 2016 abstract only

b. Confidence interval crosses minimal important difference threshold: stat. sign. difference of uncertain clinical importance

c. Statistical heterogeneity (I^2=64%) maybe due to methodological differences

d. Confidence interval crosses line of no effect and minimal important difference thresholds: uncertain whether there is any difference

Secukinumab compared to etanercept for psoriasis

Bibliography: Langley 2014

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with etanercept	Risk difference with Secukinumab
PASI 75 - induction w12	646 (1 RCT)	⨁⨁⨁⨁ HIGH	**RR 1.75** (1.53 to 2.01)	440 per 1.000	**330 more per 1.000** (233 more to 444 more)
PASI 90 - induction w12	646 (1 RCT)	⨁⨁⨁⨁ HIGH	**RR 2.61** (2.06 to 3.31)	207 per 1.000	**334 more per 1.000** (220 more to 479 more)
DLQI 0 or 1 - induction w12	646 (1 RCT)	⨁⨁⨁⨁ HIGH	**RR 1.65** (1.38 to 1.97)	344 per 1.000	**223 more per 1.000** (131 more to 333 more)
Pts. with at least 1 AE - induction w12	649 (1 RCT)	⨁⨁⨁⨁ HIGH	**RR 0.96** (0.84 to 1.10)	576 per 1.000	**23 fewer per 1.000** (92 fewer to 58 more)
Pts. with at least 1 SAE - induction w12	649 (1 RCT)	⨁⨁⨁⨁ HIGH	**RR 1.00** (0.98 to 1.01)	9 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)
Withdrawal due to AE - induction w12	649 (1 RCT)	⨁⨁⨁⨁ HIGH	**RR 1.01** (0.99 to 1.03)	19 per 1.000	**0 fewer per 1.000** (0 fewer to 1 more)

Secukinumab compared to placebo for psoriasis

Bibliography: Blauvelt 2015, Krueger2014, Langley 2014 – ERASURE; Langley 2014 – FIXTURE, Paul 2015,

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Secukinumab
PASI 75 - induction w12	1376 (4 RCTs)	⊕⊕⊕⊕ HIGH	**RR 17.65** (12.38 to 25.17)	42 per 1.000	**700 more per 1.000** (478 more to 1.016 more)
PASI 90 - induction w12	1412 (5 RCTs)	⊕⊕⊕⊕ HIGH	**RR 39.96** (21.19 to 75.38)	11 per 1.000	**444 more per 1.000** (230 more to 848 more)
DLQI 0 or 1 - induction w12	1138 (2 RCTs)	⊕⊕⊕⊕ HIGH	**RR 7.04** (4.69 to 10.58)	81 per 1.000	**487 more per 1.000** (298 more to 773 more)
Pts. with at least 1 AE - induction w12	1383 (4 RCTs)	⊕⊕⊕◯ MODERATE [a]	**RR 1.15** (1.04 to 1.27)	491 per 1.000	**74 more per 1.000** (20 more to 132 more)
Pts. with at least 1 SAE - induction w12	1383 (4 RCTs)	⊕⊕⊕◯ MODERATE [b]	**RR 1.15** (0.52 to 2.54)	17 per 1.000	**3 more per 1.000** (8 fewer to 27 more)
Withdrawal due to AE - induction w12	1384 (4 RCTs)	⊕⊕⊕◯ MODERATE [b]	**RR 0.91** (0.36 to 2.34)	13 per 1.000	**1 fewer per 1.000** (8 fewer to 17 more)

Explanations

a. Confidence interval crosses minimal important difference threshold(s): statistically significant difference of uncertain clinical importance

b. Confidence interval crosses line of no effect and minimal important difference threshold(s): uncertain whether there is any difference

Secukinumab compared to ustekinumab for psoriasis

Bibliography: Thaci 2015

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ustekinumab	Risk difference with Secukinumab
PASI 75 - induction - Sec 300mg w0-4, then every 4w vs. ust 45/90mg w0,4	669 (1 RCT)	⊕⊕⊕⊕ HIGH	**RR 1.13** (1.06 to 1.19)	827 per 1.000	**107 more per 1.000** (50 more to 157 more)
PASI 90 - induction - Sec 300mg w0-4, then every 4w vs. ust 45/90mg w0,4	669 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	**RR 1.37** (1.23 to 1.53)	576 per 1.000	**213 more per 1.000** (133 more to 305 more)
DLQI 0 or 1 - induction w12 - Sec 300mg w0-4, then every 4w vs. ust 45/90mg w0,4	664 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	**RR 1.17** (1.04 to 1.32)	565 per 1.000	**96 more per 1.000** (23 more to 181 more)
Pts. with at least 1 AE - induction - sec 300mg w0-4, then every 4w vs. ust 45/90mg w0,4	671 (1 RCT)	⊕⊕⊕⊕ HIGH	**RR 1.10** (0.98 to 1.24)	583 per 1.000	**58 more per 1.000** (12 fewer to 140 more)
Pts. with at least 1 SAE - induction - sec 300mg w0-4, then every 4w vs. ust 45/90mg w0,4	671 (1 RCT)	⊕⊕⊕◯ MODERATE [b]	**RR 1.00** (0.42 to 2.38)	30 per 1.000	**0 fewer per 1.000** (17 fewer to 41 more)
Withdrawal due to AE - induction w12 - sec 300mg w0-4, then every 4w vs. ust 45/90mg w0,4	671 (1 RCT)	⊕⊕⊕◯ MODERATE [b]	**RR 0.75** (0.17 to 3.34)	12 per 1.000	**3 fewer per 1.000** (10 fewer to 28 more)

Explanations

a. Confidence interval crosses minimal important difference threshold: statistically significant difference of uncertain clinical importance

b. Confidence interval crossed line of no effect and minimal important difference thresholds: uncertain whether there is any difference

Etanercept 50mg BIW compared to ustekimumab (45mg or 90mg) for psoriasis

Bibliography: Griffith 2010

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ustekimumab (45mg or 90mg)	Risk difference with etanercept 50mg BIW
PASI 75 - induction	903 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	**RR 0.80** (0.72 to 0.89)	714 per 1.000	**143 fewer per 1.000** (200 fewer to 79 fewer)
PASI 90 - induction	903 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	**RR 0.57** (0.45 to 0.71)	415 per 1.000	**179 fewer per 1.000** (229 fewer to 120 fewer)
Withdrawal due to AE - induction	903 (1 RCT)	⨁⨁◯◯ LOW [a,b]	**RR 1.55** (0.59 to 4.09)	14 per 1.000	**8 more per 1.000** (6 fewer to 44 more)
Pts. with at least 1 AE - induction	903 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	**RR 1.03** (0.94 to 1.13)	680 per 1.000	**20 more per 1.000** (41 fewer to 88 more)
Pts. with at least 1 SAE - induction	903 (1 RCT)	⨁⨁◯◯ LOW [a,b]	**RR 0.78** (0.24 to 2.56)	14 per 1.000	**3 fewer per 1.000** (11 fewer to 22 more)

Explanations

a. Unclear randomization methods/allocation concealment, unblinded patients

b. Confidence interval crosses line of no effect and minimal important difference thresholds: uncertain whether there is any difference

Ustekinumab 45mg compared to ustekinumab 90mg for psoriasis

Bibliography: Griffiths 2010, Igarashi 2012, Leonardi 2008, Papp 2008

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ustekinumab 90mg	Risk difference with ustekinumab 45mg
PASI 75 - induction	2013 (4 RCTs)	⨁⨁⨁⨁ HIGH	**RR 0.92** (0.86 to 0.98)	724 per 1.000	**58 fewer per 1.000** (101 fewer to 14 fewer)
PASI 90 - induction	2013 (4 RCTs)	⨁⨁⨁◯ MODERATE [a]	**RR 0.89** (0.75 to 1.05)	451 per 1.000	**50 fewer per 1.000** (113 fewer to 23 more)
DLQI 0 or 1	1454 (3 RCTs)	⨁⨁⨁⨁ HIGH	**RR 1.00** (0.91 to 1.10)	521 per 1.000	**0 fewer per 1.000** (47 fewer to 52 more)
Withdrawal due to AE - induction	2013 (4 RCTs)	⨁⨁⨁◯ MODERATE [b]	**RR 0.53** (0.16 to 1.78)	14 per 1.000	**7 fewer per 1.000** (12 fewer to 11 more)
Pts. with at least 1 AE - induction	2012 (4 RCTs)	⨁⨁⨁⨁ HIGH	**RR 1.05** (0.96 to 1.15)	563 per 1.000	**28 more per 1.000** (23 fewer to 84 more)
Pts. with at least 1 SAE - induction	2012 (4 RCTs)	⨁⨁⨁◯ MODERATE [b]	**RR 1.05** (0.45 to 2.43)	15 per 1.000	**1 more per 1.000** (8 fewer to 21 more)

Explanations

a. Moderate heterogeneity

b. Confidence interval crosses line of no effect and minimal important difference thresholds: uncertain whether there is any difference

Ustekinumab compared to placebo for psoriasis

Bibliography: Igarashi 2012, Leonardi 2008, Lebwohl 2015 – AMAGINE2, Lebwohl 2015 – AMAGINE3, Papp 2008, Tsai 2011, Zhu 2013

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with ustekinumab
PASI 75 - induction	3833 (7 RCTs)	⨁⨁⨁◯ MODERATE [a]	**RR 12.33** (9.19 to 16.53)	58 per 1.000	**661 more per 1.000** (478 more to 906 more)
PASI 90 - induction	3833 (7 RCTs)	⨁⨁⨁⨁ HIGH	**RR 17.63** (11.95 to 26.00)	28 per 1.000	**466 more per 1.000** (307 more to 701 more)
DLQI 0 or 1	2472 (4 RCTs)	⨁⨁⨁◯ MODERATE [b]	**RR 8.78** (5.04 to 15.28)	55 per 1.000	**426 more per 1.000** (221 more to 782 more)
Withdrawal du to AE - induction	3833 (7 RCTs)	⨁⨁⨁◯ MODERATE [c]	**RR 0.47** (0.24 to 0.92)	14 per 1.000	**8 fewer per 1.000** (11 fewer to 1 fewer)
Pts. with at least 1 AE - induction	2595 (5 RCTs)	⨁⨁⨁⨁ HIGH	**RR 1.04** (0.96 to 1.13)	492 per 1.000	**20 more per 1.000** (20 fewer to 64 more)
Pts. with at least 1 SAE - induction	2595 (5 RCTs)	⨁⨁⨁◯ MODERATE [d]	**RR 0.76** (0.39 to 1.49)	16 per 1.000	**4 fewer per 1.000** (10 fewer to 8 more)

Explanations

a. Moderate heterogeneity (I^2=40%) may be due to methodological differences

b. Substantial heterogeneity (I^2 > 67%) may be due to different methodological differences

c. Confidence interval crosses minimal important difference threshold: stat. sign. difference of uncertain clinical importance

d. Confidence interval crosses line of no effect and minimal important difference thresholds: uncertain whether there is any difference

Secukinumab compared to ustekinumab for psoriasis

Bibliography: Thaci 2015

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ustekinumab	Risk difference with Secukinumab
PASI 75 - induction - Sec 300mg w0-4, then every 4w vs. ust 45/90mg w0,4	669 (1 study)	-	**RR 1.13** (1.06 to 1.19)	827 per 1.000	107 more per 1.000 (50 more to 157 more)
PASI 90 - induction - Sec 300mg w0-4, then every 4w vs. ust 45/90mg w0,4	669 (1 study)	-	**RR 1.37** (1.23 to 1.53)	576 per 1.000	213 more per 1.000 (133 more to 305 more)
DLQI 0 or 1 - induction w12 - Sec 300mg w0-4, then every 4w vs. ust 45/90mg w0,4	664 (1 study)	-	**RR 1.17** (1.04 to 1.32)	565 per 1.000	96 more per 1.000 (23 more to 181 more)
Pts. with at least 1 AE - induction - sec 300mg w0-4, then every 4w vs. ust 45/90mg w0,4	671 (1 study)	-	**RR 1.10** (0.98 to 1.24)	583 per 1.000	58 more per 1.000 (12 fewer to 140 more)
Pts. with at least 1 SAE - induction - sec 300mg w0-4, then every 4w vs. ust 45/90mg w0,4	671 (1 study)	-	**RR 1.00** (0.42 to 2.38)	30 per 1.000	0 fewer per 1.000 (17 fewer to 41 more)
Withdrawal due to AE - induction w12 - sec 300mg w0-4, then every 4w vs. ust 45/90mg w0,4	671 (1 study)	-	**RR 0.75** (0.17 to 3.34)	12 per 1.000	3 fewer per 1.000 (10 fewer to 28 more)

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