

Bilaga 1.till rapport

Ljusbehandling och systemisk behandling av psoriasis, rapport nr 278 (2018)

Bilaga 1 Tabell över inkluderade studier/ Appendix 1 Description of included studies

Description of included studies

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| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|---------------------|-------------------------|---|---------------------------------------|--------------------------|----------------------------|----------------------|
| Reference | Setting Study period | | | Recults | | Comment |
| Country | Follow-up | | | Results | | |
| Study design | 10100-00 | | | | | |
| Yones et al | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
| 2006 | Inclusion criteria | PLIVA: 25 mg 8- | companion | Per protocol ("on- | As reported in all | Acceptable |
| [52] | Adult patients (18–70 | methoxypsoralen/m ² | NB-UVB: twice weekly | treatment-analysis"), of | natients (skin types I-VI) | |
| [0-] | vears) with chronic | per os given 3 hours | in incremental doses to | patients with skin types | | Comment |
| Single centre study | plaque psoriasis | before phototherapy | a final dose of 5 J/cm ² . | I–IV only | During treatment | Conflict of interest |
| performed in Great | involving ≥8% body | with UVA twice weekly | PBO per os 3 hours | , | Ervthema | None reported |
| Britain | surface area and PASI | in incremental doses to | before phototherapy | Results after 8 sessions | PUVA: 49% | |
| | ≥8. No phototherapy in | a final dose of 15 J/cm ² | | PASI | NB-UVB: 22% | |
| RCT | the previous 3 months | | n=45 (34/45 with skin | Change from baseline | | |
| | | Duration of the | types I–IV) | score | Nausea | |
| | BMI: not given | intervention | | PUVA: -6.8 | PUVA: 2/43 patients | |
| | - | Until complete | Drop-out rate | NB-UVB: -3.9 | switched from 8- | |
| | Sex: 73% male, 27% | clearance, minimal | 3 of the 47 initially | PUVA vs NB-UVB: | methoxy-psoralen to 5- | |
| | female | residual activity, no | randomised | p=0.001 | methoxypsoralen due | |
| | | improvement after 16 | | | to nausea | |
| | Study period | sessions or once a total | After completed | PGA | | |
| | April 2002–March 2005 | of 30 sessions was | therapy follow-up | Proportion clear | | |
| | | reached | <u>12 months</u> The 23/47 | PUVA: 31/37 (84%) | | |
| | Follow-up | | treated patients who | NB-UVB: 22/34 (65%) | | |
| | For effects: | n=43 (37/43 with skin | were "clear" from | PUVA vs NB-UVB: | | |
| | 8 sessions | types I–IV) | psoriasis after | p<0.001 | | |
| | | | treatment were | | | |
| | For relapse: | Drop-out rate | followed for 12 months | DLQI | | |
| | 12 months | At 8 sessions: | | Change from baseline | | |
| | | 3 of the 46 initially | | <u>score</u> | | |
| | | randomised | | PUVA vs NB-UVB: | | |
| | | | | p=0.02, favouring PUVA | | |
| | | After completed | | | | |
| | | <u>therapy \rightarrow 12 months</u> : | | Results at 6 months | | |
| | | The 34/43 treated | | | | |
| | | patients who were | | | | |

Table 5.1. PUVA vs narrowband-UVB

| "clear" from psoriasi | | No relapse (still clear | |
|-----------------------|----|-------------------------|--|
| after treatment were | | among those clear after | |
| followed for 12 mon | hs | 8 sessions) | |
| | | PUVA: 23/34 (68%) | |
| | | NB-UVB: 8/23 (35%) | |
| | | PUVA vs NB-UVB: | |
| | | p=0.02 | |
| | | | |
| | | | |

BMI – body mass index; DLQI – dermatology life quality index; NB-UVB – narrowband ultraviolet phototherapy; PASI – psoriasis area and severity index; PGA – physician's' global assessment; PUVA – psoralen and ultraviolet A phototherapy; UVA – ultraviolet A phototherapy

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|---------------------|--------------------------|------------------------|------------------------|------------------------|----------------|----------------------|
| Year | Setting | | | | | Comment |
| Reference | Study period | | | Results | | |
| Country | Follow-up | | | | | |
| Study design | | | | | | |
| Caproni et al | Population | Intervention | Comparison | Analysis Model | Adverse events | Risk of bias |
| 2009 | Inclusion criteria | Acitretin (Neotigason) | Etanercept (Enbrel) 50 | ITT | No information | Acceptable |
| [54] | Patients with moderate- | 0.4 mg/kg per day, for | mg twice weekly for 12 | | | |
| | to-severe plaque-type | 12 weeks | weeks | Results | | Comment |
| Single centre study | psoriasis, with PASI ≥10 | | | Patients reaching PASI | | Conflict of interest |
| performed in Italy | and BSA (body surface | n=30 | n=30 | ≥75 | | No information |
| | area) ≥10% | | | I: 8/30 (26.7%) | | |
| RCT | | Drop-out rate during | Drop-out rate during | C: 17/30 (56.7%) | | |
| | Baseline characteristics | treatment | treatment | I vs C: p<0.05 | | |
| | Sex | 0/30 (0.0%) | 0/30 (0.0%) | | | |
| | l: 43.3% men, 56.7% | | | Patients reaching PASI | | |
| | women | | | ≥50 | | |
| | C: 36.7% men, 63.3 | | | I: 20/30 (66.7%) | | |
| | women | | | C: 26/30 (86.7%) | | |
| | Age | | | I vs C: p<0.05 | | |
| | I: 31-65 years | | | | | |
| | C: 28-67 years | | | | | |
| | BMI: | | | | | |
| | No information | | | | | |
| | Study period | | | | | |
| | No information | | | | | |
| | Follow-up | | | | | |
| | Treatment for | | | | | |
| | 12 weeks No further | | | | | |
| | follow-up | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |

Table 6.1. Acitretin versus Etanercept

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|---------------------|--------------------------|---------------------------|-------------------------|--------------------|-----------------------|-----------------------|
| Year | Setting | | | | | Comment |
| Reference | Study period | | | Results | | |
| Country | Follow-up | | | | | |
| Study design | | | | | | |
| Gisondi et al | Population | Intervention | Comparison | Analysis Model | Adverse events | Risk of bias |
| 2008 | Inclusion criteria | Acitretin, 0.4 mg/kg in a | Control 1 (C1): | ITT | Reported treatment | Acceptable |
| [53] | Patients ≥18 years, with | single oral dose per day, | Etanercept, 25 mg twice | | emergent adverse | |
| | chronic, moderate to | for 24 weeks | weekly subcutaneously, | Results at week 24 | events | Comment |
| Single centre study | severe, plaque psoriasis | | for 24 weeks | PASI≥50 | | Conflict of interest |
| performed in Italy | | n=20 | | I: 10/20 (50.0%) | Mild mucosal dryness: | The authors have |
| | Baseline characteristics | | Control 2 (C2): | C1: 15/22 (68.2%) | I: 2/20 (10.0%) | received consultation |
| RCT | Sex | Drop-out rate during | Etanercept, 25 mg once | C2: 12/18 (66.7%) | C1: 0/22 (0.0%) | and lecture fees from |
| | I: 60% men and 40% | treatment | weekly subcutaneously, | / . | C2: 1/18 (5.6%) | Merck-Serono, |
| | women | 4/20 (20.0%) | plus oral acitretin, | PASI ≥75 (primary | | Schering-Plough, |
| | C1: 54.5% men and | | 0.4 mg/kg per day, for | endpoint) | | Wyeth, Abbott, |
| | 46.5% women | | 24 weeks | 1: 6/20 (30.0%) | | Janssen-Cilag |
| | C2: 50% men and 50% | | | C1: 10/22 (45.5%) | | |
| | women | | C1: n=22 | C2: 8/18 (44.4%) | | |
| | | | C2: n=18 | | | |
| | Mean BMI (kg/m²) | | | | | |
| | 1: 27.2 (SD 3,1) | | Drop-out rate during | | | |
| | C1: 27.3 (SD 6.0) | | treatment | | | |
| | C2: 29.1 (SD 6.1) | | C1: 0/22 (0.0%) | | | |
| | | | C2: 0/18 (0.0%) | | | |
| | Age (mean yrs±SD) | | | | | |
| | 1: 55,0 \pm 11,3 | | | | | |
| | $C1: 55,3 \pm 10,9$ | | | | | |
| | C2: 53,4 ± 12,5 | | | | | |
| | | | | | | |
| | Study pariod | | | | | |
| | No information | | | | | |
| | No information | | | | | |
| | Follow-up | | | | | |
| | Treatment for | | | | | |
| | 24 weeks No further | | | | | |
| | follow-up | | | | | |
| | | | | | | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|------------------------|---------------------------------------|------------------------|-------------------------|-------------------------|---------------------------|-------------------------|
| Year | Setting | | | | | Comment |
| Reference | Study period | | | Results | | |
| Country | Follow-up | | | | | |
| Study design | | | | | | |
| Lee et al | Population | Intervention | Comparison | Analysis Model | Adverse events | Risk of bias |
| 2016 | Inclusion criteria | Acitretin, 10 mg twice | Control 1 (C1): | Both ITT and per | Patients experiencing | Acceptable |
| [55] | Patients ≥18 years, with | daily, for 24 weeks | Etanercept, 50 mg twice | protocol is used | treatment related | |
| | active clinically stable | | weekly, for 12 weeks, | | adverse events: | Comment |
| | moderate to severe | n=19 | followed by etanercept | Results at week 24 | I: 8/18 (44.4%) | Conflict of interest |
| Multicentre study | plaque psoriasis, with | | 25 mg twice weekly for | PASI ≥50 | C1: 9/21 (42.9%) | Main author is an |
| performed in Korea | BSA (body surface area) | Drop-out rate | a further 12 weeks | A greater proportion of | C2: 10/20 (50.0%) | employee of Pfizer |
| | ≥10% or PASI ≥10 | 7/19 (36.8%) | | patients in the control | (Analysed per protocol) | |
| RCT (open-label trial) | | | Control 2 (C2): | groups achieved PASI | No treatment related | Funded by Pfizer |
| | Baseline characteristics | | Etanercept, 25 mg twice | 50 than did the | serious AEs reported | Pharmaceuticals, who |
| | Sex | | weekly, plus acitretin, | intervention group | | also supported the |
| | l: 83.3% men, 16,7% | | 10 mg twice daily, for | | TEAEs (≥10% of patients | medical writing |
| | women | | 24 weeks | PASI ≥75 (primary | in any group) | |
| | C1: 76.2% men, 23.8% | | | endpoint) | Pruritus, n (%) | Etanercept is a product |
| | women | | C1: n=21 | Reported results are | 1: 1/18 (5.6%) | of Pfizer |
| | C2: 89.5% men, 10.5% | | C2: n=20 | approximations based | C1: 3/21 (14.3%) | |
| | women | | | on Fig 3. In Lee et al | C2: 2/20 (10.0%) | |
| | | | Drop-out rate | 1: 4/19 (22.2%) | | |
| | Mean body weight (kg) | | C1: 4/21 (19.0%) | C1: 11/21 (52.4%) | Alopecia, n (%) | |
| | 1: 74.2 (SD 9.8) | | C2: 4/20 (20.0%) | C2: 12/20 (57.9%) | 1: 1/18 (5.6%) | |
| | C1: 74.1 (SD 16.0) | | | TVS C1: p<0.0978 | | |
| | C2: 74.0 (SD 11.6) | | | 1 vs C2: p<0.0448 | C2: 4/20 (20.0%) | |
| | $\Lambda ge (mean vrs+SD)$ | | | | Skin exfolicition n (%) | |
| | Age (mean yrs±50) 1. $A2 A + 12 0$ | | | | 1. 1/18 (5.6%) | |
| | C1: 38 6 +19 5 | | | | C1 - | |
| | (2) 355 + 88 | | | | $(2) \cdot 2/20 (10.0\%)$ | |
| | 02. 33,5 ± 0,0 | | | | 02, 2, 20 (10.070) | |
| | Study period | | | | Drv lip. n (%) | |
| | No information | | | | 1: 2/18 (11.1%) | |
| | | | | | C1: - | |
| | | | | | C2: 3/20 (15.0%) | |
| | | | | | , - (, | |
| | | | | | | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|-------------------------|---------------------|--------------|------------|----------------|-----------------------------|--------------|
| Year | Setting | | | | | Comment |
| Reference | Study period | | | Results | | |
| Country Study decign | Follow-up | | | | | |
| Study design | Follow-up | | | | Chalitis n (%) | |
| | Treatment for | | | | 1.2/18(11.1%) | |
| | 24 weeks No further | | | | C1'- | |
| | follow-up | | | | $(2^{\circ}, 2/20)$ (10.0%) | |
| | | | | | 02. 2/20 (10.0/0) | |
| | | | | | Chapped lips, n (%) | |
| | | | | | l: 2/18 (11.1%) | |
| | | | | | C1: - | |
| | | | | | C2: 1/20 (5.0%) | |
| | | | | | | |
| | | | | | Myalgia, n (%) | |
| | | | | | I: 2/18 (11.1%) | |
| | | | | | C1: - | |
| | | | | | C2: - | |
| | | | | | | |
| | | | | | Hypertension, n (%) | |
| | | | | | 1: - | |
| | | | | | C1: - | |
| | | | | | C2: 2/20 (10.0%) | |

BMI – body mass index; BSA – body surface area; CI – confidence interval; ITT – intention-to-treat; PASI – psoriasis area and severity index; RCT – randomised controlled trial; PGA – physician's global assessment; TNF – Tumour necrosis factor

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|-------------------------|--------------------------|--------------------------|-------------------------|---------------------------|--------------------------|----------------------------|
| rear Reference | Setting Study period | | | Results | | comment |
| Country | Follow-up | | | Results | | |
| Study design | Tonow-up | | | | | |
| Papp et al 2012 | Population | Intervention (I) | Comparsion (C) | Analysis model | Adverse events – | Risk of bias |
| [58] | Inclusion criteria | Apremilast for | Placebo for 16 weeks, | ITT | during 16 weeks | Acceptable |
| | ≥18 years of age | 24 weeks, orally 30 mg | orally, twice daily (C) | Missing data | placebo controlled | <u>·</u> |
| Multicentre study, 35 | Plaque psoriasis PASI | twice daily (60 mg/day). | | LOCF | phase | Comment |
| sites in USA and Canada | ≥12, BSA ≥10%, for ≥6 | Dose titrated for 5 days | Allocation – placebo | | Patients w ≥1 AE, n (%) | Conflict of interest study |
| | months, eligible for | | controlled phase, n | Results – 16 weeks | I: 72/88 (82%) | funded by Celgene. |
| RCT | phototherapy or | Allocation – placebo | C: 88 | PASI ≥50, n (%) | C: 57/88 (65%) | Study designed by |
| | systemic therapy | controlled phase, n | | I: 53/88 (60.2%) | | sponsor. Data analysed |
| | | I: 88 | Drop-out rate – placebo | C: 22/88 (25.0%) | Serious AE, n (%) | by sponsor |
| | Baseline characteristics | | controlled phase, n (%) | I vs C: p<0.001 | I: 2/88 (2%), (1 | |
| | Female/Male, (%) | The study also included | C: 16 (18.2%) | | myocardial infarction, 1 | |
| | I: 43.2%/56.8% | intervention groups | | Primary endpoint | prostate cancer) | |
| | C: 39.8%/60.2% | treated with 20 mg and | | PASI ≥75, n (%) | C: 2/88 (1 drug | |
| | Ethnicity – Caucasian | 40 mg per day | | I: 36/88 (40.9%) | eruption, 1 death) | |
| | I: 90.9% | | | C: 5/88 (5.7%) | | |
| | C: 94.3% | Drop-out rate – placebo | | l vs C: OR 11.5 (95% Cl, | Patients with AE leading | |
| | Body mass index | controlled phase | | 4.24 to 31.16), | to drug withdrawal, n | |
| | (kg/m²), mean±SD | I: n=18 (20.5%) | | p<0.0001 | (%) | |
| | I: 31.1±7.7 | | | | I: 10/88 (11.4%) | |
| | C: 30.8±6.7 | | | PASI ≥90, n (%) | C: 5/88 (5.7%) | |
| | | | | I: 10/88 (11.4%) | | |
| | Study period | | | 13 vs C: p=0.005 | Treatment-emergent | |
| | September 2008 - | | | C: 1/88 (1.1%) | adverse events ≥5% of | |
| | October 2009 | | | | patients in any | |
| | | | | DLQI improvement | treatment groups | |
| | Follow-up | | | I: mean improvement | | |
| | 16 weeks placebo- | | | 10.6–6.0; mean | Nausea, n (%) | |
| | controlled phase | | | difference -4.4; SD: 5.1 | I: 16 (18%) | |
| | (presented here). | | | C: mean improvement | C: 7 (8%) | |
| | Followed by 8 weeks | | | 10.7–8.6; mean | | |
| | active phase dose | | | ditterence -1.9; SD: 5.2. | | |

Table 6.2. Apremilast versus placebo

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------|---|--------------|------------|--|---|--------------|
| Year | Setting Study pariod | | | Boculto | | Comment |
| Country | Follow-up | | | Results | | |
| Study design | | | | | | |
| Study design | blinded OLE. Patients who discontinued or did not enrol in OLE were followed for 4 weeks post treatment | | | I vs C: p=0.0047 SF-36, mean change ±SD Physical component summary score I: 0.8 ±7.5 C: 0.7 ±8.5 I vs C: p=0.95 Mental component summary score I: 2.9 ±9.2 C: -0.8 ±10.0 I vs C: p=0.005 | URTI, n (%) 1: 14 (16%) C: 5 (6%) Diarrhoea, n (%) 1: 12 (14%) C: 4 (5%) Nasopharyngitis, n (%) 1: 5 (6%) C: 7 (8%) Headache*, n (%) 1: 9 (10%) C: 5 (6%) Tension headache, n (%) 1: 14 (16%) C: 6 (7%) Viral URTI, n (%) 1: 7 (8%) C: 7 (8%) Gastroenteritis, n (%) 1: 5 (6%) C: 3 (3%) Dyspepsia, n (%) 1: 4 (5%) C: 2 (2%) | |
| | 1 | | | | | |

| Year Setting Comment | |
|--|---------|
| Pafarance Study paried Baculta | |
| Country Eollow-up | |
| Study design | |
| Arthralaia, n (%) | |
| | |
| C: 6 (7%) | |
| | |
| Vomiting, n (%) | |
| 1: 4 (5%) | |
| C: 1 (1%) | |
| | |
| *migraine, sinus, and | |
| tension headaches were | |
| captured separately 0– | |
| 16 weeks | |
| | |
| Papp et al 2015PopulationIntervention (I)Comparison (C)Analysis modelAdverse EventsRisk of bias | |
| [59] Inclusion criteria 30 mg apremilast twice Placebo to match active Efficacy AEs reported during Acceptable | |
| Patients with plaque daily, 1 week titration treatment <i>Efficacy outcomes placebo controlled trial</i> | |
| Study namepsoriasis of ≥18 years ofperiodITT(week 0–16)Comment | |
| Esteem 1age w. PASI score ≥12,RandomisationSafety outcomesConflict of int | erest, |
| BSA involvement ≥10%, Randomisation C: n=282 mITT (all randomised I: n=560 study sponso | red and |
| Multicentre study, $PGA \ge 3$ (moderate to $n=562$ patients who received C: n282 supported by | Celgene |
| performed at 72 sites severe), and eligible for $Drop-out rate, \ge 1$ dose of study | |
| phototherapy/systemic Drop-out rate, $n(\%)$ medication) Patients w. AE ≥ 1 AE, n | |
| RCI therapy $n(\%)$ 33/282 (11.7%) Missing data (%) | |
| 59/562 (10.5%) LUCF and NRI I: 388 (69.3%) | |
| Baseline characteristics C: 157 (55.7%) | |
| remale/iviale Kesuits – 16 weeks | |
| $\begin{array}{c} 1: 32.0\%/07.4\% \\ C_{1} 21.2\%/07.4\% \\ C_{2} 21.2\%/07.4\% \\ A = -\frac{1}{2}\% $ | |
| $\begin{array}{c} (1.51.2\%) \ 100.8\% \\ (2.51.2\%) \ 100.8\% \\ (3$ | |
| $\begin{array}{c} \text{primary enupoint} \\ \text{Reduusiaht mean} (ka) \\ \text{Is 196 (22,1%)} \\ \text{Cs 0 (2,2%)} \end{array}$ | |
| bouyweight, meun (kg) 1: 160 (55.1%) C: 9 (5.2%) cc 1: 160 (55.1%) C: 9 (5.2%) | |
| LiO2 2+21 A | |
| $\begin{array}{c} 1.33.2121.4 \\ \hline \\ $ | |
| | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------|-----------------------|--------------|------------|---------------------------|------------------------------|--------------|
| Year | Setting | | | | | Comment |
| Reference | Study period | | | Results | | |
| Country | Follow-up | | | | | |
| Study design | | | | | | |
| | BMI, mean±SD | | | l vs C: 27.8% (95% Cl, | C: 8 (2.8%) | |
| | I: 31.2±6.7 | | | 23.1 to 32.5), p<0.0001 | | |
| | C: 31.3±7.4 | | | | Patients with ≥1 AE | |
| | | | | PASI ≥75 (NRI)* | leading to drug | |
| | Ethnicity (Caucasian) | | | I: 183 (32.6%) | withdrawal, n (%) | |
| | I: 90.2% | | | C: 14 (5.0%) | I: 29 (5.2%) | |
| | C: 88.7% | | | Difference (NRI) | C: 9 (3.2%) | |
| | | | | l vs C: p<0.0001 | | |
| | | | | | Patients with ≥1 AE | |
| | Study period | | | PASI ≥50, n (%) | leading to death, n (%) | |
| | September 2010– | | | I: 330, (58.7%) | I: 1 (0.2%) | |
| | December 2012 | | | C: 48 (17.0%) | C: 1 (0.4%) | |
| | | | | l vs C: p<0.0001 | | |
| | Follow-up | | | | <u>AE reported by ≥5% of</u> | |
| | Placebo controlled | | | DLQI change, mean ±SD | patients in any | |
| | phase 0–16 weeks | | | (also presented in #4) | <u>treatment group</u> | |
| | (presented here). | | | I: -6.6±6.66 | Diarrhoea, n (%) | |
| | Followed by | | | C: -2.1±5.69 | I: 105 (18.8%) | |
| | maintenance phase | | | I vs C: p<0.0001 | C: 20 (7.1%) | |
| | (week 16–32), and | | | | | |
| | treatment withdrawal | | | | URTI, n (%) | |
| | phase (week 32–52) | | | Descriptive endpoints | I: 57 (10.2%) | |
| | | | | w.o. statistical analysis | C: 21 (7.4%) | |
| | | | | PASI ≥90, n (%) | | |
| | | | | C: 1 (0.4%) | Nausea, n (%) | |
| | | | | I: 55 (9.8%) | I: 88 (15.7%) | |
| | | | | | C: 19 (6.7%) | |
| | | | | | | |
| | | | | | Nasopharyngitis, n (%) | |
| | | | | | l: 41 (7.3%) | |
| | | | | | C: 23 (8.2%) | |
| | | | | | Tension headache, n | |
| | | | | | (%) | |
| | | | | | I: 41 (7.3%) | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|----------------------------|-------------------------|-------------------------|-------------------------|-------------------------|------------------------------|-----------------------|
| Year | Setting | | | | | Comment |
| Reference | Study period | | | Results | | |
| Country | Follow-up | | | | | |
| Study design | | | | | | |
| | | | | | C: 12 (4.3%) | |
| | | | | | Headache n (%) | |
| | | | | | 1. 31 (5 5%) | |
| | | | | | C· 13 (4 6%) | |
| | | | | | | |
| Paul et al | Population | Intervention (I) | Comparison (C) | Analysis model | Adverse events | Risk of bias |
| 2015 | Inclusion criteria: | 30 mg apremilast twice | Placebo to match active | Modified intention to | | Acceptable |
| [56] | Patients ≥18 years of | daily, 1 week titration | treatment | treat (mITT): excluding | Adverse events – | |
| | age, with plaque | period | | patients randomized in | 0–16 weeks | Comment |
| Study name | psoriasis ≥12 months | | Randomised pop. | error and did not | | Conflict of interest, |
| ESTEEM 2 | PASI score ≥12, BSA | Randomised pop | n=137 | receive test substance | l: n=272 | study sponsored and |
| | ≥10%, sPGA ≥3 | n=274 | | Safety population: | C: n=136 | supported by the |
| Multicentre study | (moderate to severe), | | Drop-out rate at | randomised patients | | Celgene corporation |
| carried out at 40 sites in | and were eligible for | Drop-out rate at | 16 weeks: | who received ≥1 dose | Patients with ≥ 1 AE, n | |
| Austria, Canada, | phototherapy/systemic | 16 WEEKS | 25/137 (18.2%) | test substance | (%) 1.195 (69.00() | |
| Denmark, France, | therapy. Patients | 35/274 (12.8%) | | Missing data: LOCF, NRI | 1: 185 (68.0%) | |
| Switzorland and USA | previously treated with | | | Posults - 16 wooks | C. 82 (00.3%) | |
| Switzenanu, anu USA | systemic therapy | | | Primary endnoint | Patients with >1 severe | |
| RCT | (conventional or | | | PASI >75 | AF n (%) | |
| | biologic), including | | | LOCE: | 1: 12 (4.4%) | |
| | treatment failures. | | | 1: 28.8% | C: 6 (4.4%) | |
| | were permitted to enrol | | | C: 5.8% | | |
| | | | | l vs C: p<0.001 | Patients with ≥1 serious | |
| | Study period | | | NRI: | AE, n (%) | |
| | November 2010- | | | C: 5.1% | I: 5 (1.8%) | |
| | December 2012 | | | I: 28.1% | C: 3 (2.2%) | |
| | | | | l vs C: p<0.001 | | |
| | Baseline variables: | | | | AEs leading to drug | |
| | Female (%)/Male (%) | | | Other endpoints | withdrawal, n (%) | |
| | I: 35.8%/64.2% | | | PASI ≥50 | I: 15 (5.5%) | |
| | C: 27.0%/73.0% | | | LOCF | C: 7 (5.1%) | |
| | | | | I: 55.5% | | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------|------------------------|--------------|------------|------------------|------------------------|--------------|
| Year | Setting | | | | | Comment |
| Reference | Study period | | | Results | | |
| Country | Follow-up | | | | | |
| Study design | | | | | | |
| | Bodyweight (kg), | | | C: 19.7% | AE leading to death, | |
| | mean±SD | | | 1 VS C: p<0.001 | n (%) | |
| | 1: 91.4±23.0 | | | | 1: 0 (0.0%) | |
| | $C: 90.5\pm 22.5$ | | | 1: 53.6% | C: 0 (0.0%) | |
| | Bivii (kg/m²), mean±SD | | | 0.17.5% | | |
| | 1: 30.9±6.7 | | | TVS C: p<0.001 | Als reported by 25% of | |
| | C: 30./±/.1 | | | DAGINOO | treatment aroun | |
| | | | | PASI 290 | nlacabo controllad | |
| | 1. 91.2% | | | | proceed controlled | |
| | 0. 93.4% | | | 1. 0.0% | period (0-10 weeks) | |
| | Follow up | | | $C_{1,3\%}$ | Nausoa n (%) | |
| | Trootmont pariods | | | 1 vs C. p=0.0042 | 1 50 (19 A%) | |
| | A: 0-16 weeks placebo- | | | | (10.4%) | |
| | controlled phase | | | | 0.070) | |
| | (presented here) | | | | | |
| | B 16-32 weeks | | | | Diarrhoea n (%) | |
| | maintenance phase | | | | 1: 43 (15.8%) | |
| | C: 32-52 weeks. | | | | C: 8 (5.9%) | |
| | treatment withdrawal | | | | | |
| | phase | | | | Nasopharyngitis, n (%) | |
| | | | | | 1: 20 (7.4%) | |
| | | | | | C: 6 (4.4%) | |
| | | | | | | |
| | | | | | URTI, n (%) | |
| | | | | | I: 13 (4.8%) | |
| | | | | | C: 6 (4.4%) | |
| | | | | | | |
| | | | | | Tension headache, | |
| | | | | | n (%) | |
| | | | | | I: 20 (7.4%) | |
| | | | | | C: 2 (1.5%) | |
| | | | | | | |
| | | | | | | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------------------|-------------------------|-----------------------|-------------------------|--------------------------|---|--------------------------------|
| Reference | Setting Study period | | | Recults | | Comment |
| Country | Follow-up | | | Nesuits | | |
| Study design | . enem ep | | | | | |
| Study design | | | | | Vomitting, n (%) I: 14 (5.1%) C: 5 (3.7%) Headache, n (%) I: 17 (6.3%) C: 1 (0.7%) Back pain, n (%) I: 6 (2.2%) C: 2 (1.5%) Psoriasis, n (%) I: 4 (1.5%) C: 7 (5.1%) | |
| | | | | | - () | |
| Thaçi et al | Population | Intervention (I) | Comparison (C) | Analysis model | Adverse events | Risk of bias |
| 2016 | | | | Full analysis set (FAS): | | Acceptable |
| [62] | Reported in [59] and | ESIEEM 1 | For U-16 weeks | all patients randomised | Reported in [59] and | Comment |
| Study names | [50] | II: 11=562 | ESTEEIVI I C1: p=282 | as specified in the | [50] | Comment Study sponsored and |
| FSTEEM 1 | Follow-up | n=159 | Ear the DLOL outcome | Missina data | | supported by the |
| | Placebo-controlled | 11-400 | n=236 | LOCE | | Celgene corporation |
| [59] and ESTEEM 2 [56] | phase 0–16 weeks | ESTEEM 2 | | | | ce.gene corporation |
| | (presented here) | l2: n=274 | ESTEEM 2 | Results – week 16 | | |
| This article presents | | For the DLQI outcome: | C2: n=137 | | | |
| patient-reported | Maintenance phase 16– | n=226 | For the DLQI outcome | Secondary endpoints | | |
| outcomes (PRO) of | 32 weeks | | n=119 | (for primary outcomes | | |
| Health-related quality | | | | see main publications) | | |
| of life (HRQOL) from the | | | | | | |
| ESTEEM 1 and ESTEEM | | | | DLQI change (results | | |
| 2 triais | | | | JIOM ESTEEM 1 are also | | |
| | | | | ±SD | | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------|--------------|--------------|------------|-----------------------|----------------|--------------|
| Year | Setting | | | | | Comment |
| Reference | Study period | | | Results | | |
| Country | Follow-up | | | | | |
| Study design | | | | | | |
| | | | | l1: -6.6±6.66 | | |
| | | | | C1: -2.1±5.69 | | |
| | | | | I1 vs C1: p<0.0001 | | |
| | | | | 12: -6.7±6.95 | | |
| | | | | C2: -2.8±7.22 | | |
| | | | | I2 vs C2: p<0.0001 | | |
| | | | | SF-36v2 MCS score | | |
| | | | | I1: 2,4±9.50 | | |
| | | | | C1: -1.0±9.16 | | |
| | | | | I1 vs C1: p<0.0001 | | |
| | | | | I2: 2.6±10.13 | | |
| | | | | C2: 0.0±10.50 | | |
| | | | | I2 vs C2: p<0.0095 | | |
| | | | | SF-36v2 PCS. mean | | |
| | | | | chanae±SD | | |
| | | | | I1: 1.15±7.20 | | |
| | | | | C1: 0.17±6.22 | | |
| | | | | l1 vs C1: ns | | |
| | | | | I2: 1.60±7.24 | | |
| | | | | C2: 0.28 (7.29) | | |
| | | | | I2 vs C2: ns | | |
| | | | | | | |
| | | | | Exploratory endpoints | | |
| | | | | EQ-5D change, | | |
| | | | | mean±SD | | |
| | | | | l1: 0.038±0.166 | | |
| | | | | C1: -0.014±0.171 | | |
| | | | | I1 vs C1: p<0.0001 | | |
| | | | | I2: 0.051±0.178 | | |
| | | | | C2: -0.0005±0.184 | | |
| | | | | I2 vs C2: p≤0.0095 | | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|-------------------------|---------------------------|--------------------------------------|------------|--------------------------|--------------------------------|-------------------------|
| Year | Setting | | | | | Comment |
| Reference | Study period | | | Results | | |
| Country | Follow-up | | | | | |
| Study design | | | | | | |
| Crowley et al | Population | Intervention | | Effects from OLE-studies | Adverse events | Risk of bias |
| 2017 | | 30 mg apremilast twice | | are not reported | | |
| [63] | Reported in [56] and | daily | | | Patients with ≥1 AE, n | Not assessed |
| | [59] | | | | (%) | |
| This article is an open | | N in safety analysis | | | Total: 985 (83.2) | Comment |
| lable extension (OLE) | Inclusion criteria to OLE | Whole period: 0 to \leq | | | Period 1: 939 (79.3) | Study sponsored and |
| from the ESTEEM 1 and | phase: | 156 weeks: n=1184 | | | Period 2: 380 (58.1) | supported by the |
| ESTEEM 2 trials | Participants in the | | | | Period 3: 230 (57.4) | Celgene corporation |
| | ESTEEM 1 and 2 studies | | | | | |
| OLE to | who, after completion | Stratified in periods: | | | Patients with ≥1 severe | |
| | of 52 weeks agreed to | | | | AE, n (%) | **Patients with |
| [56,59,62] | continue on Apremilast | 1: | | | Total: 126 (10.6) | multiple diseases. Two |
| | treatment for up to 4 | 0 to \leq 52 weeks: n=1184 | | | Period 1: 86 (7.3) | died from heart failure |
| | additional years. | | | | Period 2: 33 (5.0) | and one from fatal |
| | | 2: | | | Period 3: 17 (4.2) | cerebrovascular |
| | Follow-up | >52 to \leq 104 weeks: | | | | accident |
| | Placebo-controlled | n=654 | | | Patients with ≥ 1 serious | |
| | phase 0–16 weeks | 2. | | | AE, 11 (%) | |
| | (presented in [56,59,62] | 3: | | | 10tal: 106 (9.0) | |
| | to E2 works, followed | $>104 \ 10 \le 150 \ \text{weeks}$: | | | Period 1: 58 (4.9) | |
| | by OLE for up to 1E6 | 11-401 | | | Period 2: 50 (5.5) | |
| | by OLE for up to 150 | | | | Periou 5. 16 (4.5) | |
| | WEEKS | | | | AEs leading to drug | |
| | | | | | withdrawal n (%) | |
| | | | | | Total: 132 (11 1) | |
| | | | | | Period 1: 93 (7 9) | |
| | | | | | Period 2: 20 (3.1) | |
| | | | | | Period 3: 14 (3.5) | |
| | | | | | | |
| | | | | | **AE leading to death, | |
| | | | | | n (%) | |
| | | | | | Total: 3 (0.3) | |
| | | | | | Period 1: 1 (0.1) | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------|--------------|--------------|------------|----------------|-----------------------------------|--------------|
| Year | Setting | | | | | Comment |
| Reference | Study period | | | Results | | |
| Study design | ronow-up | | | | | |
| Study design | | | | | Period 2: 1 (0 2) | |
| | | | | | Period 3: 1 (0.2) | |
| | | | | | | |
| | | | | | AEs reported by ≥5% of | |
| | | | | | patients | |
| | | | | | | |
| | | | | | Diarrhea, n (%) | |
| | | | | | Total: 221 (18.7) | |
| | | | | | Period 1: 205 (17.3) | |
| | | | | | Period 3: 7 (1 7) | |
| | | | | | | |
| | | | | | Nausea, n (%) | |
| | | | | | Total: 195 (16.5) | |
| | | | | | Period 1: 186 (15.7) | |
| | | | | | Period 2: 5 (0.8) | |
| | | | | | Period 3: 6 (1.5) | |
| | | | | | | |
| | | | | | UK11, 11 (%) Total: 227 (19.2) | |
| | | | | | Period 1: $184 (15.5)$ | |
| | | | | | Period 2: 58 (8.9) | |
| | | | | | Period 3: 27 (6.7) | |
| | | | | | | |
| | | | | | Nasopharyngitis, n (%) | |
| | | | | | <i>Total:</i> 196 (16.6) | |
| | | | | | Period 1: 167 (14.1) | |
| | | | | | Period 2: 43 (6.6) | |
| | | | | | Pendu 3: 24 (0.0) | |
| | | | | | Tension headache. | |
| | | | | | n (%) | |
| | | | | | Total: 115 (9.7) | |
| | | | | | Period 1: 106 (9.0) | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|----------------------|-------------------------------|--------------------------|-------------------------|------------------------|---------------------------|-------------------------|
| Year | Setting | | | | | Comment |
| Reference | Study period | | | Results | | |
| Country | Follow-up | | | | | |
| Study design | | | | | | |
| | | | | | Period 2: 8 (1.2) | |
| | | | | | Period 3: 5 (1.2) | |
| | | | | | Headache. n (%) | |
| | | | | | Total: 86 (7.3) | |
| | | | | | Period 1: 75 (6.3) | |
| | | | | | Period 2: 6 (0.9) | |
| | | | | | Period 3: 7 (1.7) | |
| | | | | | | |
| Ohtsuki et al 2017 | Population | Intervention (I) | Comparsion (C) | Analysis model | Adverse events – | Risk of bias |
| [61] | Inclusion criteria | Apremilast for | Placebo for 16 weeks | mITT and safety | during 16 weeks | Acceptable |
| | ≥20 years of age | 16 weeks, orally 30 mg | (C) | population | placebo controlled | |
| Multicentre study in | Plaque psoriasis PASI | twice daily (60 mg/day). | | Missing data | phase | Comment |
| Japan | ≥12, BSA ≥10%, for ≥6 | Dose titrated (10-mg | Allocation – placebo | LOCF | Patients w ≥1 AE, n (%) | Conflict of interest: |
| | months, eligible for | daily increments) for 6 | controlled phase, n | | I: 44/85 (51.8%) | study funded by Celgene |
| RCT | phototherapy or | days | C: 84 | Results – 16 weeks | C: 35/84 (41.7%) | |
| | systemic therapy | | | PASI ≥50, n (%) | | |
| | Describes of superstantistics | Allocation – placebo | Drop-out rate – placebo | 1: 43/85 (50.6%) | Severe AE, n (%) | |
| | Baseline characteristics | controllea phase, n | controlled phase, n (%) | C: 18/84 (21.4%) | 1: $0/85(0\%)$, | |
| | Female/Male, (%) | 1: 85 | C: 12 (14.3%) | TVS C: p<0.0001 | C: 1/84 (1.2%) | |
| | 1. 10.3%/03.3% | The study also included | | Drimany and paint DASI | Batiants with AE loading | |
| | C. 20.2%/75.8% | intervention groups | | >75 n (%) | to drug withdrawal n | |
| | Ethnicity: Asian (Janan) | treated with 20 mg per | | 1. 24/85 (28.2%) | (%) | |
| | Body mass index | dav | | $C \cdot 6/84 (7.1\%)$ | 1: 6/85 (7.1%) | |
| | (ka/m ²) mean+SD | uuy | | $L_{VS} C: n < 0.0003$ | (. 0/00)(7.170) | |
| | 1. 24 9+3 7 | Dron-out rate – nlaceho | | 1 13 C. p 10.0005 | 0. 4/04 (4.0/0) | |
| | C: 24.7±4.7 | controlled phase | | PASI ≥90. n (%) | Adverse events | |
| | | l: n=9 (10.6%) | | 1: 12/85 (14.1%) | reported by $\geq 5\%$ of | |
| | Study period | - () | | C: 1/84 (1.2%) | patients in any | |
| | July 2013 – December | | | I vs C: p<0.006 | treatment groups | |
| | 2015 | | | | | |
| | | | | DLQI improvement, | Diarrhoea, n (%) | |
| | | | | mean (SD) | I: 8 (9.4%) | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|---|--|---|--|--|---|---|
| Year | Setting | | | | | Comment |
| Reference | Study period | | | Results | | |
| Country | Follow-up | | | | | |
| | Follow-up 16 weeks placebo- controlled phase (presented here). Followed by 52 weeks active phase dose OLE, and a four-week post- treatment observational follow-up | | | I: -2.2 (SD: 5.0) C: +1.3 (SD: 5.7) I vs C: p<0.0001 | C:1 (1.2%) Nasopharyngitis, n (%) I: 10 (11.8%) C: 7 (8.3%) Abdominal discomfort, n (%) I: 6 (7.1%) C: 1 (1.2%) | |
| Reich et al 2017 [57] Multicentre study carried out at 82 sites in the USA, Australia, Canada and Europe. RCT | PopulationInclusion criteria≥18 years of age,Plaque psoriasis PASI≥12, sPGA ≥3, BSA≥10%, for ≥12 months,eligible forphototherapy orsystemic therapy,inadequate response toone or twoconventional systemicagents, and biologicnaïve.Baseline characteristicsFemale/Male, (%)I: 41%/59%C: 29.8%/70.2%Ethnicity – CaucasianI: 95.2%C: 95.2% | Intervention (I) Apremilast for 16 weeks, orally 30 mg twice daily (60 mg/day). Dose titrated for the first week. Allocation – placebo controlled phase, n I: 83 Drop-out rate – placebo controlled phase I: n=6 (7.2%) The study also included intervention groups treated with etanercept | Comparsion (C) Placebo for 16 weeks, orally, twice daily Allocation – placebo controlled phase, n C: 84 Drop-out rate – placebo controlled phase, n (%) C: 9 (10.7%) | Analysis model mITT Missing data LOCF Results – 16 weeks Primary endpoint PASI ≥75, n (%) I: 33/83 (39.8%) C: 10/84 (11.9%) I vs C: p<0.0001 | Adverse events – during 16 weeks placebo controlled phase Patients $w \ge 1$ AE, n (%) 1: 59/83 (71.1%) C: 45/84 (53.6%) Patients $w \ge 1$ serious AE, n (%) 1: 3/83 (3.6%) C: 0/84 (0%) Patients with AE leading to drug withdrawal, n (%) 1: 3/83 (3.6%) C: 2/84 (2.4%) Treatment-emergent adverse events $\ge 5\%$ of patients in any treatment groups | Risk of bias Acceptable Conment Conflict of interest: study funded by Celgene. Editorial support by sponsor The study was not powered for apremilast vs etanercept comparisons. A post hoc comparison yielded a calculated power of 19% for detecting the observed difference. Information about study period found at https://clinicaltrials.gov /ct2/show/NCT0169029 9 |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|-------------------------|-------------------------|--------------|------------|--------------------------------------|------------------------|--------------|
| Year | Setting | | | | | Comment |
| Reference | Study period | | | Results | | |
| Country Study docign | Follow-up | | | | | |
| Study design | Body mass index | | | DLOI natients receiving | | |
| | (ka/m²) mean+SD | | | a DLOI score of 0 or 1 n | Nausea n (%) | |
| | 1: 29.2+5.8 | | | (%) | 1: 9/83 (10.8%) | |
| | C: 29.5±6.6 | | | I: 22/83 (26.5%) C: 13/84 (15.5%) | C: 1/84 (1.2%) | |
| | Study period | | | , , , | URTI, n (%) | |
| | October 2012 - July | | | | I: 6/83 (7.2%) | |
| | 2014 | | | | C: 2/84 (2.4%) | |
| | Follow-up | | | | Diarrhoea. n (%) | |
| | 16 weeks placebo- | | | | I: 9/83 (10.8%) | |
| | controlled phase | | | | C: 3/84 (3.6%) | |
| | (presented here). At | | | | | |
| | week 16 placebo | | | | Nasopharyngitis, n (%) | |
| | patients were switched | | | | I: 4/83 (4.8%) | |
| | to apremilast. The OLE | | | | C: 8/84 (9.5%) | |
| | phase was maintained | | | | | |
| | until week 104. Results | | | | Headache*, n (%) | |
| | for up to 52 weeks | | | | 1: 11/83 (13.3%) | |
| | presented in the | | | | C. 3/84 (3.0%) | |
| | who did not achieve | | | | Tension headache | |
| | PASI 50 at week 32 | | | | n (%) | |
| | could add | | | | I: 5/83 (6.0%) | |
| | complementary | | | | C: 4/84 (4.8%) | |
| | therapies to their | | | | | |
| | treatments | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | 1 | | | | | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|-----------------------|--------------------------|--------------------------|-------------------------|--------------------|--------------------------|----------------------------|
| Year | Setting | | | | | Comment |
| Reference | Study period | | | Results | | |
| Country | Follow-up | | | | | |
| Study design | | | | | | |
| Strober et al 2017 | Population | Intervention (I) | Comparsion (C) | Analysis model | Adverse events – | Risk of bias |
| [60] | Inclusion criteria | Apremilast, orally 30 mg | Placebo orally, twice | ITT | during 16 weeks | Acceptable |
| | ≥18 years of age | twice daily (60 mg/day). | daily (C) | Missing data | placebo controlled | |
| Multicentre study, | Moderate cronic plaque | Dose titrated for the | | LOCF | phase | Comment |
| conducted at 25 study | psoriasis, BSA 5-10%, | first week. | Allocation – placebo | | Patients w ≥1 AE, n (%) | Conflict of interest: |
| sites in USA | and sPGA=3, for ≥6 | | controlled phase, n | Results – 16 weeks | I: 92/148 (62.6%) | study funded by |
| | months, no prior | Allocation – placebo | C: 73 | PASI ≥50, n (%) | C: 35/73 (47.9%) | Celgene. |
| RCT | exposure to | controlled phase, n | | I: 79/148 (53.4%) | | |
| | conventional systemics, | I: 148 | Drop-out rate – placebo | C: 18/73 (24.7%) | Patients w ≥1 serious | |
| | biologic naïve | | controlled phase, n (%) | I vs C: p<0.0001 | AE, n (%) | Study information found |
| | | Drop-out rate – placebo | C: 9 (12.3%) | | I: 3/148 (2.0%), | mainly at |
| | Baseline characteristics | controlled phase | | PASI ≥75, n (%) | C: 0/73 (0.0%) | https://clinicaltrials.gov |
| | Female/Male, (%) | l: n=27 (18.2%) | | I: 32/148 (21.6%) | | /ct2/show/record/NCT0 |
| | I: 50%/50% | | | C: 6/73 (8.2%) | Patients with AE leading | 2425826 |
| | C: 43.8%/56.2% | | | I vs C: p=0.0136 | to drug withdrawal, n | |
| | Ethnicity — Caucasian | | | | (%) | |
| | No information | | | DLQI improvement, | I: 5/148 (3.4%) | |
| | Body mass index | | | mean (SD) | C: 3/73 (4.1%) | |
| | (kg/m²), mean±SD | | | I: -4.8 (SD: 5.80) | | |
| | I: 30.5±7.4 | | | C: -2.4 (SD: 6.62) | Treatment-emergent | |
| | C: 30.8±6.5 | | | l vs C: p=0.0008 | adverse events ≥5% of | |
| | | | | | patients in any | |
| | Study period | | | | treatment groups | |
| | April 2015 - February | | | | | |
| | 2016 | | | | Nausea, n (%) | |
| | | | | | 1: 26 (17.7%) | |
| | Follow-up | | | | C: 7 (9.6%) | |
| | 16 weeks placebo- | | | | | |
| | controlled phase | | | | URII, n (%) | |
| | (presented here). At | | | | 1: 10 (6.8%) | |
| | week 16 placebo | | | | C: 3 (4.1%) | |
| | patients were switched | | | | | |
| | to apremilast. The OLE | | | | Diarrhoea, n (%) | |
| | | | | | l: 43 (29.3%) | |

| Study design | Year Reference Country Study design | Setting Study period Follow-up | Companison | Results | | Comment |
|--|--|--|------------|---------|---|---------|
| phase was maintained until week 52. | | phase was maintained until week 52. | | | C: 12 (16.4%) Headache, n (%) I: 30 (20.4%) C: 8 (11.0%) Decreased appetite, n (%) I: 6 (4.1%) C: 4 (5.5%) Vomiting, n (%) I: 9 (6.1%) | |

AE – adverse events; BMI – body mass index; BSA – body surface area; DLQI – dermatology quality of life index; HRQOL – health-related quality of life; ITT – intention-to-treat; LOCF – last observation carried forward; MCS – mental component summary score; mITT – modified-ITT; NRI – non-responder imputation; PASI – psoriasis area and severity index; PCS – physical component summary score; PGA – physician's global assessment; PRO – patient reported outcome; SD – standard deviation; URTI – upper respiratory tract infection

| First Author | Population | Intervention | Control | Analysis model | Adverse events | Risk of bias |
|-------------------------|-----------------------------------|-----------------------------|--------------------------|---------------------------|---|----------------------|
| Year | Setting | | | | | |
| Reference | | | | Results | | Comment |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| Flytström et al | Population | Cyclosporine | Methotrexate | Analysis model | Adverse events (AE:s) | Risk of bias |
| 2008 | Adult patients (≥18 | Initially 3 mg/kg daily. If | Initially 7.5 mg weekly. | mITT, (all patients who | Any reported AE: | |
| [65] | years of age) with | inadequate response | If inadequate response | received \geq 1 dose of | MTX: 78% | Acceptable |
| | chronic plaque psoriasis | (<50% reduction of | (<50% reduction of | test substance). | Cyclosporine: 97% | |
| The study was carried | of moderate to severe | PASI) and no | PASI) and no | | (p=0.03) | |
| out at 5 study sites in | severity according to | considerable adverse | considerable adverse | Results | | 6 |
| Sweden. | the patient's and | effects were recorded, | effects were recorded, | PASI ≥50 | Dose reduction due to | Comment |
| | physician's common | the dose was increased | the dose was increased | MTX: 24/37 (65%) | side-effects: | Conflict of interact |
| RCT | judgement. Topical | to a maximum of | to a maximum of 15 mg | Cyclosporin:27/31 (87%) | MTX: approx. 33% | conjuct of interest |
| | treatment was allowed | 5 mg/kg daily | weekly. Folic acid 5 mg | MTX vs Cyclosporine: | Ciclosporin: approx. | None stated |
| | during the treatment | | was given daily except | n.s. | 33% | None stated |
| | period, reflecting | n=43 | on the methotrexate | | | |
| | normal clinical practice. | n after dropouts: 31 | days. | PASI≥75 | <u>AE:s reported by ≥ 5</u> | |
| | | | | MTX: 9/37 (24%) | <u>patients</u> | |
| | <u>Baseline characteristics</u> | Drop-out rate | | Cyclosporine: 18/31 | Fatigue | |
| | Female/male | 12/43 (27,9%). All drop | n=41 | (58%) | MTX: 16% | |
| | MTX: 24.3%/75.7% | outs were withdrawn | n after drop outs: 37 | MTX vs Cyclosporine: p | Cyclosporine: 48% | |
| | Cyclosporine: | from the study before | | 0.0094 | (p=0.008) | |
| | 12.9%/87.1% | the first treatment | Drop-out rate | | | |
| | Age, mean (range) | dose. | 4/41 (9.8%) All drop | PASI≥90 | Gastrointestinal | |
| | MTX: 48 (23–78) | | outs were withdrawn | MTX: 4/3/ (11%) | MTX: 35% | |
| | Cyclosporine: 45 (18– | | from the study before | Cyclosporine: 9/31 | Cyclosporine: 39% | |
| | 70) M(sinht (ha)) as says | | the first treatment | (29%) | (p=0.8) | |
| | (neuron) | | dose. | MTX vs Cyclosporine | la fa atian | |
| | (range) | | | n.s. | | |
| | (viclosporino: 97 (61 | | | BASI maan change | NIIA. 30% | |
| | 120) | | | MTV EQ0/ | (n=0.0) | |
| | ISUJ BASLat hasaling maan | | | Cyclosporino: 72% | (p-0.0) | |
| | | | | MTX vs (vclosporing p | Headache | |
| | MTY: 1/ 1 (+7 0) | | | 0.0028 | MTY 1/% | |
| | WITA. 14.1 (17.0) | | | 0.0020 | Cyclosporine: 20% | |
| | (<i>SD):</i> MTX: 14.1 (±7.0) | | | 0.0028 | Headache MTX: 14% Cyclosporine: 29% | |

Table 6.3. Cyclosporine versus Methotrexate

| First Author | Population | Intervention | Control | Analysis model | Adverse events | Risk of bias |
|--------------|-------------------------|--------------|---------|------------------------|------------------------|--------------|
| Year | Setting | | | | | |
| Reference | | | | Results | | Comment |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| | Cyclosporine: 15.5 | | | DLQI, mean change | (p=0.14) | |
| | (±6.3) | | | MTX: circa -8 | | |
| | | | | Cyclosporine: circa -6 | Paresthesia | |
| | Study period | | | MTX vs Cyclosporine | MTX: 0 | |
| | February 2002– | | | n.s. | Cyclosporine: 35% | |
| | February 2005. | | | | (p=<0.0001) | |
| | Inclusion restricted to | | | | | |
| | September thru | | | | Arthralgia: | |
| | February each yr. | | | | MIX: 11% | |
| | Fellow | | | | Cyclosporine: 16% | |
| | Follow up | | | | (p=0.72) | |
| | 12 weeks | | | | Uraanay | |
| | | | | | MTY: 2% | |
| | | | | | Cyclosporine: 13% | |
| | | | | | (n=0.17) | |
| | | | | | (p=0.17) | |
| | | | | | Elevated liver enzymes | |
| | | | | | MTX: 19% | |
| | | | | | Cyclosporine: 0 | |
| | | | | | (p=0.01) | |
| | | | | | | |
| | | | | | Elevated creatinine | |
| | | | | | MTX: 0 | |
| | | | | | Cyclosporine: 19% | |
| | | | | | (p=0.007) | |
| | | | | | | |
| | | | | | | |
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| First Author | Population | Intervention | Control | Analysis model | Adverse events | Risk of bias |
|------------------------|--------------------------|-------------------------|-----------------------------|--------------------------|--------------------------|----------------------|
| Year | Setting | | | | | |
| Reference | | | | Results | | Comment |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| Heydendael et al | Population | Methotrexate | Cyclosporine | Analysis model | Adverse events over 52 | Risk of bias |
| 2003 | Adult patients (≥18 | Initially 15 mg weekly. | Initially 3 mg/kg daily. If | mITT (all who received | weeks | |
| | years of age), with | If inadequate response | inadequate response | at least 1 dose of test | Discontinuation of | Acceptable |
| [66] | chronic plaque psoriasis | after 4 weeks (<25% | after 4 weeks (<25% | substance). | treatment due to side | |
| | of moderate to severe | reduction of PASI) the | reduction of PASI) the | | effects | |
| The study was carried | severity defined as a | dose was increased to a | dose was increased to a | Results after 16 weeks | MTX: 12/43, 27.9% | Commont |
| out at local | PASI score of ≥8 and | maximum of 22.5 mg | maximum of 5 mg | PASI 75 | (due to elevated liver | Comment |
| dermatological centers | insufficient response to | weekly. If side effects | weekly. If side effects | MTX: 26/43 (60.4%) | enxymes) | Conflict of interest |
| in Amsterdam, the | topical or UVB therapy. | occurred the does was | occurred the does was | Cyclosporine: 30/42 | Cyclosporine: 1/42, | conjuct of interest |
| Netherlands | Naive to methotrexate | decreased according to | decreased according to | (70%) | 2.3% (due to elevated | None stated |
| | or cyclosporine | regular clinical | regular clinical | MTX vs cyclosporine: | bilirubin) | |
| RCT | treatment. | guidelines. | guidelines. | | | |
| | | | | PASI 90 | Total number of | |
| | Baseline characteristics | n=44 randomised (43 | n=44 randomised (42 | MTX: 17/43 (39.5%) | reported side effects | |
| | Female/male | included in analyses) | included in analyses) | Cyclosporine: 14/42 | auring treatment: | |
| | MIX: 35%/65% | Dura autorita | Dura autorita | (32.5%) | MIX: 113 events | |
| | Cyclosporine: 31%/69% | Drop-out rate | Drop-out rate | INTIX vs cyclosporine: | reported by 29 of 43 | |
| | Age, mean (SE) | 13/44 (29.5%) | 3/44 (6.9%) | Adama valativa vadvatian | patients | |
| | WIX: 41.6 (±13.0 | | | in DASI: | Cyclosporine: 166 | |
| | (+12.4) | | | III PASI: NATY: CAN | of 42 nationts | |
| | (±12.4) | | | Cyclosporine: 72% | of 42 patients | |
| | Not given | | | MTX vs cyclosporine: | Specific events | |
| | PASI at haseline mean | | | n=0.14 | (reported by n natients) | |
| | (SF)· | | | p=0.14 | Nausea: | |
| | MTX: 13 4 (+3 6) | | | SE-36 nhysical | MTX: 19/43 (44 2%) | |
| | Cyclosporine: 14.0 | | | component score – | Cyclosporine: 4/42 | |
| | (+6.6) | | | mean difference | (9.3%) | |
| | Psoriatic arthritis: | | | hetween aroups after | MTX vs Cvc: p<0.001 | |
| | MTX: n=3 | | | adjustment for baseline | | |
| | Cyclosporine: n=1 | | | values (95% CI): | Headaches | |
| | | | | MTX vs cyclosporine: - | MTX: 7/43 (16.3%) | |
| | Study period | | | 0.8 (-4.6 to 3.0) | Cyclosporine: 18/42 | |
| | | | | | (41.9%) | |

| First Author | Population | Intervention | Control | Analysis model | Adverse events | Risk of bias |
|--------------|-----------------------|--------------|---------|-------------------------|---------------------------|--------------|
| Year | Setting | | | | | |
| Reference | | | | Results | | Comment |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| | October 1998–June | | | SF-36, mental | MTX vs Cyc: p=0.009 | |
| | 2000 | | | component score – | | |
| | | | | mean difference | Muscle ache | |
| | Follow up | | | between groups after | MTX: 3/43 (7%) | |
| | 16 weeks treatment | | | adjustment for baseline | Cyclosporine: 12/42 | |
| | phase and in total 52 | | | values (95% CI): | (27.9%) | |
| | weeks follow-up. | | | MTX vs cyclosporine: - | MTX vs Cyc: p=0.007 | |
| | | | | 0.5 (-3.9 to 2.9) | | |
| | | | | | Paresthesia | |
| | | | | | MTX: 1/43 (2.3%) | |
| | | | | | Cyclosporine: 14/42 | |
| | | | | | (32.6%) | |
| | | | | | MTX vs Cyc: p<0.001 | |
| | | | | | | |
| | | | | | No serious or | |
| | | | | | irreversible side effects | |
| | | | | | were reported in either | |
| | | | | | group | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|------------------------|--------------------------|---------------------------|-----------------------|--------------------------|--------------------------|--------------------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| Mrowietz et al | Population | Intervention | Comparison | Analysis Model | Adverse events | Risk of bias |
| 2016 | Inclusion criteria | Fumarates (DMF). | Placebo | FAS (Full analysis set) | 4 serious TEAE all in I2 | Acceptable |
| [68] | Patients, 18 years or | I1: LAS41008 | | 11: 267 | | |
| | older with moderate to | I2: Fumaderm | n=138 | 12: 273 | One or more treatment- | Comment |
| Name of study | severe chronic (≥12 | Treatment was up- | | C: 131 | emergent adverse | Conflict of interest |
| BRIDGE | months) plaque | titrated over the first 9 | Drop-out rate at 16 | | events (only events | Sponsored by the |
| Main study | psoriasis, with BSA | weeks, up to a | weeks | Missing data | reported by ≥5% of the | manufacturer of the |
| | >10%, PGA ≥3 and PASI | maximum daily dose of | 40/138 (28.9%) | LOCF | patients in the safety | test substance, Almirall |
| Multicentre study | >10 | 720 mg, as per clinical | | | population are | S.A. |
| performed in Austria, | | practice | Patients entering the | Results | included) was reported | |
| Germany, the | Baseline characteristics | | follow-up period | PASI ≥50 at week 16 | by: | |
| Netherlands and Poland | Female/Male, | l1: n=286 | n=66 | 11: 53.6% | 11: 234/279 (83.9%) | |
| | I: 37,6%/62.4% | 12: n=280 | | 12: 61.9% | 12: 238/283 (84.1%) | |
| RCT | C: 32,1%/67.9% | | | C: 29.0% | C: 82/137 (59.9%) | |
| | | Drop-out rate at 16 | | | | |
| | Study period | 11: 104/280 (37.1%) | | PASI ≥75 at week 16 | (Reported events: | |
| | Start of patient | 12: 110/286 (38.5%) | | (primary endpoint) | diarrhoea, upper | |
| | recruitment: January | | | 11: 37.5% | abdominal pain, | |
| | 2013 | Patients entering the | | 12: 40.3% | abdominal pain, | |
| | | follow-up period | | C: 15.3% | nausea, flatulence, | |
| | Follow-up | n=150 | | | vomiting, pruritus, | |
| | Primary analyses at | | | $PASI \ge 90$ at week 16 | erythema, skin burning | |
| | week 16. Treatment | | | 11: 18.4% | sensation, | |
| | week 0–16, treat-ment | | | 12: 22.3% | nasopharyngitis, | |
| | free follow-up for | | | C: 4.6% | flushing, lymphopenia, | |
| | 12 month | | | | eosinophilia, headache) | |
| | | | | PGA clear or almost | | |
| | | | | ciear at week 16 | | |
| | | | | (primary endpoint) | | |
| | | | | 11: 33.0% | | |
| | | | | 12: 37.4% | | |
| | | | | C: 13.0% | | |

Table 6.4. Fumarates versus placebo

| First Author Year Reference Country Study design | Population Setting Study period Follow-up (FU) | Intervention | Comparison | Analysis model Results | Adverse events | Risk of bias Comment |
|--|---|--------------|------------|---|----------------|-------------------------|
| | | | | BSA at week 16 Mean change from baseline I1: -13,2 I2: -11,3 C: -4,9 | | |

BSA – body surface area; ITT – intention-to-treat; LOCF – last observation carried forward; PASI – psoriasis area and severity index; PGA – physician's global assessment; SD – standard deviation; TEAE – treatment emergent adverse events.

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|---------------------|---------------------------|-------------------------|-------------------------|---------------------------|-------------------------|----------------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| Fallah Arani et al | Population | Intervention | Comparison | Analysis Model | Adverse events | Risk of bias |
| 2011 | Inclusion criteria | Fumarates (per os), | Methotrexate (per os); | ITT | Patient reported total | Acceptable |
| [69] | Patients, 18 years or | 30 mg, followed by | 15 mg | | number of adverse | |
| | older with chronic | 120 mg according to a | per week | Results | events were 60 in the | Comment |
| Single centre study | plaque-type psoriasis | standard progressive | | Decrease in PASI | intervention group | Conflict of interest |
| performed in the | and PASI ≥10 | dosage regimen | n=30 | (primary endpoint, | (reported by 24 | None declared |
| Netherlands | | (maximum dose 720 mg | | mean ±SD) | patients) and 78 in the | |
| | Baseline characte-ristics | after week 9) | Drop-out rate at 12 | 1: | control group (reported | |
| RCT | for patients receiving | | weeks | Base line: 18.1±7.0 | by 27 patients) | |
| | treatment | n=30 | 5/30 (16.7%) | Week 12: 10.5±6.7 | p=0.236 for I vs C) | |
| | Intervention | | | C: | | |
| | Female: 26% | Drop-out rate at | Drop-out rate at 20 | Base line: 14.5±3.0 | Flushing | |
| | Male: 74% | 12 weeks | weeks | Week 12: 6.7±4.5 | I: 13/26 (50.0%) | |
| | Mean bodyweight 87 kg | 4/30 (13.3%) | 19 finished the follow- | | C: 2/25 (8.0%) | |
| | (SD ±21) | | up period | I vs C (week 12): | l vs C: p=0.002 | |
| | | Drop-out rate at | | Adjusted absolute mean | | |
| | Comparison | 20 weeks | | difference 1.4; 95% CI: – | Influenza-like syndrome | |
| | Female: 41% | 18 finished the follow- | | 2.0 to 4.7; p=0.417 | I: 1/26 (3.8%) | |
| | Male: 59% | up period | | | C: 7/25 (28.0%) | |
| | Mean bodyweight | | | | l vs C: p=0.050 | |
| | 83 kg (SD ±17) | | | PASI ≥50 at week 12 | | |
| | | | | I: 11/26 (42.3%) | Other adverse events | |
| | Study period | | | C: 15/25 (60.0%) | I: 2/26 (7.7%) | |
| | Recruitment between | | | l vs C: p=0.325 | (Diarrhoea, worsening | |
| | October 2006 – | | | | of psoriasis, itch) | |
| | February 2009 | | | PASI ≥75 at week 12 | C: 4/25 (16.0%) | |
| | | | | I: 5/26 (19.2%) | (Elevations in liver | |
| | Follow up | | | C: 6/25 (24.0%) | enzymes, recurrent | |
| | Primary analyses at | | | l vs C: p=0.941 | angina) | |
| | week 12. Treatment | | | | | |
| | | | | | | |

Table 6.5. Fumarates versus Methotrexate

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------|----------------------|--------------|------------|---------------------|----------------|--------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| | week 0–16, follow-up | | | PASI ≥90 at week 12 | | |
| | until week 20 | | | I: 1/26 (3.8%) | | |
| | | | | C: 2/25 (8.0%) | | |
| | | | | I vs C: p=0.610 | | |
| | | | | | | |
| | | | | PASI ≥50 at week 20 | | |
| | | | | I: 13/18 (72.2%) | | |
| | | | | C: 10/19 (52.6%) | | |
| | | | | I vs C: p=0.374 | | |
| | | | | | | |
| | | | | PASI ≥75 at week 20 | | |
| | | | | I: 7/18 (38.9%) | | |
| | | | | C: 6/19 (31.6%) | | |
| | | | | l vs C: p=0.642 | | |
| | | | | | | |
| | | | | PASI ≥90 at week 20 | | |
| | | | | I: 1/18 (5.6%) | | |
| | | | | C: 2/19 (10.5%) | | |
| | | | | l vs C: p=1.00 | | |
| | | | | | | |

BSA – body surface area; ITT – intention-to-treat; LOCF – last observation carried forward; PASI – psoriasis area and severity index; PGA – physician's global assessment; SD – standard deviation; TEAE – treatment emergent adverse events.

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------|------------------------|------------------------|----------------------|-----------------------|------------------------|------------------------------|
| Year | Setting | | | Poculto | | comment |
| Reference | Study period | | | Results | | |
| Country | Follow up (EU) | | | | | |
| Study design | Follow-up (FO) | | | | | |
| Ho et al | Population | Intervention | Comparison | Analysis model | Adverse Events | Risk of bias |
| 2010 | Patients (≥18 years of | Methotrexate, initial | Placebo | Outcomes analysed | AEs, % of patients | Acceptable |
| [71] | age) with a history of | dose 2.5-5 mg. If | | for those who | I: 65% | |
| | chronic plaque | tolerated the dose | Randomised patients | completed the study | C: 30% | Comment |
| | psoriasis (≥12 months) | increased to | n=20 | | | |
| China | with BSA involvement | 10 mg/week after 1 | | Results | Nausea, vomiting, and | Metotrexat arm was unblinded |
| | ≥20% | week. The dose was | Drop-out rate, n (%) | 6 months | increased liver enzyme | Blinding not described for |
| RCT | | increased with | 3/20=15% | | levels were common | placebo arm |
| | Baseline | 2.5 mg/week until a | | PASI ≥50, achieved by | in the methotrexate | |
| | characteristics | good clinical response | Included in analysis | % of patients | group. The placebo | Method of randomisation not |
| | Female/Male, % | was seen or to a | n=17 | I: 79% | group reported | clearly described |
| | I: 10.0%/90.0% | maximum of | | C: 24% | infections and | |
| | C: 10.0%/90.0% | 30 mg/week. In | | | increased liver | |
| | | addition patients were | | PASI ≥75, achieved by | enzymes | |
| | Ethnicity | given 5 mg folic acid | | % of patients | | |
| | No information | daily | | I: 63% | | |
| | | | | C: 18% | | |
| | Bodyweight | Randomised patients | | | | |
| | No information | n=20 | | PDI, change from | | |
| | | | | baseline (mean±SD) | | |
| | Study period | Drop-out rate, n (%) | | I: 18.3±31,6 | | |
| | No information | 1/20=5% | | C: 10.3±31.2 | | |
| | | | | I vs C:ns | | |
| | Follow-up | Included in analysis | | | | |
| | 6 months study period | n=19 | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
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| | | | | | | |

Table 6.6. Methotrexate versus placebo

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|-------------------------|-------------------------|------------------------|------------------------|--------------------|-------------------------|---------------------------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| Saurat et al | Population | Intervention | Comparison | Method of analysis | Adverse events | Risk of bias |
| 2008 | Patients (≥18 years of | Methotrexate (orally, | C: placebo, | ITT for efficacy | AEs during placebo- | Acceptable |
| [72] | age), with moderate | once a week). Titrated | administered to match | outcomes | controlled phase and | |
| | to severe psoriasis, | from 7.5 mg/week, | active treatments | | follow-up period | Comment |
| Multicentre study | with PASI score≥10, | increased to 10 mg | | Missing data | | |
| carried out at 28 sites | BSA involvement | week 2, and 15 mg | Background treatment | NRI for efficacy | Total adverse events, n | Study funded by Abbot |
| in Europe and Canada | ≥10%, diagnosed with | week 4. | with 5 mg of oral | analysis | (%) | Laboratories, who also |
| | plaque psoriasis (≥1 | If PASI ≥50 was | folate weekly for both | LOCF for mean PASI | I: 90/110 (81.8%) | participated in designing, data |
| Study name | year), which was | reached by or after | groups | improvement | C: 42/53 (79.2%) | collection/management/analysis |
| CHAMPION | stable (≥2 months). All | week 8 the dosage | | | | and preparation of the |
| | patients had to be | was maintained. Week | Randomised patients | Results | Serious AEs, n (%) | manuscript. Several of the |
| RCT | naïve to TNF- | 8, patients who did | C: n=53 | Week 12 | I: 1/110 (0.9%) | authors were affiliated with |
| | antagonist therapy | not achieve PASI ≥50 | | | C: 1/53 (1.9%) | Abbott (employed/consultants) |
| | and methotrexate | had their dosage | Drop-out rate | PASI ≥50 | | as well as other pharmaceutical |
| | | increased to | C: 5/53 (9.4%) | I: 54.5% | Serious infections | companies. |
| | Baseline | 20 mg/week. By week | | C: 26.4% | None reported | |
| | characteristics | 12, only patients who | | | | |
| | Female/Male, % | did not achieve PASI | | PASI ≥75 | Adverse events | |
| | I: 33.6%/66.4% | ≥50 and had PASI<50 | | I: 24.5% | leading to | |
| | C: 35.2%/64.8% | at week 8 had dosage | | C: 15.1% | discontinuation, n (%) | |
| | | increased to 25 mg | | | I: 6/110 (5.5%) | |
| | Ethnicity, Caucasian, % | | | PASI ≥90 | C: 1/53 (1.9%) | |
| | I: 95.5% | | | I: 9.1% | | |
| | C: 95.4% | Subcutaneous | | C: 7.5% | Adverse events, (≥5% | |
| | Bodyweight (kg), | injections with | | | of patients in any | |
| | mean±SD | placebo to match | | PASI 100 | treatment group) | |
| | l: 83.1±17.5 | control | | I: 0.9% | Infections | |
| | C: 81.7±20.0 | | | C: 0.0% | (nonserious), n (%) | |
| | | Background treatment | | | I: 46/110 (41.8%) | |
| | Study period | with 5 mg of oral | | Results | C: 23/53 (43.4%) | |
| | Not reported | folate weekly | | Week 16 | | |
| | | | | | Nasopharyngitis, n (%) | |
| | Follow-up | Randomised patients | | PASI ≥50 | I: 46/110 (41.8%) | |
| | | n=110 | | I: 61.8% | C: 11/53 (20.8%) | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------|--------------------|--------------------|------------|--------------------|------------------------------------|--------------|
| Year | Setting | | | Results | | Comment |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| | Placebo-controlled | | | C: 30.2% | | |
| | phase (16 weeks), | Drop-out rate | | 5.4 GL ; 77 | Headache, n (%) | |
| | 70 days follow-up | 6/110 (5.5%) | | PASI ≥75 – primary | 1: 12/110 (10.9%) | |
| | period | | | 1: 35.5% | C. 5/55 (9.4%) | |
| | | | | C: 18.9% | Pruritus, n (%) | |
| | | The study also | | | I: 2/110 (1.8%) | |
| | | included an | | PASI ≥90 | C: 6/53 (11.3%) | |
| | | intervention group | | I: 13.6% | | |
| | | treated with | | C: 11.3% | Rhinitis, n (%) | |
| | | auaimumab | | PASI 100 | 1. 4/ 110 (3.0%) C· 4/53 (7.5%) | |
| | | | | I: 7.3% | C. 4/33 (7.370) | |
| | | | | C: 1.9% | Nausea, n (%) | |
| | | | | I vs C: p=0.04 | I: 8/110 (7.3%) | |
| | | | | | C: 4/53 (7.5%) | |
| | | | | | Phinarrhag n (%) | |
| | | | | | I: 0/110 (0) | |
| | | | | | C: 3/53 (5.7%) | |
| | | | | | | |
| | | | | | Viral infection, n (%) | |
| | | | | | C· 1/53 (1 9%) | |
| | | | | | 0. 1/35 (1.376) | |
| | | | | | Arthralgia, n (%) | |
| | | | | | I: 5/110 (4.5%) | |
| | | | | | C: 1/53 (1.9%) | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|-----------------------|------------------------|--------------------------|-----------------------|-------------------------|-------------------------|---------------------------------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| Warren et al | Population | Intervention | Comparison | Analysis model | Adverse Events | Risk of bias |
| 2017 | Patients (≥18 years of | Methotrexate as self- | Self-administered | Modified ITT (analysis | AE data given here for | Acceptable |
| [73] | age) with a history of | administered | subcutaneous | of all patients who had | the placebo-controlled | |
| | chronic plaque | subcutaneous | injections of placebo | received at least | phase (16 weeks) for | |
| Multicenter study | psoriasis (≥6 months) | injections, initial dose | once a week. | one injection of study | the control (placebo | Comment |
| performed at 16 sites | currently moderate to | 17.5 mg/ week. Dose | Treatment was | drug) | group, n=29) and for | Study founded by |
| in Germany, France, | severe disease based | escalation to 22.5 | combined with folic | | the whole follow-up | Medac Germany. Medac also |
| the Netherlands, and | on the definition by | mg/week allowed | acid, 5 mg/week, | Missing data: NRI | period (week 0-52) for | supplied study medication. |
| the UK | *Finlay | after | 24 hours after each | | the intervention group | |
| | | 8 weeks if patients | injection | Results | (n=91) | Study design by consultant |
| RCT | Baseline | had not achieved | | 16 weeks | | experts in psoriasis in |
| | characteristics | PASI 50. Treatment | Randomised patients | | Any AE, n (%) | conjunction with SCIderm |
| | Female/Male, % | was combined with | n=29 | PASI 50, achieved by % | I: 86/91 (95%) | GmbH, Germany, |
| | I: 29%/71% | folic acid, 5 mg/week, | | of patients | C: 27/29 (93%) | which served as clinical research |
| | C: 14%/86% | 24 hours after each | Drop-out rate, n (%) | I: 60/91 (66%) | | organisation for study |
| | | injection | 7/29=24.1% | C: 9/29 (31%) | Any drug-related (as | management, data collection, |
| | Ethnicity | | | | per judgement of | and statistical analysis. |
| | White % | Randomised patients | | PASI 75, | investigator) AE, n (%) | |
| | I: 98% | n=91 | | I: 37/91 (41%) | I: 66/91 (73%) | |
| | C: 100% | | | C: 3/29 (10%) | C: 14/29 (48%) | * Reference: Finlay AY. Current |
| | | Drop-out rate, n (%) | | | | severe psoriasis and the rule of |
| | Bodyweight, Mean kg | 14/91=15.4% | | PASI 90, | Serious AEs, n (%) | tens. Br J Dermatol 2005; 152: |
| | (SD) | | | I: 16/91 (18%) | I: 3/91 (3%) | 861–67 |
| | I: 92.4 (18.6) | | | C: 0/29 (0%) | C: 4/29 (14%) | |
| | C: 95.9 (20.9) | | | | | |
| | | | | PASI 100, | Serious infections | |
| | BMI, kg/m2 (SD) | | | I: 4/91 (4%) | None reported | |
| | I: 30.1 (6.3) | | | C: 0/29 (0%) | | |
| | C: 30.1 (6.1) | | | | Adverse events, (≥5% | |
| | | | | DLQI, absolute | of patients in any | |
| | Age, Mean (SD) | | | change, mean (SD) | treatment group) | |
| | I: 45.9 (12.9) | | | I: -9.4 (6.58) | | |
| | C: 44.4 (10.8) | | | C: -2.6 (5.83) | Any infection, n (%) | |
| | | | | | I: 58/91 (64%) | |

| First Author Year | Population Setting | Intervention | Comparison | Analysis model | Adverse events | Risk of bias Comment |
|----------------------|------------------------|--------------|------------|----------------|------------------------|-------------------------|
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| | Study period | | | | C: 13/29 (45%) | |
| | Feb 22, 2013 – May | | | | | |
| | 13, 2015 | | | | White blood cell count | |
| | | | | | decrease, n (%) | |
| | Follow-up | | | | 1: 5/91 (5%) | |
| | 16 weeks placebo | | | | C: 1/29 (3%) | |
| | followed by 52 weeks | | | | Honatic onzumo | |
| | OLE where both | | | | increased n (%) | |
| | groups received active | | | | 1: 21/91 (23%) | |
| | reatment | | | | C: 2/29 (7%) | |
| | | | | | - , - , - , | |
| | | | | | Gastrointestinal | |
| | | | | | disorders, n (%) | |
| | | | | | I: 30/91 (33%) | |
| | | | | | C: 3/29 (10%) | |
| | | | | | | |
| | | | | | Nausea or vomiting, n | |
| | | | | | (%) | |
| | | | | | 1: 20/91 (22%) | |
| | | | | | C: 1/29 (3%) | |
| | | | | | Diarrhoea n (%) | |
| | | | | | 1. 6/91 (7%) | |
| | | | | | C: 1/29 (3%) | |

AE – adverse event; BSA – body surface area; ITT – intention-to-treat; LOCF – last observation carried forward; mITT – modified intention-to-treat; NRI – non-responder imputation; PASI – psoriasis area and severity index; PDI – psoriasis disability index (Health Related Quality of Life outcome); PGA – physician's global assessment; SD – standard deviation
| | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|-------------------------|-----------------------------|--------------------------|---------------------|-------------------------|-------------------------|------------------------|
| First Author | Setting | | | | | Comment |
| Year | | | | Results | | |
| Reference | Study period | | | | | |
| Country | Follow-up (FU) | | | | | |
| Study design | | | | | | |
| Asahina et al | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
| 2010 | | | | mITT (i.e. all | | Acceptable |
| [75] | Patients (≥20 years of | Subcutaneous injection | Placebo | randomised patients | AEs – week 0–24 | |
| | age) with plaque | of 40 mg adalimumab | | who received at least | | Comments |
| Multicentre study | psoriasis for ≥6 months, | every two weeks, initial | Randomised patients | one dose of study drug, | Patients with any AE, n | Funded by Abbott |
| carried out at 42 sites | with PASI score ≥ 12 , | dose 80 mg | n=46 | and had at least one | (%) | Japan, writing support |
| in Japan | and BSA involvement | | | assessment) | 1: 39/43 (90.7%) | funded by Abbott |
| | ≥10% | Randomised patients | Drop-out, n (%) | Missing value | C: 41/46 (89.1%) | Laboratories, USA |
| | | n=43 | 6/46 (13.0%) | LUCF | | |
| | Baseline characteristics, | D (0() | | | Patients with serious | |
| | (%) | Drop-out, n (%) | | Results | AE, n (%) | |
| | Female/Male, (%) | 8/43 (18.6%) | | Week 12 | 1: 3/43 (7.0%) | |
| | 1: 18.6%/81.4% | | | | C: 2/46 (4.3%) | |
| | C: 10.9%/89.1% | | | $PASI \ge 90, n(\%)$ | Detiente with severe | |
| | Bodyweight (kg), | | | 1: $13/43$ (30.2%) | Patients with severe | |
| | mean±SD | | | C: 0/46 (0.0%) | AES, N (%) | |
| | 1: 67.4±9.9 | | | 1 vs C: p<0.01 | 1: 1/43 (2.3%) | |
| | C: /1.3±15.3 | | | | C: 1/46 (2.2%) | |
| | All notionts work | | | Week 16 | Dationts with AFs | |
| | | | | Week 10 | Patients with AES | |
| | Japanese | | | BASI > 50 p(%) | discontinuation n (%) | |
| | Study period | | | 1. 25// 2 (81 /%) | 1.5/13(11.6%) | |
| | stady period | | | (. 9)/16 (19.6%) | C· 5//6 (10.9%) | |
| | Sentember 2005 – | | | 1 vs (10.070) | 0. 5/ 40 (10.5/0) | |
| | December 2006 | | | 1 V3 C. P V0.001 | Patients with any | |
| | | | | PASI>75 n(%)- | infectious AFs | |
| | Follow-up | | | nrimary endnoint | n (%) | |
| | 16 weeks placebo | | | 1: 27/43 (62.8%) | 1: 18/43 (41.9%) | |
| | controlled period, after | | | C: 2/46 (4.3%) | C: 23/46 (50.0%) | |
| | which non-responders | | | Lys C: p<0.001 | 2. 20, 10 (30.0/0) | |

Table 7.1. Adalimumab versus placebo

| | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|-------------------------|--------------------------|------------------------|------------------|--------------------------|-------------------------|----------------------|
| First Author | Setting | | | | | Comment |
| Year | Study pariod | | | Results | | |
| Country | Follow up (ELI) | | | | | |
| Study design | ronow-up (ro) | | | | | |
| | had option of rescue | | | | Patients with injection | |
| | therapy (topical | | | PASI ≥90, n (%) | site reactions, n (%) | |
| | steroids) until week 24. | | | I: 17/43 (39.5%) | I: 8/43 (18.6%) | |
| | Thereafter 28 weeks | | | C: 0/46 (0%) | C: 3/46 (6.5%) | |
| | extension period | | | l vs C: p<0.001 | | |
| | | | | DLQI change from | | |
| | | | | baseline, mean±SD | | |
| | | | | I: -5.1±5.73 | | |
| | | | | C: 1.0±6.69 | | |
| | | | | l vs C: p<0.001 | | |
| | | | | SF-36 (PCS) change | | |
| | | | | from baseline, | | |
| | | | | mean±SD | | |
| | | | | I: 4.6±7.62 | | |
| | | | | C: -0.4±7.34 | | |
| | | | | l vs C: p<0.01 | | |
| | | | | SF-36 (MCS) change | | |
| | | | | from baseline, | | |
| | | | | mean±SD | | |
| | | | | I: 2.4±10.24 | | |
| | | | | C: -2.6±10.56 | | |
| | | | | l vs C: p<0.05 | | |
| Gordon et al 2006 | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
| | | | | mITT: all patients who | | Acceptable |
| [77] | Patients (≥18-years of | 80 mg of adalimumab at | Placebo to match | received ≥1 dose of test | AEs – week 0–12 | |
| | age), with plaque | week 0, followed by 40 | intervention | substance | | Comments |
| Multicentre study at 18 | psoriasis (≥1 year), BSA | mg every other week | | Safety analysis: all | Patients reporting any | Study supported by |
| sites in the US and | involvement ≥5%. All | starting week 1. | n=52 | patients who received | AE, n (%) | Abbott Laboratories. |
| Canada | patients were naïve to | Subcutaneous injection | | ≥1 dose of medication | I: 28/45 (62.2% | Several authors were |

| First Author Year Reference Country | Population Setting Study period Follow-up (FU) | Intervention | Comparison | Analysis model Results | Adverse events | Risk of bias Comment |
|--|--|--|--|---|--|-------------------------------------|
| Study design | | | | | | |
| RCT | anti-TNF treatment. Patients were stratified according to bodyweight (<70, 70– 100, and >100 kg) Baseline characteristics Female/Male. (%) I: 29%/71% C: 35%/65% Bodyweight (kg), mean (range) I: 93 (63–159) C: 94 (50–147) Ethnicity (Caucasian), % I: 89% C: 92% Study period March 2003 – June 2004 Follow-up period Double-blind placebo- controlled phase (12 weeks), followed by double-blind active treatment phase (week 12–24), open-label phase (24–60 weeks) | n=46 mITT: n =45 One patient did not receive study medication after randomisation <i>Drop-out rate,</i> <i>n (%)</i> 3/46 (6.5%) | Drop-out rate, n (%) 2/52 (3.8%) | Missing data: NRI for binary outcomes Results (12 weeks) PASI ≥75 – percent of patients, (%) I: 24/45 (53.3%) C: 2/52 (3.8%) I vs C: p<0.001 PASI 100 – percent of patients, (%) I: 5/45 (11.1%) C: 0/52 (0%) I vs C: p<0.001 | C: $35/52 (67.3\%)$ Any serious AE, n (%) I: $1/45 (2.2\%)$ C: $0/52 (0\%)$ Any infectious SAE I and C: 0 Any AE leading to discontinuation, n (%) I: $2/45 (4.4\%)$ C: $1/52 (1.9\%)$ AEs occurring $\ge 5\%$ of patients in any group and more frequent in I than C, $n (\%)$ Nausea, $n (\%)$ I: $3/45 (6.7\%)$ C: $3/52 (5.8\%)$ Injection site pain, $n (\%)$ I: $3/45 (6.7\%)$ C: $3/52 (5.8\%)$ Increasing blood triglycerides, $n (\%)$ I: $4/45 (8.9\%)$ C: $2/52 (3.8\%)$ | affiliated or employed by Abbott |

| | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|---------------------------|--------------------------------|------------------------|------------------|-------------------------|------------------------|--------------------------|
| First Author | Setting | | | | | Comment |
| Year | | | | Results | | |
| Reference | Study period | | | | | |
| Country | Follow-up (FU) | | | | | |
| Study design | | | | | | |
| Shikiar et al | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
| 2007 | | | | | | Acceptable |
| | Patients (≥18-years of | 80 mg of adalimumab at | Placebo to match | mITT: all patients | Presented in Gordon et | |
| [80] | age), with plaque | week 0, followed by 40 | intervention | randomized who | al | Comment |
| | psoriasis (≥1 year), BSA | mg every other week | | received ≥1 dose of | 2006, [2] | Study funded by |
| HRQOL outcomes. | involvement ≥5%. All | starting week 1. | n=52 | study medication | | Abbott/Abbott |
| Efficacy results reported | patients were naïve to | Subcutaneous injection | | | | Laboratories, carried |
| in Gordon K et al 2006 | anti-TNF treatment. | | Drop-out rate, | Results (12 weeks) | | out by United BioSource |
| [77] | Patients were stratified | n=46 | n (%) | | | Corporation. |
| | according to | mITT: n=45 | 2/52 (3.8%) | DLQI – total score | | Abbott/Abbott |
| Multicenter study at 18 | bodyweight (<70, 70– | One patient did not | | change, mean (95% Cl) | | Laboratories involved in |
| sites in the US and | 100, and >100 kg) | receive study | | l: -10.8 (-13.1 to 8.5) | | the analysis of data and |
| Canada | | medication after | | C: -1.3 (-3.3 to 0.7) | | preparation of the |
| | Baseline characteristics | randomisation | | T vs C: p<0.001 | | manuscript. Several |
| RCI | Female/Male, (%) | | | 50.50 | | authors had been or |
| | 1: 29%/71% | Drop-out rate, | | EQ-5D index score | | were employed by |
| | C: 35%/65% | n (%) | | change, mean (95% CI) | | Abbott/Abbott |
| | Ethnicity (Caucasian), | 3/46 (6.5%) | | 1: 0.21 (0.11 to 0.31) | | Laboratories or United |
| | (% | | | C: 0.01 (-0.07 to 0.10) | | Biosource |
| | 1. 89% | | | 1 vs c: p<0.001 | | |
| | C. 92% Rodyweight (kg) mean | | | EQ ED MAS change | | |
| | (rango) | | | EQ-3D VAS chunge, | | |
| | (1811ge) 1. 93 (63_159) | | | 1: 17 9 (10 5 to 25 2) | | |
| | (.93(03-133)) (.94(50-147)) | | | (10.5 (10.5 (0.25.2)) | | |
| | 0. 94 (30-147) | | | 1 vs C p< 0.01 | | |
| | Study period | | | 1 V3 C. P V0.001 | | |
| | March 2003 – June | | | SE-36 PCS score change | | |
| | 2004 | | | mean (95% CI) | | |
| | | | | 1: 3.6 (0.2 to 7.0) | | |
| | Follow-up period | | | C: 0.5 (-2.4 to 3.5) | | |
| | HROOL outcomes were | | | Lvs C: p=0.118 | | |
| | reported at the end of | | | | | |

| | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------------------|--|---------------------|---------------------|---|---------------------------|-------------------------|
| First Author | Setting | | | | | Comment |
| Year | | | | Results | | |
| Reference | Study period | | | | | |
| Country | Follow-up (FU) | | | | | |
| Study design | | | | | | |
| | the double-blind placebo-controlled phase (12 weeks). Study continued with a double-blind active treatment phase (week 12–24), open-label phase (24–60 weeks) | | | SF-36 MCS score, mean (95% Cl) I: 7.8 (3.9 to 11.8) C: -0.1 (-3.5 to 3.3) I vs C: p<0.001 | | |
| Menter A et al 2008 | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
| [78] | | | | ITT during first | | Acceptable |
| | Inclusion criteria | 80 mg of adalimumab | Placebo to match | 12 weeks | AEs (week 0–12) | |
| Multicenter study | Patients (≥18 years of | week 0, 40 mg of | intervention | Missing data: | | Comments |
| conducted in 67 centers | age) with clinical | adalimumab every | | NRI for PASI/PGA | Patients with any AE, n | Abbott Laboratories |
| in the US and 14 centers | diagnosis of psoriasis | other week starting | n=398 | LOCF for continuous | (%) | funded the agency, |
| in Canada | (≥6 months) and stable | from week 1 and | | variables (PASI score | I: 506/814 (62.2%) | participated in the |
| | plaque psoriasis (≥2 | continued through | Drop-out rate (week | improvement) | C: 221/398 (55.5%) | study design, data |
| RCT | months). Patients had | week 15 | 16), n (%) | | | collection, data |
| | moderate to severe | | 43/398 (10.8%) | Results | Patients with Serious | management, data |
| | plaque psoriasis with | Adalimumab | | Week 12 | AEs, n (%) | analysis, and |
| | BSA involvement of | administered | | | I: 15/814 (1.8%) | preparation of the |
| | ≥10%, a PASI score ≥12, | subcutaneously | | PASI ≥75 (week 12), | C: 7/398 (1.8%) | manuscript. Authors |
| | and a PGA of at least | | | n (%) | | affiliated with Abbott. |
| | moderate severity at | n=814 | | I: 554/814 (68.1%) | Patients with serious | |
| | baseline | _ | | C: 20/398 (5.0%) | infectious AEs. n (%) | |
| | | Drop-out rate (week | | Lvs C: p<0.001 | 1: 235/814 (28.9%) | |
| | Randomisation | 16), n (%) | | | C: 89/398 (22.4%) | |
| | stratified by center | 31/814 (3.8%) | | PASI ≥90 (week 12). (%) | I vs C: p<0.019 (Fisher's | |
| | | - , · (, | | 1: 37% | exact test) | |
| | Baseline characteristics | | | C: 2% | | |
| | Female/Male. (%) | | | Lvs C: p<0.001 | | |
| | I: 32.9%/67.1% | | | | | |

| | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------------------|---------------------------|-----------------------|------------|---------------------------|-------------------------------|---------------------------|
| First Author | Setting | | | | | Comment |
| Year | _ | | | Results | | |
| Reference | Study period | | | | | |
| Country | Follow-up (FU) | | | | | |
| Study design | | | | | | |
| | C: 35.4%/64.6% | | | PASI 100 (week 12), (%) | Patients with AEs | |
| | Ethnicity (Caucasian), % | | | I: 14% | leading to withdrawals, | |
| | l: 91.2% | | | C: <1% | n (%) | |
| | C: 90.2% | | | l vs C: p<0.001 | I: 14/814 (1.7%) | |
| | Bodyweight (kg), | | | | C: 8/398 (2.0%) | |
| | mean±SD | | | | | |
| | I: 92.3±23.0 | | | Week 16 | AEs reported by ≥5% in | |
| | C: 94.1±23,0 | | | | treatment group | |
| | , | | | PASI ≥75 (week 16) – | Nasopharvnaitis. | |
| | Study period | | | primary endpoint. | n (%) | |
| | Not stated | | | n (%) | 1: 43/814 (5.3%) | |
| | | | | 1: 578/814 (71.0%) | C: 26/398 (6.5%) | |
| | | | | C: 26/398 (6.5%) | | |
| | Follow-up | | | Lys C: p<0.001 | URTL n (%) | |
| | Placebo-controlled | | | | 1: 59/814 (7.2%) | |
| | phase 0–15 weeks | | | PASI >90 (week 16) (%) | (1.2,0) (1.2,0) (1.2,0) | |
| | Week 16–32 open-label | | | 1. 45% | 0.11,000 (0.070) | |
| | active treatment phase | | | C· 2% | | |
| | Week 33–52 withdrawal | | | $L_{VS} C: p < 0.001$ | | |
| | nhase | | | 1 13 C. P 0.001 | | |
| | pliase | | | | | |
| Gordon et al | Population | Intervention | | Effects from OI F-studies | Adverse events | Gordon et al |
| 2012 | Inclusion criteria in the | 80 mg of adalimumah | | are not reported | N events and rates | 2012 |
| [84] | initial RCT | week 0, 40 mg of | | are not reported | (events per 100 patient | 2012 |
| [0+] | Stable moderate to | adalimumah every | | | vears of exposure to | [84] |
| Multicenter study | | other week thereafter | | | adalimumah) | [0+] Multicenter study |
| conducted in 67 centers | | other week thereafter | | | adaimamaby | conducted in 67 centers |
| in the US and 1/ conters | (17,51,212) | Maximum nossihle | | | Adverse event leading | in the US and 1/ |
| in Canada | Inclusion criteria to OLF | exposure to | | | to discontinuation | centers in Canada |
| in callaua | nhace | Adalimumah | | | Voar 1: 61 (6 0) | |
| OLE to [78] | Group A: Entered the | 165 wooks | | | $V_{02}r 2 \cdot 1/(2.8)$ | OLE to [78] |
| | OIEW DASI < 75 at work | TOD WEEKS | | | V_{02} 2. 14 (2.0) | |
| REVEAL study | 16 | N in cafaty analysis | | | 1 Cal 3. 21 (4.0) | REVEAL study |
| REVEAL-SLUUY. | 10 | iv in sujety unulysis | | | | REVEAL-SLUUY. |

| | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------|---------------------------|--------------------------|------------|----------------|---------------------------|--------------|
| First Author | Setting | | | | | Comment |
| Year | _ | | | Results | | |
| Reference | Study period | | | | | |
| Country | Follow-up (FU) | | | | | |
| Study design | | | | | | |
| | Group B: Entered the | All exposure to | | | Serious adverse events | |
| | OLE w PASI ≥50–≤75 at | adalimumab in all | | | Year 1: 60 (5.9) | |
| | week 33 | patients except one | | | Year 2: 40 (7.9) | |
| | Group C: Re- | group who received | | | Year 3: 49 (9.3) | |
| | randomised to ADA | placebo after week 33 | | | | |
| | week 33, entered OLE | | | | Serious infection | |
| | week 52 | Year 1: n=1159 (1009.5 | | | Year 1: 18 (1.8) | |
| | Group D: Randomised | yrs of exposure) | | | Year 2: 3 (0.6) | |
| | to placebo in the initial | | | | Year 3: 9 (1.7) | |
| | RCT, started ADA week | Year 2: n=621 (504,8 yrs | | | | |
| | 16 | of exposure) | | | Tuberculosis | |
| | | | | | Year 1: 2 (<1) | |
| | Baseline characteristics | Year ≥3: n=443 (529.5 | | | Year 2:0 | |
| | See [78] | yrs of exposure) | | | Year 3: 1 (0.2) | |
| | | Drop-out rates in 4 | | | | |
| | Study period | groups during OLE | | | Allergic reactions | |
| | Not stated | phase (yr 2–3) | | | Year 1: 8 (0.8) | |
| | | 17–37% | | | Year 2: 2 (0.4) | |
| | Follow-up | | | | Year 3: 2 (0.4) | |
| | 52 weeks RCT in three | | | | | |
| | phases followed by 108 | | | | Congestive heart failure | |
| | or 113 OLE | | | | Year 1: 1 (<1) | |
| | | | | | Year 2: 1 (0.2) | |
| | | | | | Year 3: 4 (0.8) | |
| | | | | | | |
| | | | | | ivialignancies, exci non- | |
| | | | | | meiunoma skincancer | |
| | | | | | Voor 1: E (0 5) | |
| | | | | | Tear 1: 5 (0.5) | |
| | | | | | 1 = d1 = 2.5 (1.0) | |
| | | | | | 1 Cal 5. 5 (0.9) | |
| | | | | | Lymphoma | |

| | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|---------------------------|-------------------------------------|-------------------------|-------------------------|--|-----------------------|-------------------------|
| First Author | Setting | | | Posulto | | Comment |
| Reference | Study period | | | Results | | |
| Country | Follow-up (FU) | | | | | |
| Study design | | | | | | |
| | | | | | Year 1:0 | |
| | | | | | Year 2:0 | |
| | | | | | Year 3:0 | |
| Revicki et al 2007 | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of Bias |
| [79] | | | | | | Acceptable |
| | Inclusion criteria | 80 mg of adalimumab | Placebo to match | mITT: all patients | Reported by Menter et | |
| HRQOL outcomes. | Patients (≥18 years of | week 0, 40 mg of | intervention | randomized who | al 2008 [78] | Comments |
| Efficacy results reported | age) with clinical | adalimumab every | | completed baseline and | | Abbott Laboratories |
| in Menter et al | diagnosis of psoriasis | other week starting | Efficacy outcomes (ITT) | one follow-up DLQI | | funded the study, |
| 2008 [78] | (≥6 months) and stable | from week 1 and | n=398 | assement within 16 | | participated in the |
| | plaque psoriasis (≥2 | continued through | HRQOL outcomes | weeks | | study design, data |
| Multicentre study | months). Patients had | week 15 | (mITT) | | | collection, data |
| conducted in 67 centres | moderate to severe | | n=397 | Results (change from | | management, data |
| in the US and 14 centres | plaque psoriasis with | Adalimumab | | baseline at week 16) | | analysis, and |
| in Canada | BSA involvement of | administered | | | | preparation of the |
| | \geq 10%, a PASI score \geq 12, | subcutaneously | III drop-out rate (week | DLQI total, mean (95% | | manuscript. Authors |
| RCI | and a PGA of at least | | 16), n (%) | | | affiliated with Abbott. |
| | moderate severity at | Efficacy outcomes (111) | 43/398 (10.8%) | 1: -8.4 (-8.8 to -7.9) | | writing support |
| | baseline | n=814 | | C: -1.9 (-2.6 to -1.3) | | provided by JK |
| | Dandomication | | | TVS C: p<0.001 | | Associates inc. |
| | stratified by contor | (11111) | | SE 26 DCS moon (0E% | | |
| | stratified by certier. | 11-000 | | SF-50 PCS, Illeall (95% | | |
| | Baseline characteristics | | | 1:37(31to 43) | | |
| | Female/Male (%) | ITT dron-out rate (week | | (.0, 1, 0, 1, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, | | |
| | I. 32 9%/67 1% | 16) n (%) | | Lvs C: p<0.01 | | |
| | C· 35 4%/64 5% | 31/814 (3.8%) | | 1 10 0. 0 10.001 | | |
| | Ethnicity (Caucasian). % | 0-, 01 (0.0/0) | | SF-36 MCS, mean (95% | | |
| | 1: 91.3% | | | CI) | | |
| | C: 90.2% | | | I: 3.8 (3.1 to 4.5) | | |
| | Bodyweight (kg), | | | C: 0.3 (-0.7 to 1.4) | | |
| | mean±SD | | | I vs C: p<0.001 | | |
| | l: 92.3±23.0 | | | | | |

| | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|----------------------------|-------------------------|---------------------------|--------------------------|---------------------------|-------------------------|------------------------|
| First Author | Setting | | | | | Comment |
| Year | | | | Results | | |
| Reference | Study period | | | | | |
| Country | Follow-up (FU) | | | | | |
| Study design | 0.044102.0 | | | | | |
| | C: 94.1±23,0 | | | | | |
| | Study-period | | | | | |
| | Not stated | | | | | |
| | Not stated | | | | | |
| | Follow-up | | | | | |
| | Placebo-controlled | | | | | |
| | phase 0–15 weeks. | | | | | |
| | Week 16–32 active | | | | | |
| | treatment phase. Week | | | | | |
| | 33–52 withdrawal | | | | | |
| | phase | | | | | |
| | | | | | | |
| Saurat et al | Population | Intervention | Comparison | Method of analysis | Adverse events | Risk of bias |
| 2008 | | | | ITT for efficacy | | Acceptable |
| [72] | Patients (≥18 years of | Adalimumab 80 mg | | outcomes | AEs during placebo- | |
| | age), with moderate to | initial dose, 40 mg every | C: placebo | | controlled phase and | Comment |
| Multicenter study | severe psoriasis, with | two weeks, from week | | Missing data | follow-up period | |
| carried out at 28 sites in | PASI score≥10, BSA | 1 through week 15. | Placebo administered to | NRI for efficacy analysis | | Study funded by Abbot |
| Europe and Canada | involvement ≥10%, | Subcutaneous injection | match active | LOCF for mean PASI | Total adverse events, n | Laboratories, who also |
| | diagnosed with plaque | of adalimumab, oral | treatments | improvement | (%) | participated in |
| Study name | psoriasis (≥1 year), | placebo to match | | | I: 79/107 (73.8%) | designing, data |
| CHAMPION | which was stable (≥2 | control | Subcutaneous injections | Results (week 12) | C: 42/53 (79.2%) | collection / |
| | months). All patients | | with placebo to match | | | management / analysis |
| RCT | had to be naïve to TNF- | Background treatment | control | PASI ≥50 | Serious AEs, n (%) | and preparation of the |
| | antagonist therapy and | with 5 mg of oral folate | | I: 90.7% | I: 2/107 (1.9%) | manuscript. Several of |
| | methotrexate. | weekly. | Background treatment | C: 26.4% | C: 1/53 (1.9%) | the authors were |
| | Candidates for systemic | | with 5 mg of oral folate | l vs C: p<0.001 | | attiliated with Abbott |
| | or phototherapy | Randomised patients | weekly | | Serious infections | (employed/consultants) |
| | | n =108 | | PASI ≥75 | None reported | as well as other |
| | Baseline characterstics | Deserved | Deve de verte est de tra | 1: 76.9% | | pharmaceutical |
| | remale/Male, % | Drop-out rate | kandomised patients | C: 15.1% | Adverse events leading | companies. |
| | 1: 35.2%/64.8% | 4/108 (3.7%) | C: n=53 | 1 vs C: p<0.001 | to discontinuation, | |

| | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------|------------------------------|-------------------------|----------------|---------------------|--------------------------|--------------|
| First Author | Setting | | | | | Comment |
| Year | | | | Results | | |
| Reference | Study period | | | | | |
| Country | Follow-up (FU) | | | | | |
| Study design | | | | | (04) | |
| | C: 34.0%/66.0% | | | 54612.00 | n (%) | |
| | Ethnicity, Caucasian, % | | Drop-out rate | PASI ≥90 | 1: 1/10/ (0.9%) | |
| | 1: 95.4% | The study also included | C: 5/53 (9.4%) | 1: 48.1% | C: 1/53 (1.9%) | |
| | C: 92.5% | an intervention group | | C: 7.5% | Advance events (SEO) of | |
| | Bodyweight (kg), | treated with | | 1 vs C: p<0.001 | Adverse events, (25% of | |
| | | methotrexat | | DASI 100 | treatment group) | |
| | 1. 01.7±20.0 C· 82 6+10 0 | | | PASI 100 | treatment group) | |
| | C. 82.0119.9 | | | C = 0.0% | Infections (nonserious) | |
| | Study period | | | $L_{VS} C: p=0.009$ | n (%) | |
| | Not reported | | | 1 vs c. p=0.005 | 1. 51/107 (47 7%) | |
| | Notreported | | | | $(\cdot 23/53 (43.4\%))$ | |
| | Follow-up | | | Results (week 16) | 0. 23/33 (43.470) | |
| | Placebo-controlled | | | | Nasopharvnaitis. | |
| | phase (16 weeks), 70 | | | PASI≥50 | n (%) | |
| | day follow-up period | | | 1: 88.0% | 1: 30/107 (28.0%) | |
| | , | | | C: 30.2% | C: 11/53 (20.8%) | |
| | | | | I vs C: p<0.001 | | |
| | | | | | Headache, n (%) | |
| | | | | PASI ≥75 – primary | I: 14/107 (13.1%) | |
| | | | | endpoint | C: 5/53 (9.4%) | |
| | | | | I: 79.6% | | |
| | | | | C: 18.9% | Pruritus, n (%) | |
| | | | | I vs C: p<0.001 | I: 4/107 (3.7%) | |
| | | | | | C: 6/53 (11.3%) | |
| | | | | PASI ≥90 | | |
| | | | | I: 51.9% | Rhinitis, n (%) | |
| | | | | C: 11.3% | I: 3/107 (2.8%) | |
| | | | | l vs C: p<0.001 | C: 4/53 (7.5%) | |
| | | | | DAGLADO | No | |
| | | | | PASI 100 | INDUSED, N (%) | |
| | | | | 1. 10./% | 1. 4/ 1U/ (3./%) | |
| | | | | C. 1.9% | U: 4/53 (7.5%) | |

| | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|----------------------------|--------------------------|-------------------|--------------|-----------------------------|-------------------------|--------------------------|
| First Author | Setting | | | Describe | | Comment |
| Year | Ctudy pariod | | | Results | | |
| Country | Study period | | | | | |
| Study design | ronow-up (ro) | | | | | |
| Study design | | | | Lvs C: n=0.004 | | |
| | | | | 1 v3 C. p=0.004 | Rhinorrhea n (%) | |
| | | | | | 1: 3/107 (2.8%) | |
| | | | | | C: 3/53 (5.7%) | |
| | | | | | | |
| | | | | | Viral infection, | |
| | | | | | n (%) | |
| | | | | | I: 0/107 (0%) | |
| | | | | | C: 1/53 (1.9%) | |
| | | | | | | |
| | | | | | Arthralgia, n (%) | |
| | | | | | I: 6/107 (5.6%) | |
| | | | | | C: 1/53 (1.9%) | |
| Gordon et al | Adult patients (>18 | Adalimumab 80 mg | Placebo in | Analysis model | Adverse events | Risk of bias |
| 2015 | years) with chronique | week 0, and 40 mg | subcutaneous | ITT with missing values | Discontinued study drug | Acceptable |
| [81] | (≥6 months) moderate | every other week | injections. | assumed and imputated | due to AEs: | |
| | to severe plaque | thereafter in | | as non-responders. | I: 3/43 (7%) | Administration of |
| Multicenter study | psoriasis defined as BSA | subcutaneous | n=42 | | C: 3/42 (7.1%) | adalimumab was not |
| carried out at 43 sites in | ≥10%, ≥3 on PGA and a | injections. | | Results | | blinded, but the |
| North America and in | PASI score ≥12. Patients | | Drop-out | PASI 75 | More than 1 AE | evaluator of effect was |
| Europe | were to be treatment | n=43 | 3/42 (7.1%) | I: 25/43 (58.1%) | I: 24/43 (55.8%) | blinded to study group |
| | naïve to adalimumab. | | | C: 2/42 (4.8%) | C: 22/42 (52.4%) | assignment. |
| Study name | | Drop-out | | l vs C: p<0.001 | | |
| X-PLORE | Baseline characteristics | 4/43 (9.3%) | | | More than 1 serious AE | Comment |
| | Female/Male, % | | | PASI 90 | I: 1/43 (2.3%) | The main aim of the |
| RCT | 1: 30%/70% | | | I: 13/43 (30.2%) | C: 1/42 (2.4%) | study was to investigate |
| | C: 33%/67% | | | C: 1/42 (2,4%) | Information of | the effect of |
| | Age, mean yrs | | | 1 vs C: p<0.001 | | Guselkumab as |
| | | | | DACI 100 | 1: 5/43 (11.6%) | compared to |
| | C: 40.5 | | | PASI 100 | 0. 6/42 (1.4%) | auaiimumab or placebo. |
| | | | | 1. 11/43 (23.0%) C: 0/42 | Sorious infactions | botwoon adalimumah |
| | | | | C. 0/42 | Serious injections | between adaimumab |

| | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------------------|--|-------------------|------------------|---|---|--|
| First Author | Setting | | | | | Comment |
| Year | | | | Results | | |
| Reference | Study period | | | | | |
| Country | Follow-up (FU) | | | | | |
| Study design | | | | | | |
| | Ethnicity. % (caucasian/non- caucasian) I: 91%/9% C: 93%/7% Bodyweight (kg), mean±SD I: 91.6 kg (±19.88) C: 93.6 kg (±22.6) Psoriatic arthritis, % I: 26% C: 29% Study period October 2011–August 2013 Follow-up 16 wees | | | vs C: p<0.001 DLQI, mean change in score post baseline (±SD) : -10.1 (±9.0) C: -2.3 (±6.8) vs C: p<0.001 | I: 0 C: 0 Infections requiring treatment I: 2/43 (4.6%) C: 3/42 (7.1%) | and placebo is reported here. <i>Conflict of interest</i> The study was sponsored by Janssen Research and Development. |
| Cai et al | Adult patients (≥18 yrs) | Adalimumab 80 mg | Matching placebo | Analysis model | Adverse events | Risk of bias |
| 2016 | with chronique (≥6 | week 0, and 40 mg | | ITT – including all | | Acceptable |
| [76] | months) moderate to | every other week | n=87 | randomised and missing | At week 12 | |
| | severe plaque psoriasis | thereafter. | | values assumed and | Any adverse event | Comment |
| Multicentre study | and inadequate | | Drop-outs | imputated as non- | I: 158/338 (46.7%) | Conflict of interest |
| performed at 16 sites in | response or intolerance | n=338 | 1/87 (1%) | responders. | C: 33/87 (37.9%) | The study was |
| China. | to prior systemic | | | | | sponsored by AbbVie. |
| | therapies. Patients were | Drop-outs | | Results week 12 | AE leading to study | Authors received help |
| RCT | to be treatment naïve | 3/338 (0.9%) | | PASI 75 | discontinuation | with design, protocol |
| | to prior biologic | | | 1: 77.8% | 1: 2/338 (0.6%) | development and data |
| | therapies. | | | C: 11.5% | C: 0 | interpretation and |
| | | | | I vs C: p<0.001 | | medical writing from |
| | Baseline characteristics | | | | Any serious AE | AbbVie. |
| | <u>PASI, mean (±SD)</u> | | | PASI 90 | I: 4/338 (1.2%) | |

| First Author Year Reference Country Study design | Population Setting Study period Follow-up (FU) | Intervention | Comparison | Analysis model Results | Adverse events | Risk of bias Comment |
|--|---|---|---|--|---|---|
| | 22.7 (±11.83) Female/Male, % 33.3%/66.7% Age, mean yrs (±SD) 43.2 (±12.0) BMI, mean (±SD) 24.3 (±3.38) Psoriatic arthritis, % 12.5% Study period August 2012–December 2013 Follow-up 12 weeks placebo controlled phase, followed by 7 weeks open label period | | | I: 55.6% C: 3.4% I vs C: p<0.001 <i>PASI 100</i> I: 13.3% C: 1.1% I vs C: p=0.001 <i>DLQI, change in core</i> <i>from baseline</i> I: -9.07 C: -4.17 I vs C: p<0.05 | C: 3/87 (3.4%) Any infection I: 59/338 (17.5%) C: 14/87 (16.1%) At week 19 (all treated w adalimumab after week 12) Any infection 128/423 (30.3%) Serious infection 5/423 (1.2%) Lung infection 2/423 (0.5%) Pneumonia 2/423 (0.5%) Tuberculosis 2/423 (0.5%) | |
| Blauvelt et al 2017 [82] The VOYAGE I study | Population Patients (≥18-years of age), with moderate to | Intervention 80 mg of adalimumab at week 0, followed by 40 | Comparison Placebo injection at week 0, 4 and 12 | Analysis model ITT: all randomized patients included | Adverse events AEs – week 0–16 | Risk of bias Acceptable Comments |
| Multicentre study at 101 global sites RCT | severe plaque psoriasis (≥6 months), BSA involvement ≥10%, IGA ≥3 and PASI ≥12. All patients were | mg every other week starting week 1, through week 47. Subcutaneous injection | n=174 Drop-out rate, n (%) | Missing data: NRI for binary outcomes, and LOCF for continuous endpoints. | Patients reporting any AE, n (%) I: 170/333 (51.1%) C: 86/174 (49.4%) | Supported by Janssen Research & Development LLC, Spring House, PA |

| | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------|--|---|------------|---|--|--------------|
| First Author | Setting | | | | | Comment |
| Year | | | | Results | | |
| Reference | Study period | | | | | |
| Country | Follow-up (FU) | | | | | |
| Study design | | | | | | |
| Study design | candidates for systemic- or phototherapy, and had not had treatment with anti-TNF therapy within 3 months. They should never have been treated with guselkumab or adalimumab. Baseline characteristics Female/Male. (%) I: 25.4%/74.6% C: 31.6%/68.4% BMI (kg/m2), mean (SD) I: 29.8 (6.48) C: 28.9 (6.89) Ethnicity (White), % I: 277/334 (82.9%) C: 145/174 (83.3%) Age mean (SD) I: 42.9 (12.58) C: 44.9 (12.90) Study period December 2014-April 2016 | n=334 Drop-out rate, n (%) 10/334 (3%) The study also included intervention groups treated with guselkumab | 7/174 (4%) | Results (16 weeks) PASI 75 – received by percent of patients, (%) I: 244/334 (73.1%) C: 10/174 (5.7%) PASI 90, (%) I: 166/334 (49.7%) C: 5/174 (2.9%) PASI 100, (%) I: 57/334 (17.1%) C: 1/174 (0.6 %) DLQI, change in score from baseline, mean (SD): I: -9.3 (7.8) C: -0.6 (6.36) | Any AE leading to discontinuation, n (%) I: $3/333 (0.9\%)$ C: $2/174 (1.1\%)$ Serious Infections, n (%) I: $2/333 (0.6\%)$ C: $0/174 (0\%)$ AEs occurring $\geq 5\%$ of patients in any treatment group, n (%) Nasopharyngitis, n (%) I: $35/333 (10.5\%)$ C: $17/174 (9.8\%)$ URTI, n (%) I: $16/333 (4.8\%)$ C: $9/174 (5.2\%)$ Infections, n (%) I: $85/333 (25.5\%)$ C: $44/174 (25.3\%)$ Pruritus, n (%) I: $7/333 (2.1\%)$ C: $10/174 (5.7\%)$ | |
| | Follow-up period Double-blind placebo- controlled phase (16 weeks), followed by | | | | Injection site erythema, n (%) I: 15/333 (4.5%) C: 1/174 (0.6%) | |

| | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------------------|---|-------------------------|----------------------|---------------------------------------|-------------------------------|-----------------------------------|
| First Author | Setting | | | | | Comment |
| Year | | | | Results | | |
| Reference | Study period | | | | | |
| Country | Follow-up (FU) | | | | | |
| Study design | | | | | | |
| | active treatment phase until week 48, (open- label) | | | | | |
| Reich et al 2017 [83] | Population | Intervention | Comparison | Analysis model ITT: all randomized | Adverse events | Risk of bias Acceptable |
| | Patients (≥18-years of | 80 mg of adalimumab at | Placebo injection at | patients included. | AEs – week 0–16 | |
| The VOYAGE II study | age), with moderate to | week 0, followed by 40 | week 0, 4 and 12 | ' | | Comments |
| , | severe plaque psoriasis | mg every other week | | Missing data: | Patients reporting any | Supported by Janssen |
| Multicentre study at | (≥6 months), BSA | starting week 1, | n=248 | NRI. | AE, n (%) | Research & |
| 115 global sites | involvement ≥10%, IGA | through week 23. | | | I: 120/248 (48.4%) | Development LLC, |
| | ≥3 and PASI ≥12. All | Subcutaneous injection | Drop-out rate, | Results (16 weeks) | C: 111/248 (44.8%) | Spring |
| RCT | patients were | | n (%) | | | House, PA |
| | candidates for systemic- | n =248 | 15/248 (6%) | PASI 75 – received by | Any AE leading to | |
| | or phototherapy, and | | | percent of patients, (%) | discontinuation, n (%) | |
| | had not had treatment | Drop-out rate, | | I: 170/248 (68.5%) | I: 4/248 (1.6%) | |
| | with anti-TNF therapy | n (%) | | C: 20/248 (8.1%) | C: 2/248 (0.8%) | |
| | within 3 months. They | 11/248 (4.4%) | | | | |
| | should never have been | | | PASI 90, (%) | Serious Infections, n (%) | |
| | treated with | | | 1: 116/248 (46.8%) | 1: 2/248 (0.8%) | |
| | guselkumab or | The study also included | | C: 6/248 (2.4%) | C: 1/248 (0.4%) | |
| | adalimumab. | Intervention groups | | DASI 100 (%) | A For a conversion of SFO(of | |
| | Descling sharestaristics | treated with | | PASI 100, (%) | AES OCCUTTING 25% Of | |
| | | guseikumab. | | 1.51/248(20.0%) | treatment group p (%) | |
| | 1. 21 EV/CO EV | | | C. 2/248 (0.8%) | treutment group, n (%) | |
| | 1. 51,5%/08.5% C· 30.2%/69.8% | | | DLOL change in score | Nasonharynaitis n (%) | |
| | BMI (ka/m2) mean (SD) | | | from baseline mean | 1. 20/248 (8 1%) | |
| | 1: 29.6 (6.6) | | | (SD): | C: 16/248 (6.5%) | |
| | C: 29.6 (6.6) | | | 1: -9.7 (6.8) | 0.20/210 (0.0/0) | |
| | Ethnicity (White). % | | | C: -2.6 (6.9) | Headache. n (%) | |
| | 1: 200/248 (80.6%) | | | | 1: 5/248 (2.0%) | |
| | C: 206/248 (83.1%) | | | | C: 7/248 (2.8%) | |

| | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------|---|--------------|------------|----------------|---|--------------|
| First Author | Setting | | | | | Comment |
| Year | | | | Results | | |
| Reference | Study period | | | | | |
| Country | Follow-up (FU) | | | | | |
| Study design | | | | | | |
| | Age mean (SD) I: 43.2 (11.9) C: 43.3 (12.4) Study period November 2014-May 2016 | | | | URTI, n (%) I: 4/248 (1.6%) C: 10/248 (4.0%) Infections, n (%) I: 58/248 (23.4%) C: 46/248 (18.5%) | |
| | Follow-up period Double-blind placebo- controlled phase (16 weeks), followed by active treatment phase until week 28, and a randomized withdrawal and retreatment period (weeks 28-72). | | | | | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|---------------------|----------------------------|-----------------------|-----------------------|---------------------------|--------------------------|------------------------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| Saurat et al | Population | Intervention | Comparison | Method of analysis | Adverse events | Risk of bias |
| 2008 | | | | ITT for efficacy outcomes | | |
| [72] | Patients (≥18 years of | Adalimumab 80 mg | C: methotrexate | | AEs during placebo- | Acceptable |
| | age), with moderate to | initial dose, 40 mg | | Missing data | controlled phase and | |
| Multicenter study | severe psoriasis, with | every two weeks, from | Metotrexate (orally) | NRI for efficacy analysis | follow-up period | |
| carried out at 28 | PASI score≥10, BSA | week 1 through week | titrated from | LOCF for mean PASI | | Comment |
| sites in Europe and | involvement ≥10%, | 15. Subcutaneous | 7.5 mg/week, | improvement | Total adverse events, n | Comment |
| Canada | diagnosed with plaque | injection of | increased to 10 mg | | (%) | |
| | psoriasis (≥1 year), which | adalimumab, oral | week 2, and 15 mg | Results (week 12) | I: 79/107 (73.8%) | |
| Study name | was stable (≥2 months). | placebo to match | week 4. | | C: 90/110 (81.8%) | Study funded by Abbot |
| CHAMPION | All patients had to be | control | If PASI≥50 was | PASI ≥50 | | Laboratories, who also |
| | naïve to TNF-antagonist | | reached by or after | I: 90.7% | Serious AEs, n (%) | narticinated in designing |
| RCT | therapy and | Background treatment | week 8 the dosage | C: 54.5% | I: 2/107 (1.9%) | data collection / |
| | methotrexate. | with 5 mg of oral | was maintained. | l vs C: p<0.001 | C: 1/110 (0.9%) | management / analysis and |
| | Candidates for systemic | folate weekly. | Week 8, patients who | | | preparation of the |
| | or phototherapy | | did not achieve PASI- | PASI ≥75 | Serious infections | manuscript Several of the |
| | | Randomised patients | 50 had their dosage | I: 76.9% | None reported | authors were affiliated with |
| | Baseline characteristics | n =108 | increased to | C: 24.5% | | Abbott |
| | Female/Male, % | | 20 mg/week. By week | l vs C: p<0.001 | Adverse events leading | (employed/consultants) as |
| | 1: 35.2%/64.8% | Drop-out rate | 12, only patients who | | to discontinuation, | well as other pharmaceutical |
| | C: 33.6%/66.4% | 4/108 (3.7%) | did not achieve PASI- | PASI≥90 | n (%) | companies |
| | Ethnicity, Caucasian, % | | 50 and had PASI<50 | 1: 48.1% | I: 1/107 (0.9%) | |
| | 1: 95.4% | | at week 8 had dosage | C: 9.1% | C: 6/110 (5.5%) | |
| | C: 95.5% | The study also | increased to 25 mg | l vs C: p<0.001 | | |
| | Bodyweight (kg), | included a control | | | Adverse events, (≥5% of | |
| | mean±SD | group treated with | Background | PASI 100 | patients in any | |
| | 1: 81./±20.0 | ріасево | treatment with 5 mg | 1: 11.1% | treatment group) | |
| | C: 83.1±17.5 | | of oral folate weekly | C: 0.9% | | |
| | | | | 1 vs C: p=0.001 | Infections (nonserious), | |
| | Study period | | | | n (%) | |
| | Not reported | | Randomised patients | | 1: 51/10/ (47.7%) | |
| | | | C: n=110 | | C: 46/110 (41.8%) | |

Table 7.2. Adalimumab versus Methotrexate

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------|--------------------------|--------------|-----------------|--------------------|--------------------------------------|--------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| | Follow-up | | | Results (week 16) | Nasopharyngitis, | |
| | Placebo-controlled phase | | Drop-out rate | | n (%) | |
| | (16 weeks), 70 day | | C: 6/110 (5.5%) | PASI ≥50 | I: 30/107 (28.0%) | |
| | follow-up period | | | I: 88.0% | C: 26/110 (23.6%) | |
| | | | | C: 61.8% | | |
| | | | | l vs C: p<0.001 | Headache, n (%) | |
| | | | | | I: 14/107 (13.1%) | |
| | | | | PASI ≥75 – primary | C: 12/110 (10.9%) | |
| | | | | endpoint | | |
| | | | | I: 79.6% | Pruritus, n (%) | |
| | | | | C: 35.5% | I: 4/107 (3.7%) | |
| | | | | l vs C: p<0.001 | C: 2/110 (1.8%) | |
| | | | | | | |
| | | | | PASI ≥90 | Rhinitis, n (%) | |
| | | | | l: 51.9% | I: 3/107 (2.8%) | |
| | | | | C: 13.6% | C: 4/110 (3.6%) | |
| | | | | l vs C: p<0.001 | | |
| | | | | | Nausea, n (%) | |
| | | | | PASI 100 | I: 4/107 (3.7%) | |
| | | | | I: 16.7% | C: 8/110 (7.3%) | |
| | | | | C: 7.3% | | |
| | | | | l vs C: p=0.04 | Rhinorrhea, n (%) | |
| | | | | | I: 3/107 (2.8%) | |
| | | | | | C: 0/110 (0%) | |
| | | | | | | |
| | | | | | Viral infection, | |
| | | | | | n (%) | |
| | | | | | | |
| | | | | | C: 0/110 (5.5%) | |
| | | | | | Arthralaia n (%) | |
| | | | | | 1. 6/107 (5. 6%) | |
| | | | | | (.0, 10) (0.0%) (.0, 5/110 (1.5%) | |
| | | | | | C. 5/ 110 (4.5/0) | |
| | | | | | | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|-------------------|-----------------------------|---------------------------|------------------------|---------------------------|---------------------------------|-------------------------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| Papp et al | Population | Intervention | Comparison | Method of analysis | Adverse events | Risk of bias |
| 2017 | | | | ITT for efficacy outcomes | | |
| [85] | Patients (≥4 and <18 | Adalimumab (I1) 0.8 | Metotrexat (orally) | | AEs during study | Acceptable |
| | years of age) with a | mg/kg (up to 40 mg | titrated from 0.1 | Missing data | periods 1 and 2 (16+26 | |
| Multicenter study | bodyweight of at least 13 | total dose), or (12), 0.4 | mg/kg) (7.5 mg/week | NRI for categorical | weeks) | Comment |
| carried out at 38 | kg, with severe plack | mg/kg (up to 20 mg | at base line, week 0), | variables; LOCF for | | Comment |
| clinics in 13 | psoriasis (PGA≥4, | total dose) | increased to 0.4 | continuous variables. | Total adverse events, n | Funded by AbbVie |
| countries. | BSA≥20%, PASI ≥20, | subcutaneously at | mg/kg (up to 25 | | (%) | Tunded by Abbvie. |
| D.CT | CDLQI210) for at least 6 | week U, and then | mg/week total dose), | Results (week 16) | 11: 26/38 (68%) | Investigators gathered the |
| RCI | months (stable for ≥ 2 | every other week, | once weekly. | DACI 75 | 12: 30/39 (77%) | data, the funder did the |
| | months), and who had | starting at week 1. | Falia asid | PASI 75 | C: 28/37 (76%) | analysis, and the authors and |
| | the responded to topical | Falia asid | | 11: 22/38 (57.9%) | | the funder interpreted the |
| | therapy or (if <12 years | FOIIC acid | supplementation was | 12: 17/39 (43.6%) | Severe AES, n (%) | data. AbbVie contributed to |
| | of age) heliotherapy of | supplementation was | provided as | C: 12/37 (32.4%) | 11. 1/38 (3%) 12. E/20 (12%) | the study design and was |
| | phototherapy. | provided as | guidelines | 11 vs C, p=0.02079 | (12.5)55(15%) | involved in the collection, |
| | Pandomisation was | guidelines | guidennes. | RASIOO | C. 2/37 (3%) | analysis, and interpretation |
| | stratified by history of | guiueimes. | Randomised nationts | 11·11/38 (20%) | Serious AEs. n (%) | of the data and in the |
| | etanercent treatment | Randomised nationts | C: n=37 | 12: 12/30 (25%) | 11.0/38 (0%) | writing, review, and approval |
| | etanercept treatment. | 11 · n = 38 | C. 11-57 | (2.12/39(31%)) | 12. 3/39 (8%) | of the publication |
| | Baseline characteristics | 12: n = 39 | Dron-out rate | 11 vs C n=0.466 | $(0.0)^{12}$ | |
| | Female/Male % | 12.11 00 | C· 5/37 (13 5%) | 12 10 0, p 0.100 | | |
| | 11: 55%/45% | Dron-out rate | 0.0707 (10.070) | PASI 100 | Serious infections, n (%) | |
| | 12: 46%/54% | 11: 1/38 (2.6%) | | 11: 7/38 (18%) | 11: 0/38 (0%) | |
| | C: 70%/30% | 12: 3/39 (7.7%) | | 12: 4/39 (10%) | 12: 1/39 (3%) | |
| | Ethnicity, White, % | , , , | | C: 1/37 (3%) | C: 0/37 (0%) | |
| | 11: 35/38 (92%) | | | l1 vs C, p=0.056 | , , , | |
| | 12: 34/39 (87%) | | | | Adverse events, (≥5% of | |
| | C: 34/37 (92%) | | | CDLQI, change from | patients in any | |
| | Bodyweight (kg), mean | | | baseline, mean (SD) | treatment group) | |
| | (SD) | | | l1: -6.6 (6.2) (n=38) | | |
| | l1: 50.8 (19.90) | | | l2: -4.9 (6.2) (n=38) | Infections (non- | |
| | 12: 50.2 (22.5) | | | C: -5.0 (7.1) (n=36) | serious), n (%) | |
| | C: 53.1 (18.7) | | | l1 vs C, p=0.304 | I1: 17/38 (45%) | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------|--------------------------|--------------|------------|----------------|--------------------------|--------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| | Age (years), mean (SD) | | | | 12: 22/39 (56%) | |
| | 11: 13.0 (3.3) | | | | C: 21/37 (57%) | |
| | 12: 12.6 (4.4) | | | | | |
| | C: 13.4 (3.5) | | | | Allergic reaction, n (%) | |
| | Previous etanercept | | | | l1: 0/38 (0%) | |
| | treatment | | | | I2: 1/39 (3%) | |
| | 11: 4/38 (11%) | | | | C: 2/37 (5%) | |
| | 12: 4/39 (10%) | | | | | |
| | C: 3/37 (8%) | | | | Injection site reaction, | |
| | | | | | n (%) | |
| | Study period | | | | 11: 4/38 (11%) | |
| | Dec 14, 2010 – Feb 5, | | | | 12: 3/39 (8%) | |
| | 2015 | | | | C: 3/37 (8%) | |
| | | | | | | |
| | Follow-up | | | | | |
| | The study included four | | | | | |
| | periods: (1) Placebo- | | | | | |
| | controlled phase (16 | | | | | |
| | weeks); (2) up to 36- | | | | | |
| | week withdrawal; (3) 16- | | | | | |
| | week re-treatment; and | | | | | |
| | (4) 52-week long-term | | | | | |
| | follow-up. | | | | | |

BSA – body surface area; DLQI – dermatology life quality index; HRQOL – health related quality of life; ITT – intention-to-treat; LOCF – last observation carried forward; MCS – mental component summary score; mITT – modified intention-to-treat; NRI – non-responder imputation; PASI – psoriasis area and severity index; PCS – physical component summary score; PGA – physician's global assessment; SD – standard deviation; VAS – visual analogue scale

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|-------------------------|--------------------------|-------------------------|-----------------------|-----------------------|----------------------------|-------------------------|
| Year | Setting | | | | | |
| Reference | | | | Results | | Comment |
| Country | Study period | | | | | |
| Study design | Follow-up | | | | | |
| van de Kerkhof et al | Population | Intervention (I) | Comparison (C) | Analysis Model | Adverse events | Risk of bias |
| 2008 | Inclusion criteria | Etanercept 50 mg per | Placebo for 12 weeks, | Modified ITT (all who | AEs (week 0–12) | Acceptable |
| [86] | Adult patients with | week for 24 weeks (sub- | and etanercept 50 mg | received ≥1 dose test | | |
| | stable plaque psoriasis | cutaneous injections, | per week for 12 weeks | substance) | Patients with serious | Comment |
| Multicentre study | involving ≥10% of body | once weekly) | thereafter (subcutan- | | AEs, n (%) | Conflict of interest |
| performed in nine | surface area and PASI | | eous injections, once | Missing data | I: 2.1% | Sponsored by Wyeth |
| European countries | ≥10. Non-responders or | n=96 | weekly). | LOCF | C: 6.5% | Parmaceuticals, the |
| (Belgium, France, | intolerant to | | | | | manufacturer of the |
| Germany, Hungary, | phototherapy or other | Drop-out rate at 12 | n=46 | Results | AEs leading to | test substance. Several |
| Italy, the Netherlands, | systemic therapy | weeks | | PASI ≥50 | discontinuation, n (%) | authors were employed |
| Poland, Romania and | | 6/96 (6.3%) | Drop-out rate at | I: 66/96 (68.8%) | I: 3/96 (3.1%) | by the study sponsor |
| Spain) | BMI (inclusion criteria) | | 12 weeks | C: 4/46 (8.7%) | C: 3/46 (6.5%) | |
| | <38 kg/m ² | | 10/46 (21.7%) | I vs C: p<0.0001 | | |
| RCT | | | | | Reported treatment | |
| | Treatment naive to any | | | PASI ≥75 (primary | emergent adverse | |
| | TNF-inhibitor | | | endpoint) | events occurring in >5% | |
| | | | | I: 36/96 (37.5%) | of participants, | |
| | Baseline characteristics | | | C: 1/46 (2.2%) | | |
| | Female/Male, (%) | | | I vs C: p<0.0001 | Headache, n (%) | |
| | I: 38.8%/61.5% | | | | I: 13/96 (13.5%) | |
| | C: 45.6%/54.4% | | | PASI ≥90 | C: 1/46 (2.2%) | |
| | | | | I: 13/96 (13,5%) | I vs C: p=0.04 | |
| | Ethnicity | | | C: 1/46 (2,2%) | | |
| | No information | | | I vs C: p<0.05 | Injection-site reaction, n | |
| | BMI (kg/m²), mean±SD | | | | (%) | |
| | l: 27.5±4.1 | | | DLQI (mean | I: 16/96 (16.7%) | |
| | C: 26.8±5.9 | | | improvement on DLQI- | C: 1/46 (2.2%) | |
| | | | | score) | I vs C: p=0.01 | |
| | | | | I: 7,4 (54.5%) | | |
| | Study period | | | C: 1,2 (5.2%) | Influenza-like syndrome, | |
| | June 2006–May 2007 | | | I vs C: p<0.0001 | n (%) | |

Table 7.3. Etanercept versus placebo

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|-------------------------|---|--------------|------------|----------------|---|--------------|
| Year | Setting | | | | | |
| Reference | | | | Results | | Comment |
| Country | Study period | | | | | |
| Study design | Follow-up | | | | | |
| Country Study design | Study period Follow-up 12 weeks placebo controlled phase (plus 12 weeks OLE, not presented here) | | | | I: 10/96 (10.4%) C: 0/46 (0%) I vs C: p=0.03 Asthenia, n (%) I: 5/96 (5.2%) C: 0/46 (0%) Diarrhoea, n (%) I: 5/96 (5.2%) C: 1/46 (2.2%) Pruritus, n (%) I: 14/96 (14.6%) C: 4/46 (8.7%) Psoriasis, n (%) I: 2/96 (2.1%) C: 3/46 (6.5%) Pharyngitis/laryngitis, n (%) I: 5/06 (5.2%) | |
| | | | | | I: 5/96 (5.2%) C: 1/46 (2.2%) URTI, n (%) I: 9/96 (9.4%) C: 5/46 (10.9%) | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------------------|--------------------------|-------------------------|--------------------------|-------------------------|---------------------------|--------------------------|
| Year | Setting | | | | | |
| Reference | | | | Results | | Comment |
| Country | Study period | | | | | |
| Study design | Follow-up | | | | | |
| Tyring et al | Population | Intervention (I) | Comparison (C) | Analysis model | Adverse events | Risk of bias |
| 2006 | Inclusion criteria | Etanercept | Placebo (two injections, | mITT (all who received | At least one adverse | Acceptable |
| [92] | Adult patients (>18 | 100 mg/week (two | twice weekly) | ≥1 dose included) | event (headache, | |
| | years) with active, | injections of 25 mg per | | | injections site bruising, | Comment |
| Multicentre study | stable psoriasis | dose, twice weekly) | n=309 | Results – week 12 | fatigue or arthralgia) | Conflict of interest |
| performed at 39 sites in | involving ≥10% body | | | | I: 153/312 (49.0%) | Sponsored by the |
| the USA and in Canada | surface area and PASI | n=311 | Drop-out rate | PASI ≥50, n (%) | C: 137/306 (44.8%) | Immunex/Amgen the |
| | ≥10. Earlier photo- | | 17/309 (5.5%) | I: 229/311 (74%) | | manufacturer of the |
| RCT | therapy or systemic | Drop-out rate | | C: 43/306 (14%) | Withdrew due to | test substance. |
| | treatment (or candidate | 6/311 (1.9%) | | I vs C mean difference | adverse event | Immunex was involved |
| | for phototherapy) | | | [95% CI]: 60% [53, 66], | I: 4/312 (1.3%) | in the design of the |
| | required | | | p<0.0001 | C: 5/306 (1.6%) | study and Amgen in the |
| | | | | | | analysis of data and the |
| | Baseline characteristics | | | PASI ≥75 (primary | At least 1 serious | writing of the |
| | Female/Male, (%) | | | outcome) | adverse event | manuscript |
| | I: 34.7%/65.3% | | | I: 147/311 (47%) | I: 6/312 (1.9%) | |
| | C: 29.6%/70.4% | | | C: 15/306 (5%) | C: 3/306 (1.0%) | |
| | | | | I vs C mean difference | | |
| | Ethnicity (Caucasian), | | | [95% Cl]: 42% [36, 48], | Reported treatment | |
| | (%)* | | | p<0.0001 | emergent adverse | |
| | I: 90.4% | | | | events occurring in >5% | |
| | C: 87.9% | | | PASI ≥ 90 | of participants | |
| | Bodyweight (kg), mean* | | | I: 65/311 (21%) | | |
| | I: 92.6 | | | C: 4/306 (1%) | At least one infection | |
| | C: 91.0 | | | I vs C mean difference: | (nasopharyngitis, upper | |
| | *Information from | | | 20% [15, 24], p<0.0001 | respiratory tract | |
| | Tying et al 2008 | | | | infection, sinusitis) | |
| | Treatment naive to any | | | DLQI (mean | I: 87/312 (27.9%) | |
| | TNF-inhibitor. | | | improvement on DLQI- | C: 71/306 (23.2%) | |
| | | | | score) | At least one injections | |
| | Study period | | | I: 69.1% | site reaction | |
| | June 2003–January | | | C: 22.1% | I: 34/312 (10.9%) | |
| | 2004 | | | I vs C mean difference | C: 2/306 (0.7%) | |
| | | | | [95% CI]: 47% [40,54] | | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|----------------|------------------------|---------------------------|------------|--------------------------|--------------------------------|----------------|
| Year | Setting | | | | | |
| Reference | | | | Results | | Comment |
| Country | Study period | | | | | |
| Study design | Follow-up | | | | | |
| | Follow-up | | | | | |
| | 12-week placebo- | | | | | |
| | controlled trial, | | | | | |
| | followed by an 84-week | | | | | |
| | OLE | | | | | |
| | | | | | | |
| Tyring et al | Population | Intervention | | Analysis model | Adverse events | [101] |
| 2007 | See [[92] | Etanercept | | All initially randomised | Discontinued OLE due to | OLE efter [92] |
| [101] | Study period | 100 mg/week (two | | patients included. All | adverse events, n (%) | |
| | | injections of 25 mg per | | data treated as | 11: 15/287 (5.3%) | |
| OLE after [92] | Follow-up | dose, twice weekly) | | observational: no | 12: 16/304 (5.2%) | |
| | 12+84 weeks | | | imputation of missing | | |
| | | n=591 of 618 (95.6%) | | values. Calculations of | Events per 100 patient | |
| | | randomised patients | | exposure adjusted | <u>years under exposure to</u> | |
| | | from the original RCT | | adverse event rates per | etanercept treatment. | |
| | | (RN 1510) entered the | | 100 patient years. | | |
| | | OLE. | | | All non-infectious | |
| | | | | | adverse events | |
| | | I1 (randomised to | | | 158.0 | |
| | | etanercept in the initial | | | | |
| | | 12 week RCT: n=304 | | | All infections | |
| | | | | | 103.9 | |
| | | 12 (randomised to | | | | |
| | | etanercept in the initial | | | Serious infections | |
| | | 12 week RCT: n=287 | | | 1.2 | |
| | | Total avpacura in the | | | Carious non infantious | |
| | | rotur exposure in the | | | serious non-injectious | |
| | | (includes 12 weeks | | | | |
| | | (Includes 12 weeks RCI) | | | 1.1 | |
| | | Soora harieur Ars | | | Death | |
| | | Drop out rate | | | | |
| | | 127/501 (21 50/) | | | 0.2 | |
| | | 121/091 (21.0%) | | | | |
| | | | | | | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------|--------------|--------------|------------|----------------|-----------------------|--------------|
| Year | Setting | | | | | |
| Reference | | | | Results | | Comment |
| Country | Study period | | | | | |
| Study design | Follow-up | | | | | |
| | | | | | All injection site | |
| | | | | | reactions | |
| | | | | | 12.2 | |
| | | | | | Most common serious | |
| | | | | | non-infections AF's | |
| | | | | | Myocardial infarction | |
| | | | | | 0.4 | |
| | | | | | | |
| | | | | | Basal cell carcinoma | |
| | | | | | 0.3 | |
| | | | | | | |
| | | | | | Depression | |
| | | | | | 0.3 | |
| | | | | | Most frequent AF·s | |
| | | | | | Headache | |
| | | | | | 9.2 | |
| | | | | | | |
| | | | | | Injection site | |
| | | | | | hemorrhage | |
| | | | | | 5.8 | |
| | | | | | Authoralain | |
| | | | | | Arthraigia A 9 | |
| | | | | | 4.0 | |
| | | | | | Back pain | |
| | | | | | 5.2 | |
| | | | | | | |
| | | | | | <u>Most frequent</u> | |
| | | | | | infections | |
| | | | | | URTI | |
| | | | | | 20.2 | |
| | | | | | | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------------------|---------------------------|--------------------------|-----------------------|---------------------|-------------------------|--------------------------|
| Year | Setting | | | | | |
| Reference | | | | Results | | Comment |
| Country | Study period | | | | | |
| Study design | Follow-up | | | | | |
| Paller et al | Population | Intervention (I) | Comparison (C) | Analysis model | Adverse events | Risk of bias |
| 2008 | Inclusion criteria | Etanercept, 0.8 mg/kg | Placebo for 12 weeks, | ITT (all randomised | Exposure adjusted | Acceptable |
| [91] | Children aged 4–17, | up to a maximum dose | and thereafter | patients) | adverse events through | |
| Etanercept Psoriasis | with stable plaque | of 50 mg/week | etanercept, 0.8 mg/kg | | week 48 (occuring ≥10 | Comment |
| Study Group | psoriasis for at least | (subcutaneous | up to a maximum dose | Missing data | times in the etanercept | Conflict of interest |
| | 6 months involving | injections, once weekly) | of 50 mg/week | NRI | group/100 patient | Sponsored by |
| | >10% body surface | | (subcutaneous | | years) | pharmaceutical |
| Multicentre study | area, PGA score ≥3, and | n=106 (of which 38 | injections) | Results – week 12 | | company |
| performed at 42 sites in | with PASI >12. Earlier or | aged 4–11 and 68 aged | | PASI ≥50 | Total n of adverse | (Immunex/Amgen and |
| the USA and in Canada | current phototherapy | 12–17) | n=105 (of which 38 | I: 79/106 (75%) | events (infections) | by Wyeth |
| | or systemic treatment, | | aged 4–11 and 67 aged | C: 24/105 (23%) | I: 554.5/100 years | Parmaceuticals) which |
| RCT | or poorly controlled | Drop-out rate at 12 | 12–17) | l vs C: p <0.001 | C: 765.4/100 years | contributed in data |
| | disease with topical | weeks | | | | collection, analysis and |
| | treatment | 6/100 (6.0%) | Drop-out rate at | PASI ≥75 (primary | Selected events through | interpretation of data, |
| | | | 12 weeks | endpoint) | week 48 (n exposure | and in writing the |
| | BMI (median at | | 27/105 (25.7%) | I: 60/106 (57%) | adjusted events/100 | report |
| | baseline) was 18.1 in | | | C: 12/105 (11%) | years) after etanercept | |
| | age group 4–11 (36% of | | | l vs C: p <0.001 | exposure | |
| | patients) and 25.2 in | | | | | |
| | age group 12–17 (64% | | | PASI ≥90 | Adverse events leading | |
| | of patients) | | | I: 29/106 (27%) | to study withdrawal | |
| | | | | C: 7/105 (7%) | I: 2.4/100 years | |
| | Baseline characteristics | | | l vs C: p <0.001 | C: 0/100 years | |
| | Female/Male, (%) | | | | | |
| | I: 48.1%/51.9% | | | CDLQI improvement | Adverse event excluding | |
| | C: 49.5%/50.5% | | | I: 55/106 (52%) | infection | |
| | Ethnicity (Caucasian), | | | C: 19/105 (18%) | I: 287.6/100 years | |
| | (%) | | | l vs C: p <0.001 | C: 430.5/100 years | |
| | I: 78.3% | | | | | |
| | C: 71.4% | | | | Infection | |
| | Bodyweight (kg), | | | | I: 229.3/100 years | |
| | median [range] | | | | C: 308.3/100 years | |
| | I: 59.6 [17.7, 168.3] | | | | | |
| | C: 59.8 [17.2, 131.5] | | | | | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|------------------------|----------------------------|--------------------------|------------------|--------------------------|-------------------------|-----------------------|
| Year | Setting | | | | | |
| Reference | | | | Results | | Comment |
| Country | Study period | | | | | |
| Study design | Follow-up | | | | | |
| | | | | | Severe adverse event, | |
| | Treatment naive to any | | | | excluding infection | |
| | TNF-inhibitor | | | | I: 1.8/100 years | |
| | | | | | C:15.9/100 years | |
| | Study period | | | | | |
| | September 2004– | | | | Severe infection | |
| | November 2005 | | | | I: 2.4/100 years | |
| | | | | | C: 0 | |
| | Follow-up | | | | | |
| | 12 weeks RCT plus 24 | | | | Injection site reaction | |
| | weeks OLE, plus 12 | | | | 1: 37.6/100 years | |
| | weeks withdrawal and | | | | C: 26.6/100 years | |
| | retreatment RCI | | | | | |
| Langley et al | Demulation study | Intervention (I) | Commerciaers (C) | Analusia madal | A duaraa ayaa ta | Diele of hiss |
| Langley et al | Population, study | Intervention (I) | Comparison (C) | Analysis model | Adverse events | RISK OF DIAS |
| 2011 | See [01] | 266 [31] | 266 [31] | 266 [31] | 266 [31] | Acceptable |
| [90] | 266 [21] | | | Poculto wook 12 | | Commont |
| For main publication | | | | (not reported under [2]) | | Conflicts of interest |
| see Paller et al. 2008 | | | | (not reported under [5]) | | |
| [Q1] | | | | total score +SD | | 266 [21] |
| | | | | 1. 5 1+5 6 | | |
| вст | | | | $C \cdot 3.1 + 5.1$ | | |
| | | | | Lvs C: not given | | |
| Paller et al | Population and study | Intervention | | Analysis model | Adverse events | Risk of bias |
| 2016 | period | Etanercept 0.8 mg/kg | | All patients who | Discontinued study | Not assessed |
| [103] | See [91] | once weekly (to a | | received ≥1 dose of | 112/182 (61.5%) | |
| L J | | maximum of 50 mg per | | study drug were | , (, | Comment |
| OLE efter [91] | Follow up | week) in s.c. injections | | included in the | Discontinued due to | Risk of bias not |
| | 5 yrs or until the patient | for up to 264 weeks | | analyses. | adverse event | assessed as only |
| | reached adulthood at | | | | 5/182 (2.7%) | observational data on |
| | 18 yrs of age | n=182 | | The subset of patients | | AE:s were collected. |
| | | (182/211, 86.3%, | | who were under 18 and | | |
| | | patients randomised in | | still in study at week | | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------|--------------|----------------------|------------|-------------------------|-------------------------------|--------------|
| Year | Setting | | | | | |
| Reference | | | | Results | | Comment |
| Country | Study period | | | | | |
| Study design | Follow-up | | | | | |
| | | the initial RCT also | | 264 were included in | Adverse events | |
| | | enrolled in the OLE) | | the analyses of growth. | expressed as incidence | |
| | | | | | rates/100 patient yrs | |
| | | Drop-out rate | | | Serious adverse events | |
| | | 69/181 (37.9%) | | | All occurred with an | |
| | | dropped out before | | | event rate of 0.2/100 | |
| | | week 264 | | | patient yrs (or 1 event | |
| | | | | | over the study): | |
| | | | | | abortion induced, | |
| | | | | | anxiety, cellulitis, | |
| | | | | | infectious | |
| | | | | | mononucleosis, | |
| | | | | | osteonecrosis, post | |
| | | | | | operative intestinal | |
| | | | | | obstruction, thyroid | |
| | | | | | cyst. | |
| | | | | | Common advance avante | |
| | | | | | <u>Common adverse events</u> | |
| | | | | | <u>occurring at a rate of</u> | |
| | | | | | <u>25/100 pullent yrs</u> | |
| | | | | | 22.2 | |
| | | | | | 23.2 | |
| | | | | | Nasonharynaitis | |
| | | | | | 15.0 | |
| | | | | | 2010 | |
| | | | | | Streptococcal | |
| | | | | | pharvnaitis | |
| | | | | | 5.8 | |
| | | | | | | |
| | | | | | Sinusitis | |
| | | | | | 5.0 | |
| | | | | | | |
| | | | | | | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|----------------------|--------------------------|---------------------|--------------------------|--------------------------|-------------------------|---------------------------|
| Year | Setting | | | | | |
| Reference | | | | Results | | Comment |
| Country | Study period | | | | | |
| Study design | Follow-up | | | | | |
| Bachelez et al | Population | Intervention (I) | Comparison (C) | Analysis model | Adverse events | Risk of bias |
| 2015 | Inclusion criteria | Etanercept | Placebo injections twice | ITT (all randomised who | | Acceptable |
| [97] | Adult patients ≥18 yrs | 100 mg/week | weekly | received at least 1 dose | AEs at 12 weeks | |
| | with chronic stable | (subcutaneous | | of study drug) | Treatment emergent | Comment |
| Multicentre study | plaque psoriasis for at | injections of 50 mg | n=108 | | adverse events (TEAE)* | The study was designed |
| performed at 122 | least 12 months, | twice weekly) | | Missing data | Any TEAE | primarily to investigate |
| centres all over the | involving at least 10% | | Drop-out rate | NRI | I: 192/335 (57%) | non-inferiority of |
| world (excluding the | body surface area, with | n=336 | 13/108 (12%) at | | C: 55/107 (51%) | tofacitinib vs etanercept |
| USA and Canada) | PASI ≥12 and PGA | | 12 weeks | Results – week 12 | | or placebo. |
| | (physician's) assessed | Drop-out rate | | PASI ≥50 | Serious TEAEs | |
| RCT | as moderate to severe. | 23/336 (6.8%) at | | I: 269/335 (80.3%) | I: 7/335 (2%) | Conflict of interest |
| | Non-responder or | 12 weeks | | C: 22/107 (20.6%) | C: 2/107 (2%) | Sponsored by |
| | intolerant to | | | I vs C: p<0.0001 | | pharmaceutical |
| | conventional systemic | | | | Discontinuation due to | company (Pfizer Inc.) |
| | therapy. No previous | | | PASI ≥75 (co-primary | TEAE | which contributed in |
| | exposure to etanercept | | | outcome) | I: 11/335 (3%) | data collection, analysis |
| | | | | I: 197/335 (58.8%) | C: 4/107 (4%) | and interpretation of |
| | Baseline charactersitics | | | C: 6/107 (5,6%) | | data, and in writing the |
| | Female/Male, % | | | l vs C: p<0.0001 | Worsening of PASI score | report |
| | I: 30%/70% | | | | ≥25% during treatment | |
| | C: 34%/66% | | | PASI ≥90 | I: 6/335 (1.8%) | |
| | Ethnicity (Caucasian), % | | | I: 108/335 (32,2%) | C: 17/107 (15.9%) | |
| | I: 87% | | | C: 1/107 (0,9%) | | |
| | C: 84% | | | l vs C: p<0.0001 | Post treatment | |
| | Bodyweight (kg), | | | | Worsening of PASI score | |
| | median [range] | | | DLQI, ≥5 point reduction | ≥25% post treatment | |
| | I: 82.0 [48.0, 143.5] | | | from baseline | I: 0/335 (0%) | |
| | C: 80.2 [46.5, 130.0] | | | I: 218/292 (74.7%)* | C: 1/107 (1%) | |
| | | | | C: 28/88 (31.8%)* | | |
| | Study period | | | I vs C: p<0.0001 | *Most common TEAE | |
| | November 2010– | | | | was infection, in most | |
| | September 2012 | | | *lower response rates | cases respiratory | |
| | | | | | infections | |
| | | | | | | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------------------|--------------------------|-------------------------|-----------------------|-----------------------------------|-------------------------|-----------------------|
| Year | Setting | | | | | |
| Reference | | | | Results | | Comment |
| Country | Study period | | | | | |
| Study design | Follow-up | | | | | |
| | Follow-up | | | | | |
| | 12 weeks treatment | | | | | |
| | plus 2–4 weeks post | | | | | |
| | treatment | | | | | |
| Papp et al | Population | Intervention (I) | Comparison (C) | Analysis model | Adverse events | Risk of bias |
| 2005 | Adult patients (≥18 | | Placebo for 12 weeks | ITT (all randomised who | Proportion afflicted by | Acceptable |
| [87] | years), with stable | Intervention 1 | and etanercept | received at least 1 dose | adverse events | |
| | psoriasis involving ≥10% | Etanercept 50 mg/week | 50 mg/week, weeks 13- | of study drug) | | Comment |
| Etanercept Psoriasis | body surface area and | (in two 25 mg | 24 (in subcutaneous | | At 0–12 weeks | Conflict of interest |
| Study Group | PASI ≥10. At least 1 | subcutaneous injections | injections twice per | Missing data | Withdrawal due to | The study was |
| | previous | per week) for 24 weeks | week) | LOCF | adverse events | sponsored by a |
| Multicenter study | phototherapeutic or | | | | 11: 3/196 (1.5%) | pharmeceutical |
| performed at 50 sites in | systemic treatment. | n=194 | n=193 | Results – week 12 | 12: 2/194 (1%) | company: Immunex |
| the USA, Canada and | Treatment naive to | | | PASI ≥50 | C: 2/193 (1%) | Corporation and Amgen |
| Western Europe | TNF-inhibitors | Drop-out rate | Drop-out rate | 11: 126/196 (64%) | | |
| | | 5/196 (2.5%) at | 15/193 (7.8%) at | 12: 150/194 (77%) | Injection site reaction | |
| RCT | Baseline characteristics | 12 weeks | 12 weeks | C: 18/193 (9%) | 11: 26/196 (13%) | |
| | Female/Male, % | 11/196 (5.6%) at | 25/193 (12.9%) at 24 | 11, 12 vs C: p<0.0001 | 12: 35/194 (18%) | |
| | 11: 35%/65% | 24 weeks | weeks | | C: 11/193 (6%) | |
| | 12: 33%/6/% | | | PASI ≥75 (primary | | |
| | C: 36%/64% | Intervention 2 | | endpoint) | | |
| | Ethnicity (Caucasian), | Etanercept | | | 11: 26/196 (13%) | |
| | (%) | 100 mg/week for | | 12: 96/194 (49%) | 12: 25/194 (13%) | |
| | 11: 92% | 12 weeks (In two 50 mg | | C: 6/193 (3%) | C: 25/193 (13%) | |
| | 12: 89% | subcutaneous injections | | 11, 12 vs C: p<0.0001 | Handricha | |
| | C. 91% | per week) and | | DAGLOOD | | |
| | Bodyweight | 50 mg/week, weeks 13- | | PASI 290 | 11: 23/196 (12%) | |
| | No mormation | 24 (III subcutatieous | | 11: 21/196 (11%) | 12.21/194(11%) | |
| | Study pariod | wook) | | 12. 40/194 (21%) C· 1/102 (1%) | C. 13/ 133 (0%) | |
| | May 2002-July 2002 | WEEK) | | (1, 1/13)(1%) | Injection site | |
| | way 2002–July 2003 | n-196 | | 11, 12 VS C. P<0.0001 | acchymosis | |
| | Follow-up | 11-130 | | | 11. 24/106 (12%) | |
| | i onow-up | Dron-out rate | | | 12. 24/130 (12/0) | |
| | | Diop-out rute | | | 12. 13/ 194 (0%) | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--|--|--|-------------------------------|---|--|---|
| Year | Setting | | | | | |
| Reference | | | | Results | | Comment |
| Country | Study period | | | | | |
| Study design | Follow-up | | | | | |
| Krueger et al. 2005 [89] | Pollow-up 12 weeks RCT plus 12 weeks OLE (all patients received etanercept during the OLE) Population, study period and follow-up See [87] | 4/194 (2%) at 12 weeks 9/194 (4,6%) at 24 weeks Interventions See [87] | Comparison See [87] | Analysis model See [87] Results at 12 weeks | C: 22/193 (11%) Accidental injury I1: 8/196 (4%) I2: 13/194 (7%) C: 12/193 (6%) "Flu syndrome" I1: 9/196 (5%) I2: 8/194 (4%) C: 3/193 (2%) Adverse events See [87] | Risk of bias and comment See [87] |
| For main publication, see [87] RCT | Baseline characteristics (DLQI only) DLQI-score at baseline, mean (SD) 11: 11.5 (7.2) 12: 11.4 (6.5) C: 12.2 (6.8) | | | DLQI, mean percentage improvement: 11: 65% 12: 70% C: 6% 11 vs C: $p<0.0001$ 12 vs C: $p<0.0001$ Patients with \geq 5 points improvement on the DLQI-score, n (%) 11: 140/194 (72.2%) 12: 150/194 (77.3%) C: 50/193 (25.9%) | | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------------------|--------------------------|---------------------------|--------------------------|--------------------------|-------------------------|-------------------------|
| Year | Setting | | | | | |
| Reference | | | | Results | | Comment |
| Country | Study period | | | | | |
| Study design | Follow-up | | | | | |
| Leonardi et al | Population | Intervention (I) | Comparison (C) | Analysis model | Adverse events | Risk of bias |
| 2003 | Adult patients (≥18 yrs) | | Placebo for 12 weeks | ITT (all randomised who | | Acceptable |
| [94] | with stable plaque | Intervention 1 | and etanercept | received at least 1 dose | Proportion adverse | |
| | psoriasis involving ≥10% | Etanercept 50 mg/week | 50 mg/week, weeks 13- | of study drug) | events occurring in at | Comment |
| Etanercept Psoriasis | body surface area and | (in 25 mg subcutaneous | 24 (in subcutaneous | | least 5% of patients in | Drop-out rates per |
| Study Group | PASI ≥10. At least 1 | injections twice weekly) | injections twice weekly) | Missing data | any treatment group | comparison groups not |
| | previous photothera- | for 24 weeks | | LOCF | | given |
| Multicentre study | peutic or systemic | | n=168 | | AEs week 0–12 | |
| performed at 47 sites in | treatment. Treatment | Allocation | | Results – week 12 | Injection site reaction | Withdrawal rates due to |
| the USA | naive to TNF-inhibitors | n=167 | Drop-out rate | PASI ≥50 | l1: 17% | adverse events per |
| | or other biologic | | Not given/group | l1: 94/162 (58%) | I2: 13% | comparisn groups not |
| RCT | therapies. | Drop-out rate | | 12: 121/164 (74%) | C: 12% | given |
| | | n.g./group | | C: 24/166 (14%) | | |
| | Baseline characteristics | | | l1, l2 vs C: p< 0.001 | Headache | Conflict of interest |
| | Female/Male, (%) | Intervention 2 | | | 11: 12% | The study was |
| | l1: 33%/67% | Etanercept | | PASI ≥75 (primary | 12: 7% | sponsored by a |
| | 12: 35%/65% | 100 mg/week (in 50 mg | | endpoint) | C: 7% | pharmeceutical |
| | C: 37%/63% | subcutaneous injections | | l1: 55/162 (34%) | | company: Immunex |
| | Ethnicity (Caucasian), | twice weekly) for 24 | | I2: 81/164 (49%) | URTI | Corporation and Amgen |
| | (%) | weeks | | C: 6/166 (4%) | I1: 9% | |
| | l1: 85% | | | l1, l2 vs C: p <0.001 | 12: 5% | |
| | 12: 87% | Allocation | | | C: 11% | |
| | C: 90% | n=168 | | PASI ≥90 | | |
| | Bodyweight | | | 11: 19/162 (12%) | Injection-site- | |
| | No information | Drop-out rate | | 12: 36/164 (22%) | ecchymosis | |
| | | Not given/group | | C: 1/166 (1%) | l1: 2% | |
| | Study period | | | l1, l2 vs C: p <0.001 | 12: 5% | |
| | December 2001– | The trial also included a | | | C: 4% | |
| | October 2002 | third intervention arm | | DLQI, mean relative im- | | |
| | | where patients received | | provement, %±SE | Asthenia | |
| | Follow-up | 25 mg etanercept per | | l1: 50.8±3.8 | l1: 4% | |
| | 12 weeks (placebo- | week | | l2: 61.0±4.3 | 12: 2% | |
| | controlled phase) plus | | | C: 10.9±4.8 | C: 3% | |
| | | | | l1, l2 vs C: p <0.001 | | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|-------------------------|--------------------------|--------------------------|------------|--------------------------|---------------------------|-----------------------|
| Year | Setting | | | | | |
| Reference | | | | Results | | Comment |
| Country | Study period | | | | | |
| Study design | Follow-up | | | | | |
| | 12 weeks of active | | | | Myalgia | |
| | treatment all groups | | | | I1: 4% | |
| | | | | | 12: 2% | |
| | Drop-out rate (overall) | | | | C: 2% | |
| | 6% at 12 weeks with | | | | | |
| | "similar" proportions of | | | | Accidental injury | |
| | patients completing | | | | I1: 3% | |
| | treatment in each | | | | 12:4% | |
| | group" | | | | C: 4% | |
| | | | | | | |
| | | | | | Sinusitis | |
| | | | | | 11:0 | |
| | | | | | 12:0 | |
| | | | | | C: 1% | |
| | | | | | | |
| | | | | | Nausea | |
| | | | | | 11:2% | |
| | | | | | 12: 2% | |
| | | | | | C: 1% | |
| | | | | | | |
| | | | | | Rash | |
| | | | | | 11:2% | |
| | | | | | 12: 3% | |
| | A 1.11 | | | | C: 2% | |
| Leonardi et al | Population | Intervention | | Analysis model | Adverse events | KISK OF DIAS |
| 2010 | OLE atter two original | Etanercept 50 mg/week | | All patients who | Expressed as exposure | NOT assessed |
| | RCI-studies. For | (in a subcutaneous | | received ≥1 dose of | adjusted incidence rates | |
| CONSORT, USA and | Inclusion criteria, see | injection once weekly) | | study drug were | per 100 patient years. | Comment |
| giobal | KN 1334 (CONSORT, | TOT 12 WEEKS from OLE- | | included in the analyses | | KISK OF DIAS NOT |
| | USA) and KN 4/6 | baseline. | | of adverse events. | All events | assessed as only |
| OLE efter [94] och [87] | (CONSORT, global). | | | | 235./ | observational data on |
| | | At week 12 eligible | | | | AE:s were collected. |
| | Baseline characteristics | patients chose either to | | | All non-infectious events | |
| | <u>(OLE)</u> | remain on 50 mg/week | | | 135.7 | |

| First Author Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|---|--|------------|----------------|--|--------------|
| Year Setting | | | | | |
| Reference | | | Results | | Comment |
| Country Study period | | | | | |
| Study design Follow-up | | | | | |
| Study designFollow-upFemale/male, % 32.3%/67.6%Ethnicity (Caucasian), (%) 800/912 (87.7%)Age, mean (SD) 45.9 (11.9)Weight in kg, mean (SD) 45.9 (11.9)Weight in kg, mean (SD) 18.9 (8.5)PASI, mean (SD) 18.9 (8.5)Follow up 60 weeks RCT+72 we OLE, for a combined follow up of 2.5 yrs | Image: Note of the second state is a second structure of the study.Image: Note of the second structure is a second struc | | | All infections 95.2 Serious non-infectious adverse events 5.6 (most common were 2 events of subdural hematoma and 2 of myocardial infarction) Serious infections 1.6 (most common were 3 events of pneumonia and 2 of cellulitis) Injection site reactions 4.8 Malignancies 1.5 | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|----------------------|--------------------------|--------------------------|-------------------------|--------------------------|--------------------------|----------------------|
| Year | Setting | | | | | |
| Reference | | | | Results | | Comment |
| Country | Study period | | | | | |
| Study design | Follow-up | | | | | |
| | | Patient yrs exposure to | | | | |
| | | first 50 and then 100 | | | | |
| | | mg/week | | | | |
| | | 728.8 | | | | |
| Gottlieb et al | Population | Intervention (I) | Comparison (C) | Analysis model | Adverse events | Risk of bias |
| 2003 | Adult patients (≥18 | Etanercept 50 mg/week | Placebo (in | ITT (all randomised who | AEs occurring in more | Acceptable |
| [93] | years) with stable | (in 25 mg subcutaneous | subcutaneous injections | received at least 1 dose | than 10% or more | |
| | plaque psoriasis | injections twice weekly) | twice weekly) for | of study drug). Missing | during 24 weeks | Comment |
| Multicentre study | involving ≥10% body | for 24 weeks | 24 weeks | values imputed by LOCF | | Conflict of interest |
| performed in the USA | surface area. At least 1 | | | | Withdrawals due to | The study was |
| | previous systemic | n=57 | n=55 | Results – week 12 | adverse events | sponsored by a |
| RCT | therapy or | | | PASI ≥50 | I: 2/57 (3.5%) | pharmaceutical |
| | phototherapy | BMI: 30.9 | BMI: 29.8 | I: 40/57 (70%) | C: 6/55 (10.9%) | company: Immunex |
| | | | | C: 6/55 (11%) | | Corporation, a |
| | Baseline characteristics | Drop-out rate, 12 weeks | Drop-out rate | l vs C: p <0.001 | URTI | subsidiary of Amgen |
| | Female/Male, % | 4/57 (7%) | 15/55 (27.3%) at | | I: 35% | |
| | I: 42%/58% | | 12 weeks | PASI ≥75 (primary | C: 20% | |
| | C: 33%/67% | Drop-out rate, 24 weeks | 43/55 (78.2%) at | endpoint) | | |
| | Ethnicity (Caucasian), | 9/57 (15.8%) | 24 weeks | I: 17/57 (30%) | Headache | |
| | (%) | | | C: 1/55 (2%) | l: 16% | |
| | I: 89% | | | l vs C: p <0.001 | C: 13% | |
| | C: 95% | | | | | |
| | Bodyweight (kg) mean | | | PASI ≥90 | Bruise at injection site | |
| | 1: 91.8 | | | 1: 7/57 (12%) | 1: 11% | |
| | C: 90.7 | | | C: 0/55 (0%) | C: 9% | |
| | | | | T vs C: p=0.03 | | |
| | Study period | | | | Sinusitis | |
| | August 2000–January | | | Results – week 12 | 1: 14% | |
| | 2001 | | | PASI ≥50 | C: 4% | |
| | | | | 1: 44/5/ (//%) | | |
| | Follow-up | | | C: 7/55 (13%) | Pain | |
| | 24 weeks placebo | | | TVS C: p < 0.001 | 1: /% | |
| | controlled phase | | | | C: 7% | |
| | (primary endpoint after | | | PASI 215 | | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|-------------------------|--------------------------|-------------------------|-------------------------|-------------------------|------------------------|---------------------------|
| Year | Setting | | | | | |
| Reference | | | | Results | | Comment |
| Country | Study period | | | | | |
| Study design | Follow-up | | | | | |
| | 12 weeks, but placebo | | | I: 32/57 (56%) | Peripheral edema | |
| | controlled phase | | | C: 3/55 (5%) | I: 2% | |
| | continued for an | | | l vs C: p <0.001 | C: 9% | |
| | additional 12 weeks) | | | | | |
| | | | | PASI ≥90 | Hypertension | |
| | | | | I: 12/57 (21%) | I: 7% | |
| | | | | C: 0/55 (0%) | C: 4¤ | |
| | | | | I vs C: p <0.001 | | |
| | | | | | Accidental injury | |
| | | | | DLQI, % improvement | I: 7% | |
| | | | | mean±SE | C: 4% | |
| | | | | I: 64±5 | | |
| | | | | C: 7±8 | 5 serious events | |
| | | | | | occurred. None of them | |
| | | | | | were considered as | |
| | | | | | drug related | |
| | | | | | | |
| Griffiths et al | Population | Intervention (I) | Comparison (C) | Analysis model | Adverse events, as | Risk of bias |
| 2015 | Adult patients (≥18 | Etanercept | Placebo (in | ITT. Continuous | reported | Acceptable |
| | years) with chronic | 100 mg/week (in 50 mg | subcutaneous injections | measures analysed | | |
| [88] | plaque psoriasis | subcutaneous injections | twice weekly) for | using a mixed model for | Any treatment | Comment |
| (UNCOVER-2) | (diagnosis ≥6 months) | twice weekly) for | 12 weeks | repeated measures | emergent adverse event | Study funded by Eli Lilly |
| | involving ≥10% body | 12 weeks | | | I: 59.1% | and Co. Study sponsor |
| Multicentre study | surface area, PGA | | n=168 | Missing data | C: 53.3% | involved in the design |
| performed at 126 study | (physician's) ≥3 and | n=358 | | NRI | | of the study and carried |
| sites in north America, | PASI ≥12. Treatment | | | | Death | out the data analysis |
| Europe and Australia | naive to etanercept | Drop-out rate | Drop-out rate | Results – week 12 | I: 0 | |
| | | 25/358 (7%) | 10/168 (5.9%) | PASI≥75 | C: 0 | The study was designed |
| RCT | Baseline characteristics | | | I: 149/358 (41.6%) | | to compare ixekizumab |
| | Female/Male, % | The study also included | | C: 4/168 (2.4%) | Non-fatal serious | with etanercept and |
| | I: 34%/66% | an intervention group | | l vs C: p <0.0001 | adverse event | placebo |
| | C: 29%/71% | treated with ixekizumab | | | I: 2.2% | |
| | Ethnicity (Caucasian), % | | | PASI ≥90 | C: 1.2% | |
| | I: 94% | | | I: 67/358 (18.7%) | | |
| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------|----------------------|--------------|------------|-----------------------|-------------------------|--------------|
| Year | Setting | | | | | |
| Reference | | | | Results | | Comment |
| Country | Study period | | | | | |
| Study design | Follow-up | | | | | |
| | C: 89% | | | C: 1/168 (0.6%) | Any infection | |
| | BMI (kg/m²), mean±SD | | | l vs C: p <0.0001 | I: 27.5% | |
| | I: 31±7 | | | | C: 27.5% | |
| | C: 31±7 | | | PASI-100 | | |
| | | | | 1: 19/358 (5.3%) | Nasopharyngitis | |
| | Study period | | | C: 1/168 (0.6%) | 1: 10.1% | |
| | May 2012–December | | | T vs C: p=0.0082 | C: 10.2% | |
| | 2013 | | | DI OL cooro chanac | Injection site reaction | |
| | | | | from baseline+SE | injection site reaction | |
| | Follow-up | | | Jrom baseline±SE | 1: 10.9% | |
| | 12 weeks placebu- | | | 17.7 ± 0.5 | C. 0.0% | |
| | | | | $C_{1} = 2.0 \pm 0.4$ | Injection site enuthema | |
| | | | | 1 V3 C. p <0.0001 | 1. 5 0% | |
| | | | | | C· 1 2% | |
| | | | | | 0. 1.2/0 | |
| | | | | | Injection-site pain | |
| | | | | | I: 1.1% | |
| | | | | | C: 1.2% | |
| | | | | | | |
| | | | | | Pruritus | |
| | | | | | I: 1.1% | |
| | | | | | C: 2.4% | |
| | | | | | | |
| | | | | | Headache | |
| | | | | | I: 5.6% | |
| | | | | | C: 1.8% | |
| | | | | | Authorita | |
| | | | | | Arthraigia | |
| | | | | | 1. 2.8% | |
| | | | | | C. 2.4% | |
| | | | | | | |
| | | | | | | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------------------|--------------------------|-------------------------|-------------------------|-------------------------|-------------------------|---------------------------|
| Year | Setting | | | | | |
| Reference | | | | Results | | Comment |
| Country | Study period | | | | | |
| Study design | Follow-up | | | | | |
| Griffiths et al | Population | Intervention (I) | Comparison (C) | Analysis model | Adverse events, as | Risk of bias |
| 2015 | Adult patients (≥18 | Etanercept | Placebo (in | ITT. Continuous | reported | Acceptable |
| [88] | years) with chronic | 100 mg/week (in 50 mg | subcutaneous injections | measures analysed | Any treatment | |
| (UNCOVER-3) | plaque psoriasis | subcutaneous injections | twice weekly) for | using a mixed model for | emergent adverse event | Comment |
| | (diagnosis ≥6 months) | twice weekly) for | 12 weeks | repeated measures | I: 49.0% | Conflict of interest |
| Multicenter study | involving ≥10% body | 12 weeks | | | C: 36.3% | Study was sponsored by |
| performed at 126 study | surface area, PGA | | n=193 | Missing data | | a pharmaceutical |
| sites in north and south | (physician's) ≥3 and | n=382 | | NRI | Death | company: Eli Lilly. Lilly |
| America, Europe and | PASI ≥12. Treatment | | Drop-out rate | | I: 0 | also provided staff who |
| Russia | naive to etanercept | Drop-out rate | 10/193 (5.2%) | Results – week 12 | C: 0 | helped analyse and |
| | | 13/382 (3.4%) | | PASI ≥75 | | interpret data |
| RCT | Baseline characteristics | | | I: 204/382 (53.4%) | Non-fatal serious | |
| | Female/Male, % | The study also included | | C: 14/193 (7.3%) | adverse event | |
| | I: 30%/70% | an intervention group | | l vs C: p<0.0001 | I: 1.3% | |
| | C: 29%/71% | treated with ixekizumab | | | C: 2.6% | |
| | Ethnicity (Caucasian), % | | | PASI ≥90 | | |
| | I: 92% | | | I: 98/382 (25.7%) | Any infection | |
| | C: 91% | | | C: 6/193 (3.1%) | I: 15.4% | |
| | BMI (kg/m²), mean±SD | | | I vs C: p<0.0001 | C: 14.0% | |
| | I: 31±8 | | | | | |
| | C: 30±6 | | | PASI-100 | Nasopharyngitis | |
| | | | | I: 28/382 (7.3%) | I: 5.0% | |
| | Study period | | | C: 0/193 | C: 5.7% | |
| | August 2012–February | | | l vs C: p<0.0001 | | |
| | 2014 | | | | Injection site reaction | |
| | | | | DLQI mean score | I: 10.7% | |
| | Follow-up | | | change ±SE | C: 1.6% | |
| | 12 weeks placebo- | | | I: -8.0±0.2 | | |
| | controlled phase | | | C: -1.7±0.3 | Injection site erythema | |
| | | | | l vs C: p<0.0001 | I: 2.9% | |
| | | | | | C: 0% | |
| | | | | | Injection-site pain | |
| | | | | | I: 1.3% | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|-------------------|--------------------------------|----------------------------|-------------------------|----------------------|-------------------------|------------------------|
| Year | Setting | | | | | |
| Reference | | | | Results | | Comment |
| Country | Study period | | | | | |
| Study design | Follow-up | | | | | |
| | | | | | C:1.6% | |
| | | | | | | |
| | | | | | Pruritus | |
| | | | | | I: 1.0% | |
| | | | | | C: 0.5% | |
| | | | | | Headache | |
| | | | | | 1: 2.9% | |
| | | | | | C: 2.6% | |
| | | | | | | |
| | | | | | Arthralgia | |
| | | | | | I: 1.8% | |
| | | | | | C: 2.1% | |
| | | | | | | |
| Langlov at al | Deputation | Intervention (I) | Comparison (C) | Analysis model | Advaraa avanta | Diek of hiss |
| Langley et al | Adult patients (>18 | Intervention (I) | Comparison (C) | | Adverse events | |
| 2014 | Adult patients (218 | 100 mg/wggk/in 50 mg | Placebo, (In | III, including all | At 0, 12 | Acceptable |
| [98] (FINTURE) | years) with moderate to | 100 mg/week (in 50 mg | subcutaneous injections | randomised patients. | At U-12 weeks (%) | Commont |
| (FIXTORE) | severe plaque | subcutaneous injections | twice weekly) for | ivissing values | Any AE | Comment |
| | alagnosea ≥ 6 months, | twice weekly) weeks U– | 12 weeks, | Imputated as non- | 1: 57.5% | the study was to |
| | | 12 and 50 mg/week | - 226 | responders | 0.49.8% | the study was to |
| DCT | surface area, with ≥ 3 on | (once weekly injections) | n=326 | Deculto un eli 12 | Death | compare securinumab |
| RUI | moumed investigator's | weeks 13-51 | Dran out rate | | | with etanercept of |
| | global assessment scale | | Drop-out rate | PASI 275 | 1:0 | placebo. Inferential |
| | and PASI 212. | n=326 | 25/326 (7.7%) at | 1: 142/323 (44.0%) | C: 0 | statistics for |
| | i reatment naive to | | 12 weeks | C: 16/324 (4.9%) | | comparison between |
| | etanercept | Drop-Out rate | | i vs c: not given | Non-Jatai serious event | etanercept and placebo |
| | Dacalina charactoristics | 21/520 (0.4%) at | | DACINO | 1.0.9% | were not calculated |
| | Buseline characteristics | 12 weeks | | PASI 290 | C. 1.8% | Conflicts of interest |
| | remale/IVIAle, % | | | 1. 07/323 (20.7%) | Discontinuation due to | Conflicts of interest |
| | 1: 28.8%//1.2% | The study class in dealers | | C: 5/324 (1.5%) | Discontinuation are to | Study was sponsored by |
| | C: 27.3%/72.7% | The study also included | | i vs c: Not given | | a pharmaceutical |
| | Ethnicity (Control 1) of | an intervention group | | DAGL 400 | 1: 1.9% | company: Novartis. |
| | Ethnicity (Caucasian), % | | | PASI 100 | C: 0.9% | Novartis also provided |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|-------------------------------|---------------------------|-------------------------|----------------------------|--------------------------|--------------------------|-------------------------|
| Year | Setting | | | | | |
| Reference | | | | Results | | Comment |
| Country | Study period | | | | | |
| Study design | Follow-up | | | | | |
| | I: 67.5% | treated with | | I: 14/323 (4.3%) | | staff who helped design |
| | C: 66.9% | sekukinumab | | C: 0/324 | Infection or infestation | the study |
| | | | | I vs C: Not given | I: 24.5% | |
| | BMI (kg/m²), mean±SD | | | | C: 19.3% | |
| | I: 28.7±5.9 | | | DLQI, mean absolute | | |
| | C:27.9±6.1 | | | change | | |
| | | | | I: -7.9 | | |
| | Study period | | | C: -1.9 | | |
| | June 2011–June 2013 | | | I vs C: Not given | | |
| | | | | | | |
| | Follow-up | | | | | |
| | 12 weeks placebo- | | | | | |
| | controlled trial | | | | | |
| | (induction period). After | | | | | |
| | 12 weeks patients in | | | | | |
| | placebo group with PASI | | | | | |
| | improvement less than | | | | | |
| | 75 were rerandomised. | | | | | |
| | Efficacy assesments | | | | | |
| | were made at the end | | | | | |
| | of induction period and | | | | | |
| | of maintenance period | | | | | |
| | (week 52) | | | | | |
| Gottlieb et al | Population | Intervention | Comparison | Analysis model | Adverse events at week | Risk of bias |
| 2011 | Adult patients (≥18 | Etanercept | Placebo in s.c. injections | ITT – all randomised | 12 | |
| [95] | years) with moderate to | 100 mg/week (in 50 mg | matching active | included. Missing values | Any adverse event | Comment |
| | severe plaque | subcutaneous injections | treatment. | imputated as non- | I: 76/141 (53.9%) | The study was primarily |
| Multicentre study | diagnosed ≥6 months, | twice weekly) week 0– | | responders. | C: 31/68 (45.6%) | designed to investigate |
| , performed at 33 sites in | involving ≥10% body | 11. | n=68 | | | the effect of |
| the USA | surface area, with ≥3 on | | | Results at week 12 | Any serious adverse | briakinumab compared |
| | Physician's Global | n=141 | Drop-out rate | PASI≥75 | event | to etanercept and to |
| RCT | Assessment scale and | | 5/68 (7.3%) | I: 56.0% | I: 1/141 (0.7%) | placebo. Only the |
| | PASI ≥12 at baseline. | Drop-out rate | | C: 7.4% | C: 1/68 (1.5%) | comparison between |
| | Treatment naive to IL- | 7/141 (5%) | | | | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------------------|---------------------------------|-------------------------|----------------------------|--------------------------|------------------------|-------------------------|
| Year | Setting | | | | | |
| Reference | | | | Results | | Comment |
| Country | Study period | | | | | |
| Study design | Follow-up | | | | | |
| | 12/23 inhibitor and to | | | PASI ≥90 | Any AE leading to | etanercept and placebo |
| | etanercept. | | | I: ca 10% | discontinuation | is reported here. |
| | | | | C: ca 0% | I: 4/141 (2.8%) | |
| | <u>Baseline characteristics</u> | | | | C: 0 | Conflict of interest |
| | Female/male | | | PASI 100 | | The study was |
| | I: 30.5%/69.5% | | | I: ca 4% | Any infection | sponsored by Abbot |
| | C: 30.9%/69.1% | | | C: ca 0% | I: 34/141 (24.1%) | Laboratories, the |
| | | | | | C: 13/68 (19.1%) | developer of |
| | Age yrs, mean (SD) | | | DLQI, patients with a | | briakinumab. |
| | I: 43.1 (12.5) | | | score of 0 week 12 | Any serious infection | |
| | C: 44.0 (13.6) | | | I: 30/141 (21.3%) | I: 1/141 (0.7%) | |
| | | | | C: 2/68 (2,9%) | C: 0 | |
| | Body weight, mean (SD) | | | | | |
| | I: 94.5 kg (20.4) | | | | | |
| | C: 96.5 kg (27.2) | | | | | |
| | | | | | | |
| | Ethnicity (caucasian) | | | | | |
| | 1: 95.6% | | | | | |
| | C: 90.1% | | | | | |
| | | | | | | |
| | Study period | | | | | |
| | June 2008–March 2009 | | | | | |
| | | | | | | |
| | Follow-up | | | | | |
| | 12 weeks | | | | | |
| Strober et al | Population | Intervention | Comparison | Analysis model | Adverse events at week | Risk of bias |
| 2011 | Adult patients (≥18 | Etanercept | Placebo in s.c. injections | ITT – all randomised | 12 | |
| [96] | years) with moderate to | 100 mg/week (in 50 mg | matching active | included. Missing values | Any adverse event | Comment |
| | severe plaque | subcutaneous injections | treatment. | imputated as non- | I: 69/139 (49.6% | The study was primarily |
| Multicentre study | diagnosed ≥6 months, | twice weekly) week 0– | | responders. | C: 32/72 (44.4%) | designed to investigate |
| performed at 41 sites in | involving ≥10% body | 11. | n=72 | | | the effect of |
| the USA | surface area, with ≥3 on | | | Results at week 12 | Any serious adverse | briakinumab compared |
| | Physician's Global | n=139 | Drop-out rate | PASI ≥75 | event | to etanercept and to |
| RCT | Assessment scale and | | 6/72 (8.3%) | I: 39.6% | I: 1/139 (0.7%) | placebo. Only the |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------|--------------------------|---------------|------------|-----------------------|-----------------------|------------------------|
| Year | Setting | | | | | |
| Reference | | | | Results | | Comment |
| Country | Study period | | | | | |
| Study design | Follow-up | | | | | |
| | PASI ≥12 at baseline. | Drop-out rate | | C: 6.9% | C: 2/72 (2.8%) | comparison between |
| | Treatment naive to IL- | 12/139 (8.6%) | | | | etanercept and placebo |
| | 12/23 inhibitor and to | | | PASI ≥90 | Any AE leading to | is reported here. |
| | etanercept. | | | I: 13.7% | discontinuation | |
| | | | | C: 4.2% | I: 4/139 (2.9%) | Conflict of interest |
| | Baseline characteristics | | | | C: 2/72 (2.8%) | The study was |
| | Female/male | | | PASI 100 | | sponsored by Abbot |
| | I: 38.9%/61.1% | | | I: 5.8% | Any infection | Laboratories, the |
| | C: 36.1%/63.9% | | | C: 0 | I: 39/139 (28.1%) | developer of |
| | | | | | C: 10/72 (13.9%) | briakinumab. |
| | Age yrs, mean (SD) | | | DLQI, patients with a | | |
| | I: 45.2 (14.8) | | | score of 0 week 12 | Any serious infection | |
| | C: 45.0 (13.9) | | | I: 21/139 (15.1%) | I: 0 | |
| | | | | C: 2/72 (2.8%) | C: 0 | |
| | Body weight, mean (SD) | | | | | |
| | I: 96.9 kg (24.9) | | | | | |
| | C: 92.9 kg (25.2) | | | | | |
| | | | | | | |
| | Ethnicity (caucasian) | | | | | |
| | I: 91.4% | | | | | |
| | C: 93.1% | | | | | |
| | | | | | | |
| | Study period | | | | | |
| | July 2008–April 2009 | | | | | |
| | | | | | | |
| | Follow-up | | | | | |
| | 12 weeks | | | | | |
| | | | | | | |
| | | | | | | |
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| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------------|--------------------------|-------------------------|-------------------------|---------------------------|--------------------------|----------------------------|
| Year | Setting | | | | | |
| Reference | | | | Results | | Comment |
| Country | Study period | | | | | |
| Study design | Follow-up | | | | | |
| Reich et al 2017 | Population | Intervention (I) | Comparsion (C) | Analysis model | Adverse events – | Risk of bias |
| [57] | Inclusion criteria | Etanercept | Placebo: two | mITT | during 16 weeks | Acceptable |
| | ≥18 years of age, | for 16 weeks, two | subcutaneous | | placebo controlled | |
| Global multicentre | Plaque psoriasis PASI | subcutaneous | injections, with saline | Missing data | phase | Comment |
| study | ≥12, sPGA ≥3, BSA | injections, 25 mg each, | placebo, twice a week | LOCF | Patients w ≥1 AE, n (%) | Conflict of interest: |
| | ≥10%, for ≥12 months, | twice a week | | | I: 44/83 (53.0%) | study funded by |
| | eligible for | | Allocation placebo | Results – 16 weeks | C: 45/84 (53.6%) | Celgene. Editorial |
| RCT | phototherapy or | Allocation placebo | controlled phase, n | Primary endpoint | | support by sponsor |
| | systemic therapy, | controlled phase, n | C: 84 | PASI ≥75, n (%) | Patients w ≥1 serious | |
| | inadequate response to | l: 83 | | I: 40/83 (48.2%) | AE, n (%) | |
| | one or two | | Drop-out rate placebo | C: 10/84 (11.9%) | I: 2/83 (2.4%) | The study was not |
| | conventional systemic | Drop-out rate placebo | controlled phase, n (%) | I vs C: p<0.0001 | C: 0/84 (0%) | powered for apremilast |
| | agents, and biologic | controlled phase | C: 9 (10.7%) | | | vs etanercept |
| | naïve. | I: 2 (2.4%) | | PASI ≥90, n (%) | Patients with AE leading | comparisons. A post |
| | | | | I: 17/83 (20.5%) | to drug withdrawal, n | hoc comparison yielded |
| | Baseline characteristics | The study also included | | C: 3/84 (3.6%) | (%) | a calculated power of |
| | Female/Male, (%) | intervention groups | | I vs C: p=0.0009 | I: 2/83 (2.4%) | 19% for detecting the |
| | I: 41%/59% | treated with Apremilast | | | C: 2/84 (2.4%) | observed difference. |
| | C: 29.8%/70.2% | | | DLQI improvement, | | |
| | Ethnicity – Caucasian | | | mean (SD) | Treatment-emergent | Information about |
| | I: 90.4% | | | I: -7.8 (SD: 6.5) | adverse events ≥5% of | study period found at |
| | C: 95.2% | | | C: -3.8 (SD: 5.6) | patients in any | https://clinicaltrials.gov |
| | Body mass index | | | l vs C: p=0.0004 | treatment groups | /ct2/show/NCT0169029 |
| | (kg/m²), mean±SD | | | | | 9 |
| | l: 29.9±6.8 | | | DLQI patients receiving | Nausea, n (%) | |
| | C: 29.5±6.6 | | | a DLQI score of 0 or 1, n | 1: 4/83 (4.8%) | |
| | | | | (%) | C: 1/84 (1.2%) | |
| | Study period | | | 1: 27/83 (32.5%) | | |
| | October 2012 - July | | | C: 13/84 (15.5%) | URTI, n (%) | |
| | 2014 | | | | 1: 2/83 (2.4%) | |
| | | | | | C: 2/84 (2.4%) | |
| | Follow-up | | | | | |
| | | | | | Diarrhoea, n (%) | |
| | | | | | I: 1/83 (1.2%) | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------------------|-------------------------|-------------------------|----------------------|-----------------------|------------------------|-------------------------|
| Year | Setting | | | | | |
| Reference | | | | Results | | Comment |
| Country | Study period | | | | | |
| Study design | Follow-up | | | | | |
| | 16 weeks placebo- | | | | C: 3/84 (3.6%) | |
| | controlled phase | | | | | |
| | (presented here). At | | | | Nasopharyngitis, n (%) | |
| | week 16 etanercept and | | | | I: 8/83 (9.5%) | |
| | placebo patients were | | | | C: 8/84 (9.5%) | |
| | switched to apremilast. | | | | | |
| | The OLE phase was | | | | Headache*, n (%) | |
| | maintained until week | | | | I: 5/83 (6.0%) | |
| | 104. Results for up to | | | | C: 3/84 (3.6%) | |
| | 52 weeks presented in | | | | | |
| | the publication. | | | | Tension headache, | |
| | Patients who did not | | | | n (%) | |
| | achieve PASI 50 at week | | | | I: 3/83 (3.6%) | |
| | 32 could add | | | | C: 4/84 (4.8%) | |
| | complementary | | | | | |
| | therapies to their | | | | | |
| | treatments | | | | | |
| Reich et al | Population | Intervention (I) | Comparison (C) | Analysis Model | Adverse events | Risk of bias |
| 2017 | Adult patients (age ≥18 | Etanercept | Placebo in | Modified ITT (all who | AEs (week 0–12) | Acceptable |
| [99] | years) with moderate to | 100 mg/week (in 50 mg | subcutaneous | received ≥1 dose test | | |
| | severe chronic plaque | subcutaneous injections | injections, matching | substance) | Any adverse event | |
| Multicentre study, | psoriasis, involving | twice weekly) for | active treatment. | | I: 169/313 (54%) | Comment |
| reSURFACE 2 (at 132 | ≥10% of body surface | 12 weeks. | | Missing data | C: 86/156 (55%) | Funded by Merck & Co. |
| sites in Europe, Canada, | area, PGA ≥3 and PASI | | n=156 | NRI | | The study funder had |
| Israel and USA) | ≥12. Candidates for | n=313 | | | Serious AEs, n (%) | roles in study design, |
| | phototherapy or other | | Drop-out rate at | Results (12 weeks) | I: 7/313 (2%) | data analysis, and data |
| RCT | systemic therapy | Drop-out rate at 12 | 12 weeks | PASI 75 | C: 4/156 (3%) | interpretation. |
| | | weeks | 14/156 (9.0%) | I: 151/313 (48%) | | |
| | Randomisation was | 24/313 (7.7%) | | C: 9/156 (6%) | AEs leading to | |
| | done by region and | | | | discontinuation, n (%) | |
| | stratified for | | | PASI 90 | I: 6/313 (2%) | |
| | bodyweight (≤90 kg or | The study also included | | 1: 6//313 (21%) | C: 2/156 (1%) | |
| | >90 kg) and previous | intervention groups | | C: 2/156 (1%) | | |
| | | | | | | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------|-----------------------------------|----------------|------------|---------------------------|--------------------------|--------------|
| Year | Setting | | | | | |
| Reference | | | | Results | | Comment |
| Country | Study period | | | | | |
| Study design | Follow-up | | | | | |
| | exposure to biologics | treated with | | PASI 100 | adverse events | |
| | therapy for psoriasis | tildrakizumab. | | I: 15/313 (5%) | occurring in >5% of | |
| | | | | C: 0/156 (0%) | participants, | |
| | Baseline characteristics | | | | | |
| | Female/Male, (%) | | | DLQI (% patients | Injection-site erythema, | |
| | 1: 29%/71% | | | receiving a score of 0 or | n (%) | |
| | C: 28%/72% | | | 1 after 12 weeks | 1: 27/313 (9%) | |
| | Ethnicity | | | treatment | C: 1/156 (1%) | |
| | Ellinicity White | | | 1.100/500(50%) | Naconhanungitic n (9/) | |
| | (%) | | | C. 12/150 (8%) | 1. 26/212 (12%) | |
| | (<i>20</i>) 1: 289/313 (92%) | | | | C· 12/156 (8%) | |
| | C· 144/156 (92%) | | | | 0. 12/ 130 (0/0) | |
| | 0. 1 1 1 1 200 (02/0) | | | | | |
| | Weiaht (ka), mean (SD) | | | | | |
| | I: 87.97 (21.48) | | | | | |
| | C: 88.74 (22.73) | | | | | |
| | | | | | | |
| | Age (years), mean (SD) | | | | | |
| | I: 45.8 (14.0) | | | | | |
| | C46.4 (12.2) | | | | | |
| | | | | | | |
| | Study period | | | | | |
| | Feb 12, 2013–Sep 28, | | | | | |
| | 2015 | | | | | |
| | Follow up | | | | | |
| | 12 weeks placebo | | | | | |
| | controlled phase (plus | | | | | |
| | up to 52 weeks OLF not | | | | | |
| | presented here) | | | | | |
| | , | | | | | |

AE – adverse event; BMI – body mass index; CDLQI – children's DLQI; CI – confidence interval; DLQI – dermatology life quality index; ITT – intention-to-treat; LOCF – last observation carried forward; n.g. – not given; NRI – non-responder imputation; OLE – open-label extension; PASI – psoriasis area and severity index; PGA – physician's global assessment; RCT – randomised controlled trial; SD – standard deviation; SE – standard error; TNF – tumour necrosis factor; URTI – upper respiratory tract infection

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|-------------------------|--------------------------|-------------------------|----------------------|--------------------|------------------------|---------------------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| Reich et al | Population | Intervention (I) | Comparison (C) | Analysis model | Adverse events | Risk of bias |
| 2005 | Inclusion criteria: | Infliximab 5 mg/kg, | Placebo | ITT | I: n=298 | Acceptable |
| [106] | Moderate to severe | intravenous infusion at | | | C: n=76 | |
| | plaque psoriasis ≥6 | week 0, 2 and 6 then | n=77 | Missing data | | Comment |
| Study name: | months, eligible for | every 8 weeks through | | NRI for ITT | Serious AE (week 0–24) | Study supported and |
| EXPRESS | phototherapy or | to week 46 | Placebo (week 0-24), | | I: 17/298 (5.7%), | funded by Centocor, |
| | systemic therapy, PASI | | infliximab 5mg/kg at | Results – week 10 | (1 death) | manufacturer of |
| Multicenter at 32 | score of ≥12, BSA ≥10% | n=301 | weeks 24, 26 and 30 | | C: 2/76 (2.6%) | infliximab. The |
| locations in Europe and | | | then every 8 weeks | PASI ≥50, n (%) | | manufacturer was |
| Canada | Permitted concomitant | Drop-out rate | through to week 46 | I: 274/301 (91.0%) | AE (week 0–24) | involved in study |
| | therapies after week 10 | 32/301=10.6% | Ū. | C: 6/77 (7.8%) | I: 82% | design, data acquisition, |
| RCT | 2.5% hydrocortisone or | | Drop-out rate | I vs C: p<0.0001 | C: 71% | data analysis and |
| | equivalent, applied to | | 9/77=11.7% | | | preparation of the |
| | groin and/or face after | | | Primary endpoint | AE in ≥5% in any group | manuscript |
| | week 10 | | | PASI ≥75, n (%) | (0–24 weeks) | |
| | | | | I: 242/301 (80.4%) | URTI, n (%) | Randomisation of study |
| | Baseline characteristics | | | C: 2/77 (2.6%) | I: 46/298 (15.4%) | population (without |
| | Female/Male, (%) | | | I vs C: p<0.0001 | C: 12/76 (15.8%) | stratification for nail |
| | I: 31.2%/68.8% | | | | | psoriasis) |
| | C: 20.8%/79.2% | | | PASI ≥90, n (%) | Headache, n (%) | |
| | Ethnicity | | | I: 172/301 (57.1%) | I: 43/298 (14.4%) | |
| | No information | | | C. 1/77 (1.3%) | C: 9/76 (11.8%) | |
| | Bodyweight | | | I vs C: p<0.0001 | | |
| | No information | | | | Fatigue, n (%) | |
| | | | | | I: 25/298 (8.4%) | |
| | Allocation stratified by | | | Results – week 24 | C: 3/76 (3.9%) | |
| | investigation site | | | PASI ≥50, n (%) | | |
| | | | | I: 248/276 (89.9%) | Hepatic enzymes | |
| | | | | C: 6/77 (7.8%) | Increased, n (%) | |

Table 7.4. Infliximab versus placebo

| First Author Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|-----------------------------|--------------|------------|---------------------|------------------------|--------------|
| Year Setting | | | | | Comment |
| Reference | | | Results | | |
| Country Study period | | | | | |
| Study design Follow-up (FU) | | | | | |
| Study period | | | I vs C: p<0.0001 | I: 26/298 (8.7%) | |
| Not clear | | | | C: 0/76 | |
| | | | Secondary endpoints | | |
| Follow-up | | | PASI ≥75, n (%) | Pruritus, n (%) | |
| 24 weeks placebo | | | I: 227/276 (82.2%) | I: 22/298 (7.4%) | |
| controlled trial | | | C 3/77 (3.9%) | C: 5/76 (6.6%) | |
| (reported here), | | | l vs C: p<0.0001 | | |
| followed by 26 weeks | ; | | | Arthralgia, n (%) | |
| OLE | | | PASI ≥90, n (%) | I: 21/298 (7.0%) | |
| | | | I: 161/276 (58.3%) | C: 3/76 (3.9%) | |
| | | | C: 1/77 (1.3%) | | |
| | | | I vs C: p<0.0001 | Rhinitis, n (%) | |
| | | | | I: 18/298 (6.0%) | |
| | | | | C: 1/76 (1.3%) | |
| | | | | | |
| | | | | Pain, n (%) | |
| | | | | l: 17/298 (5.7%) | |
| | | | | C: 4/76 (5.3%) | |
| | | | | | |
| | | | | Pharyngitis, $n(\%)$ | |
| | | | | 1: 17/298 (5.7%) | |
| | | | | C: 6/76 (7.9%) | |
| | | | | Hornos simploy n (%) | |
| | | | | 1.10/208 (2.4%) | |
| | | | | $C \cdot 4/76 (5.3\%)$ | |
| | | | | 0.4770 (3.376) | |
| | | | | Psoriasis n(%) | |
| | | | | 1. 9/298 (3.0%) | |
| | | | | C: 10/76 (13 2%) | |
| | | | | 0. 10/ / 0 (10.2/0) | |
| | | | | Sinusitis n (%) | |
| | | | | 1: 4/298 (1.3%) | |
| | | | | C: 4/76 (5.3%) | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|---------------------|-----------------------------------|-------------------------|--|------------------------------------|---|---------------------|
| Year | Setting | | | Boculto | | Comment |
| Country | Study period | | | Results | | |
| Study design | Follow-up (FLI) | | | | | |
| | | | | | | |
| | | | | | AEs leading to withdrawals, n (%) I: 27/298 (9.1%) C: 5/77 (6.6%) Infections, n (%) I: 125/298 (41.9%) C: 30/76 (39.5%) Neoplasms, n (%) I: 3/298 (1.0%) C: 0/76 Infusion reactions, number of infusions, n (%) I: 38/1416 (3%) C: 7/347 (2%) | |
| Cattlink at al 2004 | Demulation | | | A such as to such a dial | | Disk of his s |
| [105] | Population Inclusion criteria: | l: Infliximab 5 mg/kg, | Comparison (C) Placebo, intravenous | Analysis model | Adverse events (through week 30) | Acceptable |
| | Age ≥18 years, | intravenous infusion at | infusion | | Patients with $\geq 1 \text{ AE}$, n | |
| Study name: | diagnosis of plaque | week 0, 2 and 6 | | Results – week 10 | (%) | Comment |
| SPIKII | psoriasis ≥ 6 months, | Detionts with a DCA >2 | n=51 | Drimary and naint | 1: 78/99 (78.8%) | Study supported and |
| Multicontor at | previously treated with | Patients with a PGA 23 | | Primary enapoint $PASI > 75 m (%)$ | C: 32/51 (62.7%) | funded by Centocor |
| 24 contors in USA | POVA or other systemic | for a single additional | Drop-out rate | raji 275, 11 (%) | Discontinued treatment | |
| 24 Centers In USA | anupsonasis unerapy, | infusion of their | 37/51=72.5% | 1. 87/00 (87 00/) | as result of an AE | |
| DCT | PASI SCOLE OI 212, | assigned treatment | | 1.07/33(87.3%) | us result of ull AE | |
| nul | B3A 210% | assigned treatment | | (. 5/51 (5.5%)) | 1.11-3(3%) | |
| | Baseline characteristics | l: n-99 | | 1 vs C. h<0.001 | C. II-1 (270) | |
| | Female/Male (%) | 1. 11-33 | | Secondary endpoints | Serious AF n (%) | |
| | 1: 26.3%/73.7% | | | | l: 8/99 (8.1%) | |

| First Author Year Reference Country Study design | Population Setting Study period Follow-up (FU) C: 39.2%/60.8% Ethnicity No information Bodyweight No information Randomisation stratified by investigational site Study period 2001 to 2003 Follow up 26-week placebo controlled trial. (Treatment week 0, 2, 6 and additional treatment dose at week 26 if PGA≥3). Follow up until week 30 | Intervention Drop-out rate I: 18/99=18.2% The trial also included a treatment arm where patients received infliximab 3 mg/kg | Comparison | Analysis model Results PASI ≥50, n (%) I: 96/99 (97.0%) C: 11/51 (21.6%) I vs C: p<0.001 PASI ≥90, n (%) I: 57/99 (57.6%) C: 1/51 (2.0%) I vs C: p<0.001 DLQI, median change from baseline to week 10 (median score at week 10) I: -10 (1) C: 0 (10) I vs C: p<0.001 | Adverse events C: 0/51 (0.0%) Patients with infusion reactions, n (%) I: 22/99 (22.2%) C: 1/51 (2.0%) Patients newly positive for antinuclear antibodies, n (%) I: 20/80 (25.0%) C: 1/44 (2.3%) Patients newly positive for antibodies against double stranded DNA, n (%) I: 4/94 (4.3%) C: 1/48 (2.1%) Patients with antibodies to infliximab I: 17/87 (19.5%) C: NA | Risk of bias Comment |
|--|---|---|--|--|---|--|
| | | | | | C: NA | |
| Feldman et al 2005 [104] Same as study population as in [105] Study name: SPIRIT | Population Inclusion criteria: Age ≥18 years, diagnosis of plaque psoriasis ≥6 months, previously treated with PUVA or other systemic antipsoriasis therapy, | Intervention (I) I: Infliximab 5 mg/kg, intravenous infusion at week 0, 2 and 6 Patients with a PGA ≥3 at week 26 were eligible for a single additional | Comparison (C) Placebo, intravenous infusion n=51 Drop-out rate 37/51=72.5% | Analysis model ITT Missing data: NRI before week 10 LOCF after week 10 Results – week 10 | Adverse events See study Gottlieb 2004 [105] | Risk of bias Acceptable Comment Study supported and funded by Centocor |

| Year Setting Com | Comment |
|---|--------------------|
| Reference Results | |
| Country Study period | |
| Study design Follow-up (FU) | |
| Multicenter at 24 PASI score of ≥12, BSA infusion of their Baseline | |
| centers in USA $\geq 10\%$ assigned treatment $DLQI, mean \pm SD$ | |
| I: 13.2 ± 7.0 | |
| RCT Baseline characteristics I: n=99 C: 13.8 ± 6.6 Female/Male (%) C: 13.8 ± 6.6 | |
| I: 26.3%/73.7% Drop-out rate Change from baseline, | |
| C: 39.2%60.8% I: 18/99=18.2% mean±SD | |
| I: -10.3 ± 7.3 | |
| EthnicityThe trial also included aC: -2.6 ± 5.7 | |
| No information treatment arm where I vs C: p<0.001 | |
| Bodyweight patients received | |
| No information infliximab 3 mg/kg | |
| Study period 2001 to 2003 Follow-up 26 weeks placebo | |
| controlled trial. | |
| (Treatment week 0, 2, 6 | |
| and additional | |
| treatment dose at week | |
| 26 if PGA≥3). Follow up | |
| until week 30 | |
| Montor at al Deputation Intervention (I) Commentary (C) Applying model Adverse synches Diele | lick of hiss |
| 2007 Analysis model Adverse events Risk | |
| [107] Adult nations with intravenous infusion at infusion | liceptable |
| moderate to severe week 0.2 and 6. | `omment |
| Study name: plaque psoriasis. Cross querte influiment NRI I: 216/314 (68.8%) Stur | tudy supported and |
| EXPRESS II candidates for At week 14 patients 5 mg/kg at week 16 19 | unded by Centocor |
| phototherapy or were re-randomised to and 22 and every 8 Results – week 10 | |
| systemic therapy, PASI either every-8-week weeks thereafter Primary endpoint Patients with ≥ 1 serious | |
| score of ≥ 12 , BSA $\geq 10\%$ continuous PASI ≥ 75 , n (%) AE, n (%) | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------------------|-------------------------|---------------------------|----------------------|-----------------------|-----------------------|--------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| Multicenter study, at 63 | | maintenance therapy | n=208 | I: 237/314 (75.5%) | I: 9/314 (2.9%) | |
| sites in USA, Canada | Baseline variables: | (week 14, 22, 30, 38 | | C: 4/208 (1.9%) | C: 5/207 (2.4%) | |
| and Europe | Female/Male, (%) | and 46) or intermittent | Drop-out rate, n (%) | l vs C: p<0.001 | | |
| | I: 35.0%/65.0% | as-needed maintenance | 24/208=11.5% | | Patients with ≥1 | |
| RCT | C: 30.8%/69.2% | therapy (infliximab at | | Secondary endpoints | infection, n (%) | |
| | Bodyweight (kg), mean | original dose if PASI | | PASI ≥90, n (%) | I: 97/314 (30.9%) | |
| | ±SD | ≤75%, otherwise | | I: 45.2% | C: 62/207 (30.0%) | |
| | I: 92.2 ± 23.2 | placebo) | | C: 0.5% | | |
| | C: 91.1 ±22.6 | | | l vs C: p<0.001 | Patients with ≥1 | |
| | Ethnicity - Caucasian | l: n=314 | | | infusion reactions | |
| | I: 93.3% | | | DLQI, median change | I: 30/314 (9.6%) | |
| | C: 90.9% | Drop-out rate, n (%) | | from baseline to week | C: 12/207 (5.8%) | |
| | | I: 17/314=5.4% | | 10 | | |
| | Study period | | | I: -9.0 | Common adverse events | |
| | No information | The trial also included a | | C: 0.0 | in ≥5% in any group | |
| | | treatment arm where | | I vs C: p<0.001 | URTI, n (%) | |
| | Follow up | patients received | | | I: 42 (13.4%) | |
| | 16-week placebo | infliximab 3 mg/kg | | | C: 29 (14.0%) | |
| | controlled trial | | | | | |
| | (reported here). | | | | Headache, n (%) | |
| | (Treatment week 0, 2, 6 | | | | I: 38 (12.1%) | |
| | and thereafter | | | | C: 11 (5.3%) | |
| | additional dose per | | | | | |
| | treatment schedule | | | | Pharyngitis, n (%) | |
| | (see the "Intervention" | | | | I: 16 (5.1%) | |
| | and "Control" columns) | | | | C: 7 (3.4%) | |
| | OLE until week 50 | | | | | |
| | | | | | Nausea, n (%) | |
| | | | | | I: 12 (3.8%) | |
| | | | | | C: 8 (3.9%) | |
| | | | | | | |
| | | | | | Sinusitis, n (%) | |
| | | | | | 1: 20 (6.4%) | |
| | | | 1 | | C: 3 (1.4%) | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|-------------------------|-------------------------|--------------------------|--------------------------|-----------------------|---------------------------|--------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| Yang et al | Population | Intervention (I) | Comparison (C) | Analysis model | Adverse events | Risk of bias |
| 2012 | Inclusion criteria: | Infliximab 5 mg/kg, | Placebo, intravenous | ITT | 10 weeks | Acceptable |
| [108] | Patients aged 18-65, | intravenous infusion at | infusion, week 0, 2 and | | Patients with AE, n (%) | |
| | diagnosis of plaque | week 0, 2 and 6, and | 6. | Results – week 10 | I: 36/84 (42.9%) | Comment |
| Multicenter study, at 9 | psoriasis ≥6 months, | every 8 weeks | Cross-over to infliximab | Secondary endpoints | C: 17/45 (37.8%) | |
| centers in China | have failed to respond | thereafter (week 14, 22) | 5mg/kg at week 10, 12 | PASI ≥50, n (%) | | |
| | to conventional | | and 16 | I: 79/84 (94.0%) | Patients with serious | |
| RCT | systemic anti-psoriasis | n=84 | | C: 6/45 (13.3%) | AE, n (%) | |
| | therapy, PASI score of | | n=45 | l vs C: p<0.001 | I: 1/84 (1.2%) | |
| | ≥12, BSA ≥10%, no | Drop-out rate through | | | C: 0/45 (0.0%) | |
| | history of serious | week 10 (placebo- | Drop-out rate through | Primary endpoint | | |
| | infections, | controlled phase) | week 10 (placebo- | PASI ≥75, n (%) | Tuberculosis, n (%) | |
| | lymphoproliferative | 1/84=1.2% (due to | controlled phase) | I: 68/84 (81.0%) | I: 0/84 (0%) | |
| | disease or active | adverse event) | 1/45=2.2% (Withdrawal | C: 1/45 (2.2%) | C: 0/45 (0%) | |
| | tuberculosis. | | of informed consent) | l vs C: p<0.001 | | |
| | | | | | Infusion reactions, n (%) | |
| | Baseline variables: | | | PASI ≥90, n (%) | 1: 3/84 (3.6%) | |
| | Female/Male (%) | | | I: 48/84 (57.1%) | C: 0/45 (0%) | |
| | I: 28.6%/71.4% | | | C: 0/45 (0.0%) | | |
| | C: 22.2%/77.8% | | | l vs C: p<0.001 | URTI, n (%) | |
| | | | | | I: 6/84 (7.1%) | |
| | Bodyweight (kg), mean | | | DLQI change, mean ±SD | C: 4/45 (8.9%) | |
| | ± SD | | | I: -8.0 ±7.1 | | |
| | I: 68.2 ± 9.2 | | | C: -1.5 ±5.1 | Asthenia, n (%) | |
| | C: 67.4 ±9.9 | | | I vs C: p<0.001 | I: 6/84 (7.1%) | |
| | | | | | C: 2/45 (4.4%) | |
| | Ethnicity | | | | | |
| | No information, but | | | | | |
| | study conducted in | | | | | |
| | China to validate | | | | | |
| | efficacy and safety in | | | | | |
| | Chinese patients | | | | | |
| | | | | | | |
| | | | | | | 1 |

| First Author | Population Setting | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------|-------------------------|--------------|------------|----------------|----------------|--------------|
| Reference | Setting | | | Results | | comment |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| | Study period | | | | | |
| | February 2009 – | | | | | |
| | February 2010 | | | | | |
| | | | | | | |
| | Follow up | | | | | |
| | 10 weeks placebo | | | | | |
| | controlled trial. | | | | | |
| | (Treatment week 0, 2 | | | | | |
| | and 6) and thereafter a | | | | | |
| | maintenance phase | | | | | |
| | (week 10–26), where | | | | | |
| | the control group were | | | | | |
| | switched to active | | | | | |
| | treatment as well. | | | | | |

AE – adverse event; BSA – body surface area; CI – confidence interval; DLQI –dermatology life quality index; ITT –intention-to-treat; LOCF – last observation carried forward; NRI – nonresponder imputation; OLE – open-label extension; PASI – psoriasis area and severity index; PGA – physician's global assessment; RCT – randomised controlled trial; SD – standard deviation; URTI – upper respiratory tract infection

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|-------------------------|---------------------------|-------------------------|---------------------------|------------------------|--------------------------|--------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| de Vries et al | Population | Intervention (I) | Comparison (E) | Analysis model | Adverse events at 48 | Risk of bias |
| 2017 | Adult patients ≥18 yrs | Infliximab 5 mg/kg, | Etanercept 100 mg/week | ITT – all who received | weeks | Acceptable |
| [109] | with moderate to severe | intravenous infusion at | in self- administered s.c | ≥1 dose of test | Patients reporting any | |
| | plaque psoriasis (PASI | week 0, 2 and 6, and | injections (50 mg twice | substance included. | adverse event | Comment |
| Multicenter study | ≥10, and/or BSA ≥10, | every 8 weeks | weekly). In case of | | IFX: 24/25 (96%) | |
| performed at 5 sites in | and or PASI≥8 plus | thereafter. In case of | inadequate response or | Results week 12 | ETA: 23/23 (100%) | |
| the Netherlands | Skindex-29 ≥35). | inadequate response or | AE:s patients could | PASI ≥50 | | |
| | Contraindicated or | AE:s patients could | switch to the other | IFX: 24/25 (96%) | Patients reporting | |
| RCT | intolerant for UV | switch to the other | treatment arm. | ETA: 14/23 (60.9%) | serious adverse events | |
| | therapy, MTX or | treatment arm (1/25 did | | l vs E: p<0.05 | IFX: 1 (stomach pain) | |
| | cyclosporine. No prior | switch to etanercept)). | n=25 | | ETA: 1 (angina pectoris) | |
| | inadequate response to | | _ | PASI≥75 | | |
| | etanercept or infliximab. | n=25 | | IFX: 19/25 (76%) | Adverse events leading | |
| | | | Drop-out rate | ETA: 5/23 (21.7%) | to discontinuation | |
| | Baseline characteristics | Drop-out rate | 2/25 (8%) | l vs E: p<0.05 | IFX: 3 (1 reactive | |
| | Male/female | 1/25 (4%) | | | arthritis, 1 | |
| | I: 72%/28% | | | PASI ≥90 | erythroderma, 1 | |
| | E: 66%/44% | | | IFX: 5/25 (20%) | liverdysfunction) | |
| | Mean age (SD) | | | ETA: 0/23 (0) | ETA: 2 (1 neutropenia, | |
| | I: 45.9 (13.9) | | | l vs E: p=0.05 | 1 exacerbation of | |
| | E: 42.4 (13.2) | | | | psoriasis) | |
| | PASI, mean (SD) | | | PASI ≥100 | | |
| | I: 17.8 (9.7) | | | IFX: 1/25 (4%) | <u>Adverse events w</u> | |
| | E: 15.9 (5.1) | | | ETA: 0/23 (0) | significant differences | |
| | Body weight or BMI | | | l vs E: p=1 | <u>btw groups (in n</u> | |
| | Not given | | | | <u>patients)</u> | |
| | | | | PASI, absolute mean | Circulatory disorders | |
| | Study period | | | reduction (SD) | IFX: 8/25 (32%) | |
| | April 2009–June 2011 | | | IFX: 14.8 (9.6) | ETA: 4 (17.4%) | |
| | | | | ETA: 9.1 (6.0) | l vs E: p=0.01 | |
| | Follow-up | | | l vs E: p=0.02 | | |

Table 7.5. Infliximab versus Etanercept

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------|--------------------------|--------------|------------|-----------------------|------------------------|--------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| | RCT for 12 weeks, with a | | | | Abnormalities in blood | |
| | total follow up for 48 | | | PASI, relative mean | count | |
| | weeks. | | | reduction (SD) | IFX: 12/25 (48%) | |
| | | | | IFX: 79.8% (17.8) | ETA: 5/23 (21.7%) | |
| | | | | ETA: 52.9% (24.0 | | |
| | | | | l vs E: p<0.05 | | |
| | | | | | | |
| | | | | SF-36 – physical | | |
| | | | | component scale, mean | | |
| | | | | improvement (SD) | | |
| | | | | IFX: 7.7 (9.7) | | |
| | | | | ETA: 8.9 (10.6) | | |
| | | | | I vs E: p=0.69 | | |
| | | | | | | |
| | | | | SF-36 – mental | | |
| | | | | component scale, mean | | |
| | | | | improvement (SD) | | |
| | | | | IFX: 1.4 (11.7) | | |
| | | | | ETA: 0.5 (7.8) | | |
| | | | | I vs E: p=0.76 | | |

AE – adverse event; BSA – body surface area; CI – confidence interval; DLQI –dermatology life quality index; ITT –intention-to-treat; LOCF – last observation carried forward; NRI – nonresponder imputation; OLE – open-label extension; PASI – psoriasis area and severity index; PGA – physician's global assessment; RCT – randomised controlled trial; SD – standard deviation; URTI – upper respiratory tract infection

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|------------------------|--------------------------|-------------------------|-------------------------|-------------------------|--------------------------|---------------------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up | | | | | |
| Lebwohl et al 2015 | Population | Intervention (I) | Comparison (C) | Analysis Model | Adverse events | Risk of bias |
| [111] | Inclusion criteria | I: Brodalumab | Subcutaneous injection | ITT | | Acceptable |
| | Patients 18–75 years of | 210 mg/injection | with placebo on day 1 | | AMAGINE-2, (week 12) | |
| Data from the | age, candidates for | | and weeks 1, 2, 4, 6, 8 | Safety population: all | Any AE, n (%) | Comment |
| AMAGINE-2 (A) and | biologic therapy, with | Subcutaneous injection | and 10 | patients who received | I: 354/612 (57.8%) | Study funded and |
| AMAGINE 3 (B) studies | plaque-psoriasis for ≥6 | day 1 and week 1, 2, 4, | | ≥1 dose of the study | C: 165/309 (53.4%) | supported by Amgen. |
| are presented | months with a PASI | 6, 8 and 10 | At 12 weeks patients | product | | |
| | score ≥12, sPGA score | | randomised to placebo | | Serious AE, n (%) | Weight-based analysis |
| Multicentre trials | ≥3 and BSA ≥10% | Randomisation | switched to | Missing data | I: 6/612 (1.0%) | group was a prespecified |
| AMAGINE-2 was | | stratified by body | brodalumab | NRI | C: 8/309 (2.6%) | subgroup that included |
| conducted at 142 sites | Baseline characteristics | weight (≤100 kg, | | | | patients with a body |
| worldwide, AMAGINE-3 | Female/Male, (%) | >100 kg), geographic | AMAGINE-2 (n) | Results | Fatal AE, n (%) | weight of 100 kg or less |
| was conducted at 142 | AMAGINE 2: 31%/69% | region, previous use of | C: 309 | AMAGINE-2 week 12 | I: 1/612 (0.2%) | who were in the group |
| different sites | AMAGINE 3: 32 %/68 % | biologic agents | | | C: 0/309 (0%) | that received 140 mg of |
| worldwide | | | Drop-out rate | PASI ≥75, % (95% CI), n | | brodalumab every 2 |
| | BMI (kg/m²), mean ±SD | AMAGINE-2 (n) | (12 weeks) | – primary endpoint | AE leading to | weeks and patients with a |
| RCT | AMAGINE 2: 30.6 ±7.2 | I: 612 | C: 9/309 (2.9%) | I: 86% (83, 89), 528 | discontinuation of | body weight greater that |
| | AMAGINE 3: 30.1±6.9 | | | C: 8% (5,12), 25 | study, n (%) | 100kg who were in the |
| | | Drop-out rate | | I vs C: p<0.001 | I: 6/612 (1.0%) | group that received 210 |
| | Ethnicity (Caucasian), % | (12 weeks) | AMAGINE-3 (n) | | C: 0/309 (0%) | mg of brodalumab every |
| | AMAGINE 2: 90% | I: 15/612 (2.5%) | C: 315 | PASI 100, % (95% CI), n | | 2 weeks. |
| | AMAGINE 3: 91% | | | I: 44% (41, 49), 272 | Leading to | |
| | | AMAGINE-3 (n) | Drop-out rate | C: 1% (0, 2), 2 | discontinuation of study | |
| | Study period | I: 624 | (12 weeks) | I vs C: p<0.001 | drug, n (%) | |
| | AMAGINE-2: August | | C: 14/315 (4.4%) | | I: 6/612 (1.0%) | |
| | 2012-September 2014 | Drop-out rate | | AMAGINE-3 week 12 | C: 1/309 (0.3%) | |
| | AMAGINE-3: | (12 weeks) | | | | |
| | September 2012- | I: 16/624 (2.6%) | | PASI ≥75, % (95% CI), n | Common AE (≥5% of | |
| | August 2014 | At week 12 placebo | | – primary endpoint | patients in any | |
| | | controlled phase | | I: 85% (82, 88), 531 | treatment group) | |
| | | ended. Results from | | C: 6% (4,9), 19 | Nasopharyngitis, n (%) | |

Table 7.6. Brodalumab versus placebo

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------|-------------------------|-----------------------|------------|-------------------------|----------------------|--------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up | | | | | |
| | | maintenance phase not | | l vs C: p<0.001 | I: 45/612 (7.4%) | |
| | Follow-up | included here | | | C: 14/309 (4.5%) | |
| | 12 weeks induction | | | PASI 100, % (95% CI), n | | |
| | phase (placebo | | | I: 37% (33, 41), 229 | URTI, n (%) | |
| | controlled), plus | | | C: 0.3% (0, 2), 1 | I: 30/612 (5.4%) | |
| | 40 weeks maintenance | | | I vs C: p<0.001 | C:23/309 (7.4%) | |
| | phase | | | | | |
| | | | | | Headache, n (%) | |
| | The study also included | | | | I: 31/612 (5.1%) | |
| | treatment group where | | | | C: 9/309 (2.9%) | |
| | patients received 140 | | | | | |
| | mg brodalumab, same | | | | Arthralgia, n (%) | |
| | regime as for | | | | I: 28/612 (4.6%) | |
| | intervention, or | | | | C: 12/309 (3.9%) | |
| | ustekinumab (45 mg | | | | | |
| | ≤100 kg bodyweight, 90 | | | | AMAGINE-3, (week 12) | |
| | mg >100 kg) at day 1, | | | | | |
| | week 4 and wevery 12 | | | | Any AE, n (%) | |
| | weeks thereafter | | | | I: 353/622 (56.8%) | |
| | | | | | C: 152/313 (48.6%) | |
| | | | | | | |
| | | | | | Serious AE, n (%) | |
| | | | | | I: 9/622 (1.4%) | |
| | | | | | C: 3/313 (1.0%) | |
| | | | | | | |
| | | | | | Fatal AE, n (%) | |
| | | | | | I: 0/622 (0%) | |
| | | | | | C: 0/313 (0%) | |
| | | | | | | |
| | | | | | AE leading to | |
| | | | | | discontinuation of | |
| | | | | | stuydy, n (%) | |
| | | | | | I: 5/622 (0.8%) | |
| | | | | | C: 2/313 (0.6%) | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|---|------------------------|
| Year | Setting | | | Poculto | | Comment |
| Country | Study period | | | Results | | |
| Study design | Follow-up | | | | | |
| Study design | | | | | Leading to discontinuation of study drug, n (%) 1: 7/622 (1.1%) C: 3/313 (1.0%) Common AE (≥5% of patients in any treatment group) Nasopharyngitis, n (%) 1: 31/622 (5.0%) C: 22/313 (7.0%) URTI, n (%) 1: 33/622 (5.3%) C:17/313 (5.4%) Headache, n (%) 1: 21/622 (3.4%) C: 14/313 (4.5%) Arthralgia, n (%) | |
| | | | | | 1: 36/622 (5.8%) C: 10/313 (3.2%) | |
| Nakagawa et al. 2016 | Population | Intervention (I) | Comparison (C) | Analysis model | Adverse Events | Risk of bias |
| [112] | Patients 20-70 years of | Subcutaneous injection | Subcutaneous injection | ITT | All AE, n (%) | Acceptable |
| Church a service 1 and 1 and 1 and 1 | age, stable plaque | with Brodalumab | with Placebo on day 0 | A disating a such | 1: 27/37 (73.0%) | |
| Study carried out at 56 | psoriasis for ≥6 months | 210 mg, on day 0 and | and week 1, 2, 4, 6, 8, | Missing values | C: 17/38 (44.7%) | Comment |
| sites in Japan | with a PASI score ≥12 | week 1, 2, 4, 6, 8, and | and 10 | Baseline value carried- | | Study supported by |
| | and BSA ≥10%. | 10 | | torward was used for | Serious AE, n (%) | Kyowa Hakko Kirin Co., |
| RCT | Received or were | | | the percentage | I: 1/37 (2.7%) | Ltd |
| | candidates for photo | Dose & randomised | Dose & randomised | improvement in PASI | C: 1/38 (2.6%) | |
| | | population | population | scores and BSA. | | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------|--------------------------|--------------------------|----------------------|---------------------|-----------------------|-----------------------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up | | | | | |
| | therapy or systemic | I: 210 mg, n=37 | C: n=38 | NRI used for other | Common adverse | Randomisation of 151 |
| | therapy | | | efficacy endpoints | events (cut-off not | patients, stratification |
| | | Drop-out rate, n (%) | Drop-out rate, n (%) | | specified) | based on 4 parameters, |
| | Baseline characteristics | I: 0/37 | 4/38 (10.5%) | Results – week 12 | Nasopharygitis, n (%) | including 56 "institutions" |
| | Female/Male | | | | I: 4/37 (10.8%) | (study sites), may lead to |
| | I: 21.6%/78.4% | | | PAS I≥75, n (%) | C: 3/38 (7.9%) | selection bias |
| | C: 28.9%/ 71.1% | The trial also included | | 1: 35/37 (94.6%) | | |
| | | study groups that | | C: 3/38 (7.9%) | Diarrhoea, n (%) | |
| | BMI (kg/m²), mean±SD | received injections with | | l vs C: p<0.001 | 1: 3/37 (8.1%) | |
| | 1: 26.34±5.63 | 70 mg or 140 mg | | | C: 0/38 (0%) | |
| | C: 26.02±4.68 | brodalumab | | PASI ≥90, n (%) | E 11: 1:1: (0() | |
| | All patients described | | | 1: 34/37 (91.9%) | Folliculitis, n (%) | |
| | as Japanese | | | C:1/38 (2.6%) | 1: 2/37 (5.4%) | |
| | Developsiontion | | | TVS C: p<0.001 | C: 0/38 (0%) | |
| | Randomisation | | | DACI 100 - (0/) | | |
| | stratified by psoriatic | | | PASI 100, N (%) | UR11, N (%) | |
| | artifitis, additional | | | 1. 22/37 (59.5%) | 1.0/37(0%) | |
| | | | | C. 0/30 | C. 0/38 (0%) | |
| | biological therapy and | | | 1 V3 C. p<0.001 | | |
| | study site | | | DI OI change from | | |
| | study site | | | haseline mean +SD | | |
| | Study period | | | 10 0+6 0 | | |
| | Not clear | | | C: -2.0±6.7 | | |
| | | | | l vs C: p<0.001 | | |
| | Follow-up | | | | | |
| | 12-week placebo- | | | SF-36 (change from | | |
| | controlled trial | | | baseline), mean ±SD | | |
| | followed by a 1 year | | | PCS | | |
| | open-label extension | | | I: 8.09±16.58 | | |
| | | | | C: 0.16±10.66 | | |
| | | | | l vs C: p<0.05 | | |
| | | | | MCS | | |
| | | | | I: 5.00±6.85 | | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|------------------------|---------------------------|-----------------------|------------|-----------------------|-------------------------|----------------------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up | | | | | |
| | | | | C: -1.05±9.55 | | |
| | | | | I vs C: p<0.05 | | |
| Umezawa et al | Population | Intervention | | Analysis model | Results | Risk of bias |
| 2016 | For inclusion criteria to | Brodalumab 210 mg in | | ITT (all patients who | Adverse events at 52 | |
| [116] | the initial RCT, see | s.c. injections every | | received ≥1 dose of | <u>weeks</u> | Comment |
| | [112] | second week | | study drug included). | Any AE: | Risk of bias for OLE:s not |
| OLE (for main RCT, see | | | | | 66/72 (91.7%) | assessed (observational |
| [112]) | Follow-up | | | | | data collected only) |
| | 52 weeks | n=72 | | | AE:s resulting in | |
| | | | | | discontinuation: | |
| | | Drop-out rate | | | None | |
| | | Total: 3/72 (4.2%) | | | Detiente de tiente | |
| | | | | | Patients electing to | |
| | | | | | suspend study | |
| | | | | | | |
| | | | | | 12/72 (10.7%) | |
| | | | | | Serious adverse events: | |
| | | | | | 4/72 (55.6%) | |
| | | | | | Most common AF's (% | |
| | | | | | in both aroups | |
| | | | | | combined): | |
| | | | | | Nasopharvnaitis: | |
| | | | | | 35.2% | |
| | | | | | | |
| | | | | | URTI: | |
| | | | | | 10.3% | |
| | | | | | Contact dermatitis: | |
| | | | | | 9.7% | |
| | | | | | AE:s of interest: | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|-------------------------|--------------------------|----------------------------|-------------------------|------------------------|---|--------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up | | | | | |
| | | | | | Neutrophilia: | |
| | | | | | 1/72 (1.4%) | |
| | | | | | | |
| | | | | | Candidiasis: | |
| | | | | | 8/72 (11.1%) | |
| | | | | | | |
| | | | | | Injection site reactions: | |
| | | | | | 2/72 (2.8%) | |
| Papp et al | Population | Intervention (I) | Comparison (C) | | Adverse events | |
| 2012 | Patients 18–70 years, | 1: 210 mg brodalumab | C: placebo | Efficacy outcomes II I | Safety population (n) | Acceptable |
| [113] | stable plaque psoriasis | Dendemined a | Dan damiaad n | Safety outcomes | 1:40 | Comment |
| Multicontro study at 22 | 20 months, candidates | Randomised, n | Kandomised, n | nationts who received | 0.37 | Comment |
| international sites | nhotothorany or | 1. 40 | C.59, mITT: 28 | >1 doco of tost | AEs - 12 wooks | |
| international sites. | systemic psoriasis | Drop out rate (week | 11111.30 | 21 UUSE OF LESL | ALS - 12 WEEKS | Aingen |
| Same study as | therapy BSA >10% | 12) · n (%) | Dron-out rate (week | Patient-reported | $\Lambda n \sqrt{\Lambda E > 1} n (\%)$ | |
| described in Gordon et | PASI score > 12 | 12).11(70) 1.3/10(7.5%) | 12) · n (%) | outcomes | 1. 33 (82%) | |
| al 2014 [110] | | 1. 5/ 40 (7.570) | $(\cdot 3/38 (7.9\%))$ | mITT (all randomized | C· 23 (62%) | |
| al. 2014 [110] | Baseline characteristics | Subcutaneous injection | C. 3730 (7.370) | natients who | 0270 | |
| RCT | Female/Male. (%) | day 1 and week 1. 2. 4. | Subcutaneous injection | completed >1 post | Serious AF. n (%) | |
| | 1: 38%/62% | 6. 8. and 10 | day 1 and week 1. 2. 4. | baseline assessment). | 1: 1 (2%) | |
| | C: 42%/58% | -, -, | 6, 8, and 10 | Primary endpoint | C: 1 (3%) | |
| | | | , , | analysed with baseline | | |
| | BMI (kg/m²), mean ±SD | | | BMI and PASI score as | Leading to withdrawal | |
| | l: 29.8±6.6 | | | covariates | from study, n (%) | |
| | C:29.3±6.8 | | | | I: 0 (0%) | |
| | | | | Missing data | C: 0 (0%) | |
| | Ethnicity (Caucasian), % | | | Baseline value carried | | |
| | I: 85% | | | forward | Leading to | |
| | C: 84% | | | | discontinuation of study | |
| | | | | Results – week 12 | drug, n (%) | |
| | Study period | | | | I: 2 (5%) | |
| | Enrolment: December | | | PASI ≥50, n (%) | C: 1 (3%) | |
| | 2009-April 2010 | | | I: 36 (90%) | | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------|-------------------------|--------------|------------|--------------------------------|--------------------------|--------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up | | | | | |
| | | | | I vs C: p<0.001 | Common AEs (≥4 | |
| | Follow-up | | | C: 6 (16%) | patients in any | |
| | Treatment (placebo | | | | treatment group, | |
| | controlled trial) week | | | PASI ≥75, n (%) | ~9.8%, 12 weeks) | |
| | 0–10. | | | I: 33 (82%) | Nasopharyngitis, n (%) | |
| | Efficacy and safety | | | l vs C: p<0.001 | I: 4 (10%) | |
| | assessment at week 12 | | | C: 0 (0%) | C: 3 (8%) | |
| | and 16. | | | | | |
| | | | | PASI ≥90 <i>,</i> n (%) | URTI, n (%) | |
| | The trial also included | | | I: 30 (75%) | I: 2 (5%) | |
| | treatment arms where | | | l vs C: p<0.001 | C: 2 (5%) | |
| | patients received 70, | | | C: 0 (0%) | | |
| | 140 or 280 mg | | | | Arthraliga, n (%) | |
| | brodalumab | | | PASI 100, n (%) | I: 0 (0%) | |
| | | | | I: 25 (62%) | C: 1 (3%) | |
| | | | | I vs C: p<0.001 | | |
| | | | | C: 0 (0%) | Injection-site erythema, | |
| | | | | SF-36 | 1:3 (8%) | |
| | | | | PCS – baseline: w12: | (3,0) | |
| | | | | (change) mean +SD | 0.1(5) | |
| | | | | 13· /8 1+8 9)· | Pain in extremity n (%) | |
| | | | | $(52 1+7 8) \cdot (4 0+8 4)$ | 1. 2 (8%) | |
| | | | | (52.127.0), (4.020.4) | C = 0 (0%) | |
| | | | | $(50.1+10.5) \cdot (1.5+10.2)$ | 0.0(0)0) | |
| | | | | $(30.1\pm10.5), (1.3\pm10.2)$ | Nausea n (%) | |
| | | | | 1 13 6.113 | 1. 1 (2%) | |
| | | | | MCS – baseline; w12; | C: 1 (3%) | |
| | | | | (change), mean ±SD | | |
| | | | | I: 48.7±12.6; 53.8±7.5; | | |
| | | | | (5.1±10.4) | | |
| | | | | C: 45.2±14.5; | | |
| | | | | 46.9±11.2; (1.7±13.0) | | |
| | | | | l vs C: p<0.01 | | |

| Reference Country Study period Follow-up Study period Results Results Study design Follow-up Intervention (I) Analysis Model Adverse Events Risk of bias Gordon et al 2014 Population Intervention (I) Comparison (C) Analysis Model Adverse Events Risk of bias [110] Inclusion criteria As described in Papp et As described in Papp et As described in Papp et Acceptable | Year | Setting | intervention | Comparison | Analysis model | Adverse events | Comment |
|--|-------------------------|---|-------------------------|-------------------------|----------------------------|-----------------|-------------------------|
| Country Study period Study design Follow-up Follow-up Comparison (C) Gordon et al 2014 Population Intervention (I) Comparison (C) Analysis Model Adverse Events Risk of bias [110] Inclusion criteria As described in Papp et As described in Papp et MITT all patients who Reported in Papp et al Acceptable | Reference | | | | Results | | |
| Study design Follow-up Follow-up Gordon et al 2014 Population Intervention (I) Comparison (C) Analysis Model Adverse Events Risk of bias [110] Inclusion criteria As described in Papp et As described in Papp et mITT all patients who Reported in Papp et al Acceptable | Country | Study period | | | | | |
| Gordon et al 2014 Population Intervention (I) Comparison (C) Analysis Model Adverse Events Risk of bias [110] Inclusion criteria As described in Papp et As described in Papp et MITT all patients who Reported in Papp et al Acceptable | Study design | Follow-up | | | | | |
| [110] Inclusion criteria As described in Papp et As described in Papp et MITT all patients who Reported in Papp et al Acceptable | Cardan at al 2014 | Demulation | Interreption (I) | Companian (C) | Analusia Madal | Advance Friends | Dials of hims |
| [110] $[110]$ $[110$ | Gordon et al 2014 | | As described in Papp of | Comparison (C) | Manalysis Wodel | Adverse Events | Accontable |
| As described in Papp et al 2012 [113] al 2012 [113] received >1 dose of test 2012 [113] | [110] | As described in Pann et | al 2012 [112] | AS described in Papp et | received >1 dose of test | 2012 [112] | Acceptable |
| Same study as al 2012 [113] al. 2012 [115] al. 2012 [115]. Substance | Same study as | al 2012 [113] | ai 2012 [115] | ai. 2012 [115]. | substance | 2012 [115] | Comment |
| described in Papp et al. Patients 18–70 years. I: 210 mg brodalumab. C: placebo | described in Papp et al | Patients 18–70 years. | I: 210 mg brodalumab | C: placebo | Substance | | Funded and supported by |
| 2012 [113]. Stable plaque psoriasis Missina data Amgen | 2012 [113]. | stable plaque psoriasis | | | Missina data | | Amgen |
| In this publication ≥6 months, BSA ≥10%, Randomised, n Randomised, n LOCF | In this publication | ≥6 months, BSA ≥10%, | Randomised, n | Randomised, n | LOCF | | C |
| additional DLQI data PASI score ≥12 I: 40 C:38 | additional DLQI data | PASI score ≥12 | I: 40 | C:38 | | | |
| and psoriasis symptom P-value adjusted w, | and psoriasis symptom | | | | P-value adjusted w, | | |
| inventory (PSI) score Baseline characteristics Drop-out rate (week Drop-out rate (week linear model for | inventory (PSI) score | Baseline characteristics | Drop-out rate (week | Drop-out rate (week | linear model for | | |
| are reported Female/Male, (%) 12), n (%) 12): n (%) baseline BMI≤35, >35 | are reported | Female/Male, (%) | 12), n (%) | 12): n (%) | baseline BMI≤35, >35 | | |
| I: 38%/62% I: 3/40 (7.5%) C: 3/38 (7.9%) | | I: 38%/62% | I: 3/40 (7.5%) | C: 3/38 (7.9%) | | | |
| Multicentre study at 23 C: 42%/52% Results – week 12 | Multicentre study at 23 | C: 42%/52% | | | Results – week 12 | | |
| international sites Bodyweight (kg), mean Subcutaneous injection Subcutaneous injection | international sites | Bodyweight (kg), mean | Subcutaneous injection | Subcutaneous injection | | | |
| ±SD day 1 and week 1, 2, 4, day 1 and week 1, 2, 4, DLQI improvement: | DOT | ±SD | day 1 and week 1, 2, 4, | day 1 and week 1, 2, 4, | DLQI improvement: | | |
| RCT 1: 90.4±20.4 6, 8, and 10 6, 8, and 10 mean ±5D, n | RCI | 1: 90.4±20.4 | 6, 8, and 10 | 6, 8, and 10 | mean ±SD, n | | |
| $\begin{array}{c} C. 80.9 \pm 20.0 \\ \hline \\ Ethnicity (Caucasian) \\ \% \\ \hline \\ \end{array}$ | | C. 80.9±20.0 Ethnicity (Caucasian) % | | | $1.9.0\pm0.1,40$ | | |
| Limitly (caasain), % | | 1. 85% | | | C = 3 + 6 = 6 = 37 | | |
| C: 84% | | C· 84% | | | C. J.1±0.0, J7 | | |
| | | 0.01/0 | | | | | |
| Study period | | Study period | | | | | |
| December 2009-April | | December 2009-April | | | | | |
| 2010 | | 2010 | | | | | |
| | | | | | | | |
| Follow-up | | Follow-up | | | | | |
| Treatment (placebo | | Treatment (placebo | | | | | |
| controlled trial) week | | controlled trial) week | | | | | |
| | | 0-10. | | | | | |
| Efficacy and safety | | Efficacy and safety | | | | | |
| assessment at week 12 | | assessment at week 12 | | | | | |
| | | | | | | | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------------|---------------------------|--------------------------|------------|--------------------------|-------------------------------|-----------------------|
| Year Reference | Setting | | | Results | | Comment |
| Country | Study period | | | Results | | |
| Study design | Follow-up | | | | | |
| Papp et al | Population | Intervention | | Analysis model | Adverse events | Risk of bias |
| 2016 | For inclusion criteria to | Initially (from OLE | | ITT (all patients who | Treatment emergent | Not assessed |
| [117] | the initial RCT, see | baseline) Brodalumab | | received at least 1 dose | <u>AE:s over 120 weeks, n</u> | |
| OLE (for main RCT, | [113] | 210 mg s.c. every other | | of test substance | <u>(%)</u> | Comment |
| [113]) | | week. After protocol | | included). Missing | Any AE: | Risk of bias for OLE- |
| | Study period | adjustment the dose | | values were not | 171/181 (94.5%) | studies not assessed |
| | | was reduced to 140 mg | | imputed. | | (observational data |
| | Follow-up | in patients weighing ≤ | | | Serious AE: | collected only) |
| | 120 weeks | 100 kg. If inadequate | | | 15 (8.3%) | |
| | | response the dose was | | | | |
| | | increased back to 210 | | | AE:s leading to | |
| | | mg. | | | discontinuation of study | |
| | | | | | drug: | |
| | | n=181 (all patients, | | | 11 (6.1%) | |
| | | regardless of test dose | | | | |
| | | in the RCT-phase were | | | <u>Common AE:s (reported</u> | |
| | | included). Of those | | | <u>by ≥10 %):</u> | |
| | | patients who originally | | | Nasopharyngitis: | |
| | | had 210 mg | | | 48 (26.5%) | |
| | | Brodalumab every | | | | |
| | | other week, 35 | | | URTI: | |
| | | remained, and of those | | | 36 (19.9%) | |
| | | who originally had | | | | |
| | | placebo, 33 remained | | | Arthralgia: | |
| | | at the start of the OLE- | | | 29 (16%) | |
| | | study. | | | | |
| | | | | | Back pain: | |
| | | Drop-out rate (patients | | | 20 (11%) | |
| | | still on brodalumab | | | | |
| | | therapy at week 120) | | | Events of interest | |
| | | All: 33/181 (18.2%) | | | Neutrophilia | |
| | | | | | (transient): | |
| | | Group ≤100 kg: 8/119 | | | 4 (2%) | |
| | | (6.7%) | | | | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|-----------------------|--------------------------|-----------------------|-----------------------|--------------------------|------------------------------|------------------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up | | | | | |
| | | | | | Candidiasis: | |
| | | Group >100 kg: 25/62 | | | 5 (3%) | |
| | | (40.3%) | | | | |
| | | | | | Injection site reactions: | |
| | | | | | 15 (8%) | |
| | | | | | Infontiona landina ta | |
| | | | | | Injections leading to | |
| | | | | | $\sqrt{20}$ | |
| Pann et al | Population | Intervention (I) | Comparison (C) | Analysis model | Adverse Events | Risk of higs |
| 2016 | | l: 210 mg/injection | Discobo injections | Efficacy and points | Auverse Events | |
| [114] | Patients aged 19-75 | 1. 210 mg/mjection | | | AEs – wook 12 | Acceptable |
| [114] | vears with stable | Brodalumah injections | of administration not | Safety population | ALS - WEEK 12 | Comment |
| Multicentre study | plaque psoriasis for >6 | every two weeks route | stated | All randomised natients | $\Delta n v \Delta F n (\%)$ | Study funded and |
| nerformed carried out | months BSA >10% | of administration not | Stated | who received >1 dose | 1. 131/222 (59 0%) | supported by Amgen and |
| at 73 sites in Europe | PASI > 12 and sPGA > 3 | stated | Allocation | of test substance | $C \cdot 112/220 (50.9\%)$ | AstraZeneca/MedImmune |
| Canada and USA. | | stated | n=220 | | 0.112/220 (30.370) | |
| | Baseline characteristics | Allocation | | Results – week 12 | Serious AE. n (%) | |
| Study name | Female/Male (%) | l: n=222 | Drop-out rate – week | | I: 4/222 (1.8%) | |
| AMAGINE-1 | I: 27%/73% | | 12 | PASI ≥75, n (%) (95% CI) | C: 3/220 (1.4%) | |
| | C: 27%/73% | Drop-out rate – week | C: 11/220 (5.0%) | I: 185 (83.3%) | | |
| RCT | BMI (kg/m²), mean ±SD | 12 | | (77.8, 88.0) | Fatal AE, n (%) | |
| | I: 31.0±7.7 | I: 10/222 (4.5%) | | C: 6 (2.7%) (1.0, 5.8) | I and C both 0 | |
| | C: 30.3±6.6 | | | l vs C: p<0.001 | | |
| | Ethnicity (Caucasian), % | | | | Leading to | |
| | I: 91% | | | PASI ≥90, n (%) (95% CI) | discontinuation from | |
| | C: 92% | | | I: 156 (70.3%) | study <i>, n (%)</i> | |
| | | | | (63.8, 76.2) | I: 2/222 (0.9%) | |
| | Study period | | | C: 2 (0.9%) (0.1, 3.2) | C: 3/220 (1.4%) | |
| | August 2012 – March | | | l vs C: p<0.001 | | |
| | 2014 | | | | Leading to | |
| | | | | PASI 100, n (%) (95% Cl) | discontinuation of | |
| | Follow-up | | | I: 93 (41.9%) | study drug, n (%) | |
| | | | | (35.3, 48.7) | l: 2/222 (0.9%) | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------|---------------------------|--------------|------------|------------------------|------------------------|--------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up | | | | | |
| | 12 weeks placebo- | | | C: 1 (0.5%) (0.0, 2.5) | C: 3/220 (1.4%) | |
| | controlled phase | | | l vs C: p<0.001 | | |
| | (reported here), | | | | Common AE (≥5% of | |
| | followed by 40 weeks | | | | patients in any | |
| | of withdrawal and | | | | treatment group) | |
| | retreatment phase | | | | Nasopharyngitis, n (%) | |
| | | | | | I: 21 (9.5%) | |
| | Induction phase | | | | C: 22 (10.0%) | |
| | Randomisation at | | | | | |
| | baseline stratified by | | | | URTI, n (%) | |
| | bodyweigh (≤100 kg, | | | | I: 18 (8.1%) | |
| | >100 kg), prior | | | | C: 14 (6.4%) | |
| | biological use (capped | | | | | |
| | at 50%), and | | | | Headache, n (%) | |
| | geographical region. | | | | I: 11 (5.0%) | |
| | Randomisation to | | | | C: 7 (3.2%) | |
| | brodamulab 140 mg, | | | | | |
| | 210 mg or placebo | | | | | |
| | | | | | | |
| | The trial also included a | | | | | |
| | treatment arm in which | | | | | |
| | patients received 140 | | | | | |
| | mg brodalumab | | | | | |

AE – adverse events; BMI – body mass index; BSA – body surface area; DLQI – dermatology life quality index; ITT – intention-to-treat; LOCF – last observation carried forward; MCS – mental component summary score; mITT – modified ITT; PASI – psoriasis area and severity index; PCS – physical component summary score; PGA – physician's global assessment; pp – palmoplantar psoriasis; SD – standard deviation; SE – standard error; sPGA – static physician's global assessment; URTI – upper respiratory tract infection

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|---------------------------|--------------------------|----------------------------|--------------------------|------------------------------------|------------------------|-------------------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| Gordon <i>et al.</i> 2016 | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
| [119] | | | | ITT | | Acceptable |
| Study name | Adult patients (≥18 yrs) | 80 mg of ixekizumab | Placebo to match active | | Pooled for UNCOVER-1, | |
| UNCOVER-1 | with chronic plaque | every 2 weeks after a | treatments. | Safety population | UNCOVER-2 and | Comment |
| | psoriasis (diagnosis ≥6 | starting dose of 160 mg | | included all patients | UNCOVER-3 [88,119] | Conflict of interest |
| Multicentre study | months), involving | at week 0. | n: 431 | who received ≥1 dose | | study sponsored, |
| perfomed at over 100 | ≥10% body surface | | | of test substance or | Safety population, n | designed, data analysed |
| sites worldwide | area, sPGA ≥3 and PASI | Subcutaneous injection. | Drop-out rate (12 | placebo | I: 1167 | and publication written |
| | ≥12. Candidates for | Injection with placebo | weeks), n (%) | | C: 791 | by Eli Lilly, |
| RCT | phototherapy and/or | to match active | 24/431 (5.6%) | Missing values | | |
| | systemic therapy. | treatments | | For PASI and sPGA NRI | Week 0-12 | |
| | | | Baseline characteristics | | | |
| | Study period | Patients were stratified | Female/Male, (%) | Results UNCOVER-1 | Any AE, (%) | |
| | No information | by geographic region | n: 29.7%/70.3% | Week 12 | 1: 58.4 | |
| | | (North America vs. | Ethnicity (Caucasian), % | | C: 46.8 | |
| | Follow-up | other), weight (<100 kg | n:93.0% | PASI ≥75, n (%) - | | |
| | Induction period: 12 | or ≥100 kg), and | Bodyweight (kg), | primary endpoint | Serious AE, (%) | |
| | weeks. Week 12-60 | previous non-biologic | mean±SD | 1: 386/433 (89.1%) | 1:1.7 | |
| | withdrawal period. | systemic therapy | 92±25 | C: 17/431 (3.9%) | C: 1.5 | |
| | | (Inadequate response, | | T vs C: p<0.0001 | Discontinuation due to | |
| | | Intolerance, or | | | Discontinuation due to | |
| | | contraindication to <3 | | PASI 290, 11 (%) | an AE, (%) | |
| | | or 23 conventional | | 1.307/433(70.9%) | 1.2.1 | |
| | | systemic therapies). | | C_{2}^{\prime} | C. 1.1 | |
| | | | | 1 vs C: p<0.0001 | Common AEs | |
| | | UNCOVER-1 | | PASI 100 p (%) | Common AES | |
| | | n-422 | | 1. 152/122 (25 20/) | Nacophanunaitic (%) | |
| | | 11-433 | | 1. 133/433 (33.3%) C·0/421 (0%) | 1.0 E | |
| | | Dron-out rate (12 | | C. 0/451 (0/0) | 0.87 | |
| | | $w_{\rho\rho}(s) = n (\%)$ | | 1 v3 C. p<0.0001 | 0.0.7 | |
| | | WEEKSJ, 11 (70) | | | I | |

Table 7.7. Ixekizumab versus placebo

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|-------------------------|------------------------|--------------------------|--------------------------|-----------------------|-----------------------|--------------------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| | | 18/433 (4.2%) | | | URTI, (%) | |
| | | | | | I: 4.4 | |
| | | Baseline characteristics | | | C: 3.5 | |
| | | Female/Male, (%) | | | | |
| | | n: 32.8%/67.2% | | | Injection site | |
| | | Ethnicity (Caucasian), % | | | reaction(%) | |
| | | n: 92.6% | | | I:10.0 | |
| | | Bodyweight (kg), mean | | | C: 1.1 | |
| | | ±SD | | | | |
| | | n: 92±23 | | | Arthralgia, (%) | |
| | | | | | I: 2.5 | |
| | | | | | C: 2.1 | |
| | | | | | | |
| | | | | | Headache, (%) | |
| | | | | | I: 4.4 | |
| | | | | | C: 2.9 | |
| Griffiths et al. 2015 | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
| [88] | | | | | | Acceptable |
| | Adult patients (≥18 | 80 mg of ixekizumab | C: Placebo | ITT | Pooled data for | |
| Multicentre studies | years) with chronic | every 2 weeks after a | | | UNCOVER-1, UNCOVER- | Comment |
| carried out at sites in | plaque psoriasis | starting dose of 160 mg | Injection with placebo | Safety population | 2 and UNCOVER-3 | |
| USA, Canada, Mexico, | (diagnosis ≥6 months), | at week 0. | to match active | included all patients | (except AEs for | Study funded, designed |
| Argentina, Chile, the | involving ≥10% body | | treatments | who received ≥1 dose | etanercept treated | and carried out with the |
| UK, Germany, Poland, | surface area, sPGA ≥3 | Subcutaneous injection. | | of test substance or | patients) reported in | involvement of Eli Lilly |
| Austria, France, the | and PASI ≥12. | Injection with placebo | UNCOVER-2 | placebo | [119] | |
| Netherlands, Spain, | Candidates for | to match active | | | | |
| Bulgaria, Czech | phototherapy and/or | treatments | n: 168 | Missing values | AE:s for etanercept | |
| Republic, Hungary, | systemic therapy. | | Drop-out rate (12 | For categorical | treated patients | |
| Romania, Russia, and | | UNCOVER-2 | weeks), n (%) | variables: NRI | Week 0-12 | |
| Australia. | Study period | | 10/168 (6.0%) | | | |
| | UNCOVER-2: | n: 351 | | Results UNCOVER-2 | Any AE | |
| Study name | May 2012 – December | | | Week 12 | 54% | |
| UNCOVER-2 and | 2013 | Drop-out rate (12 | Baseline characteristics | | Serious AE | |
| UNCOVER-3 | UNCOVER-3: | weeks), n (%) | Female/Male, (%) | | 2% | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------|------------------------|------------------------------|-----------------------------|----------------------|-------------------------|--------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| | August 2012-February | n: 9/351 (2.6%) | 28.6%/71.4% | PASI ≥75, n (%) - | | |
| RCT | 2014 | | Ethnicity (Caucasian), % | primary endpoint | Common AEs | |
| | | Baseline characteristics | 88.7 | I: 315/351 (89.7%) | Nasopharyngitis | |
| | Follow-up | Female/Male, (%) | BMI (kg/m²), mean±SD | | 7 % | |
| | Induction period: 12 | n: 27.0%/63.0% | 31±7 | C: 4/168 (2.4%) | URTI | |
| | weeks, placebo- | Ethnicity (Caucasian), % | | | 5% | |
| | controlled. Week 12-60 | n: 94.3% | UNCOVER-3 | PASI ≥90, n (%) | Injection site reaction | |
| | withdrawal period in | BMI, kg/m ² ±SD | | I: 248/351 (70.7%) | 11% | |
| | UNCOVER-2, long-term | n: 30±7 | n: 193 | C: 1/168 (0.6%) | Arthralgia | |
| | extension period in | | | | 2% | |
| | UNCOVER-3 | UNCOVER-3 | Drop-out rate (12 | PASI 100, n (%) | Headache | |
| | | | weeks), n (%) | 1: 142/351 (40.5%) | 4% | |
| | | n: 385 | 10/193 (5.2%) | | | |
| | | Dec | Describes also establistica | C: 1/168 (0.6%) | | |
| | | Drop-out rate (12 | Baseline characteristics | | | |
| | | Weeks), n (%) | Female/Male, (%) | DLQI change from | | |
| | | n: 22/385 (5.7%) | 29.0%/71.0% | baseline, mean±SE | | |
| | | Recaling characteristics | ethnicity (Caucasian), % | $110.4 \pm 0.3, 351$ | | |
| | | Econolo (Mala (%) | 91.2% | C2.0±0.4, 108 | | |
| | | p: 24.0% /66.0% | 20+6 | | | |
| | | Ethnicity (Caucasian) % | 50±0 | Poculte LINCOVER 2 | | |
| | | n· 03.8% | | Wook 12 | | |
| | | $\frac{11.93.8\%}{1.93.8\%}$ | | WEEK 12 | | |
| | | n· 30+7 | | PASI > 75 n (%) - | | |
| | | | | nrimary endnoint | | |
| | | | | 1. 336/385 (87 3%) | | |
| | | The studies also | | C: 14/193 (7.3%) | | |
| | | included intervention | | 0.11/100 (7.070) | | |
| | | groups treated with | | PASI ≥90. n (%) | | |
| | | etanercept | | 1: 262/385 (68.1%) | | |
| | | | | C: 6/193 (3.1%) | | |
| | | | | , (, | | |
| | | | | | | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|-------------------------|--------------------|-------------------------|------------|--------------------------|--|----------------------------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| | | | | PASI 100, n (%) | | |
| | | | | 1: $145/385(37.7\%)$ | | |
| | | | | C. 0/195 (0%) | | |
| | | | | DLQI change from | | |
| | | | | baseline, mean±SE | | |
| | | | | I: -10.2±0.2, 385 | | |
| | | | | C:1.7±0.3, 193 | | |
| | | | | | | |
| Blauvelt et al. | Population | Intervention | | Effects from OLE-studies | Adverse events | Risk of bias |
| 2017 | | 80 mg of ixekizumab | | are not reported | | |
| [120] | Reported in [88] | every 2 weeks after a | | | Patients with $\geq 1 AE$, n | Not assessed |
| | | starting dose of 160 mg | | | (%) | 6 |
| This article is an open | Follow-up | at week 0 | | | 10///12/4 (84.5%) | Comment Study funded designed |
| from the UNCOVER 2 | Placebo-controlled | Cubautanaana iniaatian | | | Detiente with severe AF | and carried out with the |
| trial | phase 0–12 weeks | Subcutaneous injection. | | | patients with severe AE, | involvement of Fli Lilly |
| [00] | OLE for up to 108 | to match activo | | | 11 (%) 167/1274 (12 1%) | Involvement of Lifelity |
| [00] | weeks | treatments | | | 107/1274 (13.1%) | |
| Some pooled AEs from | Weeko | ti cutificitits | | | Patients with serious | |
| The UNCOVER-3 trial is | | N in safety analysis | | | AE, n (%) | |
| also reported in [119] | | 1274 | | | 148/1274 (11.6%) | |
| | | | | | | |
| | | | | | Death, n (%) | |
| | | | | | 5/1274 (0.4%) | |
| | | | | | | |
| | | | | | Common AEs reported | |
| | | | | | by ≥5% of patients | |
| | | | | | Naconharmaitic (01) | |
| | | | | | Nusopharyngitis, (%) 200/1274/22 EV | |
| | | | | | 500/12/4 (23.5%) | |
| | | | | | URTI. (%) | |
| | | | | | 96/1274 (7.5%) | |

| First Author | Population Setting | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------|-----------------------|--------------|------------|----------------|---|--------------|
| Reference | Jetting | | | Results | | comment |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| | | | | | Injection site reaction(%) 96/1274 (7.5%) Arthralgia, (%) 80/1274 (6.3%) Bronchitis, (%) 72/1274 (5.7%) Headache, (%) 71/1274 (5.7%) Neutropenia, Grade 1, (%) 107/1274 (8.4%) | |

BSA - body-surface area; DLQI - dermatology life quality index; EQ-5D – EuroQoL 5-Dimension health status; IGA – investigator's global assessment; ITT – intention to treat; NRI – nonresponder imputation; PASI – psoriasis area and severity index; pp – palmoplantar psoriasis; SD – standard deviation; SE – standard error; sPGA – static physician's global assessment; URTI – upper respiratory tract infection
| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|-------------------------|------------------------|--------------------------|-----------------------------------|-----------------------|---------------------------|--------------------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| Griffiths et al. 2015 | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
| [88] | | | | | | Acceptable |
| | Adult patients (≥18 | 80 mg of ixekizumab | C: 50 mg etanercept | ITT | Pooled data for | |
| Multicentre studies | years) with chronic | every 2 weeks after a | twice weekly, | | UNCOVER-1, UNCOVER- | Comment |
| carried out at sites in | plaque psoriasis | starting dose of 160 mg | subcutaneous injection | Safety population | 2 and UNCOVER-3 | |
| USA, Canada, Mexico, | (diagnosis ≥6 months), | at week 0. | | included all patients | (except AEs for | Study funded, designed |
| Argentina, Chile, the | involving ≥10% body | | UNCOVER-2 | who received ≥1 dose | etanercept treated | and carried out with the |
| UK, Germany, Poland, | surface area, sPGA ≥3 | Subcutaneous injection. | | of test substance or | patients) reported in [2] | involvement of Eli Lilly |
| Austria, France, the | and PASI ≥12. | Injection with placebo | n: 358 | placebo | | |
| Netherlands, Spain, | Candidates for | to match active | Drop-out rate (12 | | AE:s for etanercept | |
| Bulgaria, Czech | phototherapy and/or | treatments | weeks), n (%) | Missing values | treated patients | |
| Republic, Hungary, | systemic therapy. | | : 25/358 (7.0%) | For categorical | Week 0-12 | |
| Romania, Russia, and | | UNCOVER-2 | | variables: NRI | | |
| Australia. | Study period | | | | Any AE | |
| | UNCOVER-2: | n: 351 | Baseline characteristics | Results UNCOVER-2 | 54% | |
| Study name | May 2012 – December | | Female/Male, (%) | Week 12 | Serious AE | |
| UNCOVER-2 and | 2013 | Drop-out rate (12 | 34.1%/65.9% | | 2% | |
| UNCOVER-3 | UNCOVER-3: | weeks), n (%) | Ethnicity (Caucasian), % | PASI ≥75, n (%) - | | |
| | August 2012-February | n: 9/351 (2.6%) | 93.5% | primary endpoint | Common AEs | |
| RCT | 2014 | | BMI (kg/m ²), mean±SD | 1: 315/351 (89.7%) | Nasopharyngitis | |
| | | Baseline characteristics | 31±7, (n=2 missing) | C: 149/358 (41.6%) | 7% | |
| | Follow-up | Female/Male, (%) | | | | |
| | Induction period: 12 | n: 27.0%/63.0% | UNCOVER-3 | PASI ≥90, n (%) | 5% | |
| | weeks, placebo- | Ethnicity (Caucasian), % | 202 | 1: 248/351 (70.7%) | Injection site reaction | |
| | controlled. Week 12-60 | n: 94.3% | n: 382 | C: 67/358 (18.7%) | 11% | |
| | withdrawal period in | BIVII, Kg/m²±SD | Dava suturts (12 | | Arthraigia | |
| | UNCOVER-2, long-term | n: 30±7 | Drop-out rate (12) | PASI 100, N (%) | Z% | |
| | extension period in | | weeks), n (%) | 1: 142/351 (40.5%) | Heudache | |
| | UNCOVER-3 | UNCOVER-3 | 13/382 (3.4%) | C: 19/358 (5.3%) | 4% | |
| | | n: 20F | Decalina charactoristics | DI Ol change from | | |
| | | 11: 365 | Buseline characteristics | becaling mean+SE | | |
| | | | remale/iviale, (%) | baseline, mean±SE | 1 | |

Table 7.8. Ixekizumab versus Etanercept

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------|-----------------|--------------------------|--------------------------|-----------------------|----------------|--------------|
| Year | Setting | | | Deculto | | Comment |
| Country | Study pariod | | | Results | | |
| Study docign | Follow up (FLI) | | | | | |
| Study design | | Dran out rate (12 | 20 69/ /70 49/ | 1. 10.4+0.2.251 | | |
| | | Diop-out rate (12) | 29.0%/70.4% | $110.4\pm0.3, 551$ | | |
| | | weeks), // (%) | Ethnicity (Caucasian), % | C: -7.7±0.3, 358 | | |
| | | 11. 22/385 (5.7%) | 91.9% | | | |
| | | Pasalina characteristics | 21+9 | Posulte UNCOVER 2 | | |
| | | Ecomple/Male (%) | 5110 | Wook 12 | | |
| | | n: 34.0%/66.0% | | WEEK 12 | | |
| | | Fthnicity (Caucasian) % | | PASI>75 n(%)- | | |
| | | n: 93.8% | | nrimary endpoint | | |
| | | $BMI (kg/m^2)$ mean+SD | | 1. 336/385 (87 3%) | | |
| | | n: 30+7 | | C: 204/382 (53.4%) | | |
| | | | | 0. 10 1/001 (001 1/0/ | | |
| | | | | PASI ≥90. n (%) | | |
| | | The studies also | | 1: 262/385 (68.1%) | | |
| | | included control groups | | C: 98/382 (25.7%) | | |
| | | treated with placebo | | | | |
| | | | | PASI 100, n (%) | | |
| | | | | I: 145/385 (37.7%) | | |
| | | | | C: 28/382 (7.3%) | | |
| | | | | | | |
| | | | | DLQI change from | | |
| | | | | baseline, mean±SE | | |
| | | | | I: -10.2±0.2, 385 | | |
| | | | | C:8.0±0.2, 382 | | |
| | | | | | | |

BSA - body-surface area; DLQI - dermatology life quality index; EQ-5D – EuroQoL 5-Dimension health status; IGA – investigator's global assessment; ITT – intention to treat; NRI – nonresponder imputation; PASI – psoriasis area and severity index; pp – palmoplantar psoriasis; SD – standard deviation; SE – standard error; sPGA – static physician's global assessment; URTI – upper respiratory tract infection

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|----------------------------|---|---------------------------|--------------------------|-----------------------|-----------------------|---------------------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| Reich et al | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
| 2017 | | | | | | Acceptable |
| [121] | Adult patients (≥18 | 80 mg of ixekizumab, | Ustekinumab, | ITT | AE:s through week 24 | |
| | years) with chronic | subcutaneous injection, | subcutaneous | | | Comment |
| Multicentre studies | plaque psoriasis | every 2 weeks, through | injections, at weeks 0, | Safety population | Any AE | |
| carried out at 51 sites in | (diagnosis ≥6 months), | week 12, after a starting | 4, 16, 28 and 40, per | included all patients | I: 94/135 (69.6%) | Study fully funded by Eli |
| 13 countries. | and PASI ≥10. Had | dose of 160 mg at week | label. Patients ≤ 100 kg | who received ≥1 dose | C: 125/166 (75.3%) | Lilly |
| | previously failed | 0. Thereafter 80 mg | receiving 45 mg and | of test substance (I: | P=0.299 | |
| Study name | phototherapy and/or | every 4 week until week | patients > 100 kg | n=135; C: n=166) | | |
| IXORA-S | systemic therapy. | 52. | receiving 90 mg. | | Severe AE | |
| | | | | Missing values | I: 6/135 (4.4%) | |
| RCT | Baseline characteristics | Injection with placebo | Injection with placebo | NRI | C: 10/166 (6.0%) | |
| | Female/Male, (%) | to match active | to match intervention | | P=0.613 | |
| | I: 33.8%/66.2% C: | comparison treatment | treatment | Results | | |
| | 32.5%/67.5% | | | (Week 12) | Infections | |
| | Ethnicity (Caucasian), n, | | | | I: 57/135 (42.2%) | |
| | % | n: 136 | n: 166 | PASI 75, n (%) - | C: 87/166 (52.4%) | |
| | I:125/136 (93.3%) | | | I: 120/136 (88.2%) | P=0.083 | |
| | C: 157/166 (95.7%) | Drop-out rate (12 | Drop-out rate (12 | C: 114/166 (68.7%) | | |
| | Age | weeks), n (%) | weeks), n (%) | P<0.001 | Common AEs reported | |
| | mean (SD) | n: 4/136 (2.9%) | n: 2/166 (1.2%) | | by ≥5% of patients in | |
| | I: 42.7 (12.7) | | | PASI 90, n (%) - | any treatment group | |
| | C: 44.0 (13.3) | | | I: 99/136 (72.8%) | | |
| | Weight (kg), mean (SD) | | | C: 70/166 (42.2%) | Nasopharyngitis | |
| | 1: 85.8 (20.3) | | | P<0.001 | I: 33/135 (24.4%) | |
| | C: 89.4 (24.8) | | | | C: 45/166 (21.7%) | |
| | Weight>100 kg, n (%) | | | PASI 100, n (%) - | | |
| | I: 31/136 (23.0%) | | | I: 49/136 (36.0%) | Headache | |
| | C: 45/166 (27.1%) | | | C: 24/166 (14.5%) | I: 10/135 (7.4%) | |
| | <i>BMI, (kg/m²),</i> mean (SD) | | | P=0.009 | C: 13/166 (7.8%) | |
| | I: 28.8 (5.6) | | | | | |

Table 7.9. Ixekizumab versus Ustekinumab

| C: 29.7 (7.0) | | | Arthralgia | |
|------------------------|--|-------------------------------------|------------------|--|
| | | | I: 6/135 (4.4%) | |
| Study period | | DLQI (% patients | C: 10/166 (6.0%) | |
| Oct 21, 2015 – Aug 3, | | receiving a score of 0 or | , (, | |
| 2016 | | 1) | | |
| 2010 | | -/ I [·] 83/136 (61 0%) | | |
| Follow-up | | $C \cdot 74/166 (44.6\%)$ | | |
| Induction pariod: 12 | | P=0.012 | | |
| mudection period. 12 | | 1-0.012 | | |
| weeks, thereafter | | Poculto | | |
| extension period up to | | (Mark 24) | | |
| 52 weeks. | | (Week 24) | | |
| | | | | |
| | | PASI 75, n (%) - | | |
| | | 1: 124/136 (91.2%) | | |
| | | C: 136/166 (81.9%) | | |
| | | P=0.015 | | |
| | | | | |
| | | PASI 90, n (%) - | | |
| | | I: 113/136 (83.1%) | | |
| | | C: 98/166 (59.0%) | | |
| | | P<0.001 | | |
| | | | | |
| | | PASI 100, n (%) - | | |
| | | I: 67/136 (49.3%) | | |
| | | C: 39/166 (23.5%) | | |
| | | P=0.001 | | |
| | | | | |
| | | | | |
| | | DLOL (% patients | | |
| | | receiving a score of 0 or | | |
| | | 1) | | |
| | | +/ 1· 00/126 (66 2%) | | |
| | | (00.270) | | |
| | | $C. \delta\delta/100 (53.0\%)$ | | |
| | | P=0.030 | | |

AE – adverse event; BMI – body mass index; CDLQI – children's DLQI; CI – confidence interval; DLQI – dermatology life quality index; ITT – intention-to-treat; LOCF – last observation carried forward; n.g. – not given; NRI – non-responder imputation; OLE – open-label extension; PASI – psoriasis area and severity index; PGA – physician's global assessment; RCT – randomised controlled trial; SD – standard deviation; SE – standard error; TNF – tumour necrosis factor; URTI – upper respiratory tract infection

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|-------------------------|-------------------------|----------------------------|----------------------------|--------------------------|---------------------------|------------------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| Langley et al 2014 | Population | Intervention | Comparison | Analysis method | Adverse events | Risk of Bias |
| [98] | Patients ≥18 years of | 300 mg secukinumab | Placebo | ITT for efficacy | | Acceptable |
| | age with plaque | | | outcomes | Induction period – | |
| Study name: ERASURE | psoriasis diagnosis | Subcuntaneous | Placebo injections to | | week 0–12 | Comment |
| | (≥6 months). PASI score | injections at baseline, | match active | Per protocol: PASI score | | |
| Multicentre study | ≥12, modified IGA score | week 1, 2, 3, 4 then | treatments as required | | Any AE, n (%) | Novartis |
| carried out at 88 sites | of ≥3, BSA ≥10% | every 4 weeks until | | Missing data | I: 135/245 (55.1%) | Pharmaceuticals |
| worldwide | | week 48. Placebo | n=248 | NRI | C: 116/247 (47.0%) | funded, designed and |
| | Study period | injections to match | | | | were involved in |
| | June 2011–April 2013 | active treatments as | Drop-out rate (week | Safety endpoints were | Death, n (%) | carrying out the study |
| | | required | 12), n (%) | evaluated for all | I, C: 0 | and writing the |
| | Follow-up | | 16/248 (6.5%) | patients who received | | manuscript. |
| | 12-weeks induction | n=245 | | ≥1 treatment dose | Serious AE, n (%) | |
| | period, 40 weeks | | Baseline characteristics | | I: 6/245 (2.4%) | Co-primary end points |
| | maintenance period, | Drop-out rate (week | Male: 69.4% | Results – week 12 | C: 4/247 (1.6%) | were analysed with |
| | and 8 week follow-up | 12), n (%) | Ethnicity (Caucasian): | | | stratification by |
| | period | 7/245 (2.9%) | 71.0% | PASI ≥75, n (%) – | Discontinuation due to | geographic region and |
| | | | BMI kg/m ² ±SD: | primary endpoint | AE, n (%) | body weight |
| | | Baseline characteristics | 30.3±7.8 | 1: 200/245 (81.6%) | I: 3/245 (1.2%) | |
| | | Male: 69.0% | Age (yr) | C: 11/246 (4.5%) | C: 4/247 (1.6%) | |
| | | Ethnicity (Caucasian): | mean±SD: 45.4±12.6 | l vs C: p<0.001 | | |
| | | 69.8% | | | Infection or infestation, | |
| | | BMI kg/m ² ±SD: | | PASI ≥90, n (%)t | n (%) | |
| | | 30.3±7.2 | | 1: 145/245 (59.2%) | 1: /2/245 (29.4%) | |
| | | Age (yr) | | C: 3/246 (1.2%) | C: 40/247 (16.2%) | |
| | | mean±SD: 44.9±13.5 | | T vs C: p<0.001 | | |
| | | | | | Common adverse events | |
| | | | | PASI 100, n (%) | (affected more than 2% | |
| | | | | 1: /0/245 (28.6%) |) | |
| | | | | C: 2/246 (0.8%) | | |
| | | | | T vs C: p<0.001 | Nasopharyngitis, n (%) | |
| | | | | | 1: 22/245 (9.0%) | |

Table 7.10. Secukinumab versus placebo

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------|----------------|--------------|------------|------------------------|---------------------------|--------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| | | | | DLQI change (week 0 vs | C: 19/247 (7.7%) | |
| | | | | 12) | | |
| | | | | 1: -11.4 | Headache, n (%) | |
| | | | | C: -1.1 | 1: 12/245 (4.9%) | |
| | | | | | C: //24/(2.8%) | |
| | | | | | Pruritus, n (%) | |
| | | | | | I: 9/245 (3.7%) | |
| | | | | | C: 5/247 (2.0%) | |
| | | | | | URTI. n (%) | |
| | | | | | 1: 9/245 (3.7%) | |
| | | | | | C: 0/247 (0%) | |
| | | | | | Fatiaue. n (%) | |
| | | | | | 1: 2/245 (0.8%) | |
| | | | | | C: 2/247 (0.8%) | |
| | | | | | Influenza-like illness, n | |
| | | | | | (%) | |
| | | | | | I: 5/245 (2.0%) | |
| | | | | | C: 3/247 (1.2%) | |
| | | | | | Hypertension, n (%) | |
| | | | | | I: 0/245 (0%) | |
| | | | | | C: 3/247 (1.2%) | |
| | | | | | Oropharyngeal pain, n | |
| | | | | | (%) | |
| | | | | | I: 4/245 (1.6%) | |
| | | | | | C: 3/247 (1.2%) | |
| | | | | | | |
| | | | | | | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------------------|-------------------------|--------------------------|--------------------------|--|---------------------------|------------------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| Langley et al 2014 | Population | Interventon | Comparison | Analysis method | Adverse events | Risk of Bias |
| [98] | Patients ≥18 years of | 300 mg secukinumab | C: placebo | ITT for efficacy | | Acceptable |
| | age with plaque | | | outcomes | Induction period – | |
| Study name: FIXTURE | psoriasis diagnosis (≥6 | Subcuntaneous | . Placebo injections to | | week 0-12 | Comment |
| | months). PASI score | injections at baseline, | match active | Per protocol: PASI score | | |
| Multicentre study | ≥12, modified IGA score | week 1, 2, 3, 4 then | treatments as required | | Any AE, n (%) | Novartis |
| carried out at 231 sites | of ≥3, BSA ≥10%. | every 4 weeks until | | Missing data | I: 181/326 (55.5%) | Pharmaceuticals |
| worldwide. | Treatment naïve to | week 48. Placebo | n=326 | NRI | C: 163/327 (49.8%) | funded, designed and |
| | etanercept | injections to match | | | | were involved in |
| | | active treatments as | Drop-out rate (week | Safety endpoints were | Death, n (%) | carrying out the study |
| | Study period | required | 12), n (%) | evaluated for all | I, C: 0 | and writing the |
| | June 2011–June 2013 | | 25/326=7.7% | patients who received | | manuscript. |
| | | n=327 | | ≥1 treatment dose | Serious AE, n (%) | |
| | Follow-up | | Baseline characteristics | | 1: 4/326 (1.2%) | Co-primary end points |
| | 12-weeks induction | Drop-out rate | Female/Male, % | Results – week 12 | C: 6/32/ (1.8%) | were analysed with |
| | period, 40 weeks | (week 12), n (%) | 27.3%/72.7% | | | stratification by |
| | maintenance period, | 15/32/= 4.6% | Ethnicity (Caucasian) | PASI ≥75, n (%) – | Discontinuation due to | geographic region and |
| | and 8 week follow-up | | 66.9% | primary endpoint | AE, n (%) | body weight. |
| | period | Baseline characteristics | BIVII (kg/m²), mean ±SD | 1: 249/323 (77.1%) | 1: 4/326 (1.2%) | |
| | | | 27.9 ± 0.1 | C: 16/324 (4.9%) | C: 3/327 (0.9%) | |
| | | 31.3%/08.3% | Age (yr) | TVS C: p<0.001 | Infaction or infactation | |
| | | | | DASI > 00 p (0) | njection or injestation, | |
| | | $BMI(ka/m^2)$ moon+SD: | 44.1112.0 | PASI ≥90, 11 (%) 1. 175/222 (51.2%) | 11 (70) | |
| | | 28 4+6 4 | | (.5/324 (1.5%)) | $C \cdot 63/327 (10.3\%)$ | |
| | | $\Delta ge(yr)$ | | 1×10^{-10} | 03/327 (13.370) | |
| | | mean+SD: 11 5+13 2 | | 1 v3 c. p<0.001 | Common adverse events | |
| | | 111CU112001 771021012 | | PASI 100 n (%) | (affected more than 2%) | |
| | | | | 1. 78/323 (24 1%) | | |
| | | The study also included | | C: 0/324 (0%) | Nasopharynaitis, n (%) | |
| | | an intervention group | | | 1: 35/326 (10.7%) | |
| | | treated with etanercent | | No comparison done | C: 26/327 (8.0%) | |
| | | | | with C, since there were | | |
| | | | | no patients with a | | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------|----------------|--------------|------------|-------------------------|---------------------|--------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| | | | | response in the placebo | Headache, n (%) | |
| | | | | group | I: 30/326 (9.2%) | |
| | | | | | C: 23/327 (7.0%) | |
| | | | | DLQI change (week 0 vs | | |
| | | | | 12) | Diarrhoea, n (%(| |
| | | | | I: -10.4 | I: 17/326 (5.2%) | |
| | | | | C: -1.9 | C: 6/327 (1.8%) | |
| | | | | | | |
| | | | | | Pruritus, n (%) | |
| | | | | | I: 8/326 (2.5%) | |
| | | | | | C: 11/327 (3.4%) | |
| | | | | | | |
| | | | | | Arthralgia, n (%) | |
| | | | | | I: 5/326 (1.5%) | |
| | | | | | C: 10/327 (3.1%) | |
| | | | | | | |
| | | | | | URTI, n (%) | |
| | | | | | I: 7/326 (2.1%) | |
| | | | | | C: 3/327 (0.9%) | |
| | | | | | | |
| | | | | | Back pain, n (%) | |
| | | | | | I: 8/326 (2.5%) | |
| | | | | | C: 6/327 (1.8%) | |
| | | | | | | |
| | | | | | Cough, n (%) | |
| | | | | | I: 11/326 (3.4%) | |
| | | | | | C: 4/327 (1.2%) | |
| | | | | | | |
| | | | | | Hypertension, n (%) | |
| | | | | | I: 5/326 (1.5%) | |
| | | | | | C: 4/327 (1.2%) | |
| | | | | | | |
| | | | | | Nausea, n (%) | |
| | | | | | I: 8/326 (2.5%) | |

| First Author Population Intervention Comparison Analysis model Adverse events Risk of | bias |
|--|-----------------|
| Year Setting Comm | ent |
| Reference Results | |
| Country Study period | |
| Study design Follow-up (FU) | |
| C: 7/327 (2.1%) | |
| | |
| Oropharyngeal pain, n | |
| | |
| | |
| C. 7/327 (2.1%) | |
| Blauvelt <i>et al</i> 2015 Population Intervention Comparison Analysis method Adverse events Risk or | bias |
| [122] Inclusion criteria 300 mg secukinumab Placebo No information AE, n (%) Accept | able |
| Patients ≥18 years of I: 30/59 (50.8%) | |
| Multicentre study age with plaque Subcutaneous injections Subcutaneous injections Results (12 weeks) C: 28/59 (47.5%) Comm | ents |
| carried out at 32 psoriasis (diagnosis ≥6 at baseline, week 1, 2, 3 at baseline, week 1, 2, 3 Study | funded by |
| centres in North months), PASI score and every 4 th week and every 4 th week PASI ≥75 (week 12), n <i>Death, n (%)</i> Novar | is |
| America and Europe.≥12, 2011 modifiedfrom week 4from week 4(%) – primary endpointI: 0/59 (0%)Pharm | aceuticals |
| investigators global I: 75.9% C: 0/59 (0%) | |
| Study nameassessment (IGA modn = 59C: 0%Patien | ts injected |
| FEATURE 2011) score ≥3, BSA I vs C: p<0.0001 Serious AE, n (%) substa | nce themselves, |
| involvement ≥10% Drop-out rate Drop-out rate I: 3/59 (5.1%) but du | ring week 0-12 |
| RCT 3/59= 5.1% 3/59= 5.1% PASI ≥90, (%) C: 1/59 (1.7%) weeks | all injections |
| Randomisation was I: 60.3% were r | nonitored at a |
| stratified by body C: 0% Discontinuation due to study | site. |
| weight (≥90 kg or I vs C: p<0.0001 AE, n (%) | |
| >90kg) | |
| PASI 100, (%) C: 1/59 (1.7%) | |
| Baseline characteristics | |
| remale/iviale, % C: U% Injection site reactions, | |
| I: 35.0%/64.4% | |
| $\begin{array}{c} 1.35.9\%/00.1\% \\ \text{Ethnicity} (Caucasian) \% \\ \end{array}$ | |
| C: 1/59 (1.7%) | |
| C: 06.6% | |
| C. 30.0% Rody weight (kg) | |
| Dody weight (Ag), mean+SD | |
| | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------|------------------------|--------------|------------|----------------|------------------------|--------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| | C: 88.4±21.55 | | | | Common AEs | |
| | Age (yr) | | | | | |
| | mean±SD: | | | | Diarrhoea, n (%) | |
| | I: 45.1±12.57 | | | | I: 5/59 (8.5%) | |
| | C: 46.5±14.14 | | | | C: 1/59 (1.7%) | |
| | Study period | | | | Nasopharvnaitis. n (%) | |
| | May 2012 – January | | | | 1: 3/59 (5.1%) | |
| | 2013 | | | | C: 5/59 (8.5%) | |
| | Follow-up | | | | Headache n (%) | |
| | 12-week placebo- | | | | 1.0/59 (0%) | |
| | controlled treatment | | | | (5,3) (5,1%) | |
| | nhase Maintenance | | | | C. 5/55 (5.170) | |
| | (12–52 weeks) ontional | | | | Purevia n (%) | |
| | treatment extension | | | | 1.2/59 (3.4%) | |
| | (week 52–208) and 8- | | | | C· 2/59 (3.4%) | |
| | week treatment follow- | | | | 0. 2/00 (0. 1/0/ | |
| | up. Efficacy data here | | | | Back pain, n (%) | |
| | reported for the | | | | I: 3/59 (5.1%) | |
| | placebo-controlled | | | | C: 0/59 (0%) | |
| | phase | | | | | |
| | | | | | Bursitis, n (%) | |
| | | | | | I: 2/59 (3.4%) | |
| | | | | | C: 0/59 (0%) | |
| | | | | | Couah. n (%) | |
| | | | | | I: 1/59 (1.7%) | |
| | | | | | C: 0/59 (0%) | |
| | | | | | , , , | |
| | | | | | Depression, n (%) | |
| | | | | | I:1/59 (1.7%) | |
| | | | | | C: 0/59 (0%) | |
| | | | | | | |

| Reference Results | comment |
|--|---|
| Country Study period | |
| | |
| Study design Follow-up (FU) | |
| Study design Follow-up (FU) Nausea, n (%) I: 3/59 (5.1%) I: 3/59 (5.1%) C: 1/59 (1.7%) C: 1/59 (1.7%) Gottlieb et al Population 2016 Reported in [122] Follow-up Placebo-controlled ris article is an open and every 4 th week from the FEATURE trial, Presented in [122], OLE for up to 52 weeks Number of patients in sofety population for in=86 Number of patients in any treetment group Number of patients in any treetment group Number of patients in any treetment group Number of patients in any treetment group Number of patients in any treetment group Number of patients in any treetment group Number of patients in any treetment group Number of patients in any treetment group Number of patients in any treetment group Number of patients in any treetment group Number of patients in any treetment group Number of patients in any treetment group | Risk of bias Not assessed Comment Study funded by Novartis Pharmaceuticals |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|------------------------|-----------------------------|---------------------------|---------------------------|--------------------|--------------------------|------------------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| | | | | | Headache, n (%) | |
| | | | | | 2/86 (2.3%) | |
| | | | | | | |
| | | | | | Cougn, n (%) | |
| | | | | | 6/86 (7.0%) | |
| | | | | | LIPTI n (%) | |
| | | | | | 7/86 (8 1%) | |
| | | | | | 7700 (0.170) | |
| | | | | | Diarrhea, n (%) | |
| | | | | | 6/86 (7.0%) | |
| | | | | | , , , | |
| | | | | | Neutropenia, ≥ grade 2, | |
| | | | | | n (%) | |
| | | | | | 1/86 (1.2%) | |
| | | | | | | |
| | | | | | Candidiasis, n (%) | |
| | | | | | 3/86 (3.5%) | |
| | | | | | | |
| | | | | | Severe infections, n (%) | |
| | | | | | 4/86 (4.7%) | |
| Paul <i>et al</i> 2015 | Population | Intervention | Comparison | Analysis method | Adverse events | Risk of bias |
| [123] | Patients ≥ 18 years of | 300 mg secukinumab | Ріасеро | | AE, n (%) | Acceptable |
| Multicontro study | age with plaque | Subautanagus inigetieres | Subautanaaus inigetieree | Missing data | | Commonto |
| carried out at 29 | psoriasis (diagnosis 26 | subcutaneous injections | subcutaneous injections | | C. 33/01 (54.1%) | Study funded by |
| worldwido | NOTURS, PASI SCORE | at baseline, week 1, 2, 3 | at baseline, week 1, 2, 3 | | Sarious AE n (%) | Novartic |
| wonuwiue. | investigators global | from week A | from week A | Results (12 weeks) | 1. 1/60 (1 7%) | Pharmaceuticals and |
| Study name | assessment (IGA mod | | | NESULS (IL WEEKS) | (1, 1/6) $(1, 7%)$ | designed by the |
| JUNCTURF | 2011) score >3 RSA | n =60 | n=61 | PASI 75, n (%) | C. 1, 01 (1.770) | scientific steering |
| | involvement >10% | | | 1: 86.7% | Discontinuation due to | committee and Novartis |
| RCT | | Drop-out rate, week 0- | Drop-out rate, week 0- | C: 3.3% | AE, n (%) | personnel. Novartis |
| | Randomisation was | 12: | 12: | l vs C: p<0.0001 | 1: 0/60 (0%) | conducted the data |
| | stratified by body | 0/60= 0% | 2/61= 3.3% | | C: 1/61 (1.6%) | analyses. |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------|--------------------------|--------------|------------|------------------|------------------------|-----------------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| | weight (≥90 kg or | | | PASI 90, (%) | | |
| | >90kg) | | | I: 55.0% | Common AEs reported | Patients injected |
| | | | | C: 0% | by ≥5% of patients in | substance themselves, |
| | Baseline characteristics | | | I vs C: p<0.0001 | any treatment group | by autoinjector |
| | Female/Male, % | | | | | |
| | I: 23.3%/76.7% | | | PASI 100, (%) | Nasopharyngitis, n (%) | |
| | C: 37.7%/62.3% | | | I: 26.7% | I: 19/60 (31.7%) | |
| | Ethnicity | | | C: 0% | C: 10/61 (16.4%) | |
| | (Caucasian)n,(%) | | | I vs C: p<0.0001 | | |
| | I: 56/60 (93.3%) | | | | Headache, n (%) | |
| | C: 59/61 (96.7%) | | | | I: 3/60 (5.0%) | |
| | Body weight (kg), mean | | | | C: 3/61 (4.9%) | |
| | (SD) | | | | | |
| | I: 91.0 (23.13) | | | | Pruritus, n (%) | |
| | C: 90.2 (21.16) | | | | I: 5/60 (8.3%) | |
| | BMI (kg/m2), mean (SD) | | | | C: 2/61 (3.3%) | |
| | I: 30.0 (6.9) | | | | | |
| | C: 30.0 (6.82) | | | | Sinusitis, n (%) | |
| | Age (yr) | | | | I: 3/60 (5.0%) | |
| | mean (SD): | | | | C: 0/61 (0.0%) | |
| | I: 46.6 (14.23) | | | | | |
| | C: 43.7 (12.74) | | | | Cough, n (%) | |
| | | | | | I: 3/60 (5.0%) | |
| | Study period | | | | C: 2/61 (3.3%) | |
| | October 2012 – April | | | | | |
| | 2013 | | | | Hypertension, n (%) | |
| | | | | | I: 1/60 (1.7%) | |
| | Follow-up | | | | C: 4/61 (6.6%) | |
| | 12-week placebo- | | | | | |
| | controlled treatment | | | | | |
| | phase. Maintenance | | | | | |
| | (12–52 weeks), optional | | | | | |
| | treatment extension | | | | | |
| | (week 52–208), and 8- | | | | | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|-------------------------|------------------------|--------------------------------|------------|--------------------------|------------------------|------------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| | week treatment follow- | | | | | |
| | up. Efficacy data here | | | | | |
| | reported for the | | | | | |
| | placebo-controlled | | | | | |
| | phase | | | | | |
| Lacour et al | Population | Intervention | | Effects from OLE-studies | Adverse events | Risk of bias |
| 2017 | | 300 mg secukinumab | | are not reported | | |
| [125] | Reported in [123] | | | | AE, n (%) | Not assessed |
| | | Subcutaneous injections | | | 78/88 (88.6%) | |
| This article is an open | Follow-up | at baseline, week 1, 2, 3 | | | | Comment |
| lable extension (OLE) | Placebo-controlled | and every 4 th week | | | Serious AE, n (%) | Study funded by |
| from the JUNCTURE | phase 0–12 weeks | from week 4 | | | 7/88 (8.0%) | Novartis |
| trial, [123] | (presented in [123]), | | | | | Pharmaceuticals. |
| | OLE for up to 52 weeks | Number of patients in | | | Discontinuation due to | |
| | presented here | safety population for | | | AE, n (%) | |
| | | intervention at week 52: | | | 0/88 (0.0%) | |
| | | n=88 | | | | |
| | | | | | Common AEs reported | |
| | | | | | by ≥5% of patients in | |
| | | | | | any treatment group | |
| | | | | | | |
| | | | | | Nasopharyngitis, n (%) | |
| | | | | | 35/88 (39.8%) | |
| | | | | | | |
| | | | | | Headache, n (%) | |
| | | | | | 10/88 (11.4%) | |
| | | | | | | |
| | | | | | Pruritus, n (%) | |
| | | | | | 8/88 (9.1%) | |
| | | | | | | |
| | | | | | Sinusitis, n (%) | |
| | | | | | 5/88 (5.7%) | |
| | | | | | | |
| | | | | | | |

| First Author Year | Population Setting | Intervention | Comparison | Analysis model | Adverse events | Risk of bias Comment |
|----------------------|-----------------------|--------------|------------|----------------|--------------------------|-------------------------|
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| | | | | | Cough, n (%) | |
| | | | | | 9/88 (10.2%) | |
| | | | | | LIBTL n (%) | |
| | | | | | 5/88 (5 7%) | |
| | | | | | 5/00 (5.770) | |
| | | | | | Hypertension, n (%) | |
| | | | | | 6/88 (6.8%) | |
| | | | | | | |
| | | | | | Arthralgia, n (%) | |
| | | | | | 5/88 (5.7%) | |
| | | | | | | |
| | | | | | Oropharyngeal pain, n | |
| | | | | | (%) | |
| | | | | | 5/88 (5.7%) | |
| | | | | | Noutrononia grada 2/2 | |
| | | | | | neutropenia, grade 2/3, | |
| | | | | | L (70) | |
| | | | | | 5/00 (5.770) | |
| | | | | | Candidiasis, n (%) | |
| | | | | | 4/88 (4.5%) | |
| | | | | | // | |
| | | | | | Severe infections, n (%) | |
| | | | | | 2/88 (2.3%) | |

AE – adverse event; BSA – body-surface area; BMI – body mass index; DLQI – dermatology life quality index; IGA – investigator's global assessment; ITT – intention-to-treat; NRI – non-responder imputation; PASI – psoriasis area and severity index; SD – standard deviation; SE – standard error; URTI – upper respiratory tract infection

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------------------|-------------------------|--|--------------------------|--|--|------------------------|
| Year | Setting | | | | | |
| Reference | | | | Results | | Comment |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| Langley et al 2014 | Population | Interventon | Comparison | Analysis method | Adverse events | Risk of Bias |
| [98] | Patients ≥18 years of | 300 mg secukinumab | C: 50 mg etancercept | ITT for efficacy | | |
| | age with plaque | | | outcomes | Induction period – | Acceptable |
| Study name: FIXTURE | psoriasis diagnosis (≥6 | Subcuntaneous | Subcuntaneous | | week 0-12 | |
| | months). PASI score | injections at baseline, | injections of | Per protocol: PASI score | | |
| Multicentre study | ≥12, modified IGA score | week 1, 2, 3, 4 then | etancercept twice | | Any AE, n (%) | Commont |
| carried out at 231 sites | of ≥3, BSA ≥10%. | every 4 weeks until | weekly from baseline to | Missing data | I: 181/326 (55.5%) | Comment |
| worldwide. | Treatment naïve to | week 48. Placebo | week 12 thereafter | NRI | C: 186/323 (57.6%) | |
| | etanercept | injections to match | once weekly through | | | |
| | | active treatments as | week 51. Placebo | Safety endpoints were | Death, n (%) | Novartis |
| | Study period | required | injections to match | evaluated for all | I, C: 0 | Pharmaceuticals |
| | June 2011–June 2013 | | active treatments as | patients who received | | funded, designed and |
| | | n=327 | required | ≥1 treatment dose | Serious AE, n (%) | were involved in |
| | Follow-up | | 225 | | 1: 4/326 (1.2%) | carrying out the study |
| | 12-weeks induction | Drop-out rate | n=326 | Results – week 12 | C: 3/323 (0.9%) | and writing the |
| | period, 40 weeks | (week 12), n (%) | Duran automate (succh | | Discontinuation due to | manuscript. |
| | maintenance period, | 15/32/= 4.6% | Drop-out rate (week | PASI ≥75, n (%) - | Discontinuation due to $\Delta \Gamma = (0)$ | |
| | and 8 week follow-up | Decelie e eksysterieties | 12), П (%) | primary enapoint | $AE, \Pi(\%)$ | |
| | period | | 21/326=6.4% | 1: 249/323 (77.1%) | 1: 4/326 (1.2%) | |
| | | 70//////////////////////////////////// | Pacalina characteristics | C.142/323(44.0%) | C. 0 / 323 (1.9%) | Co-primary end points |
| | | 51.5%/00.5% Ethnicity (Caucacian): | Eamala/Mala % | 1 VS C. P<0.001 | Infaction or infactation | were analysed with |
| | | 68 5% | 28 8% /71 2% | PASI >00 n (%) | n (%) | stratification by |
| | | $BMI(ka/m^2)$ mean+SD: | Ethnicity (Caucasian) | 1. 175/222 (51 2%) | 11 (70) | geographic region and |
| | | 29 4+6 4 | 67.2% | 1. 175/525 (54.276) | (20.776) | body weight. |
| | | $\Delta g \rho (vr)$ | BMI (kg/m^2) mean +SD | C· 67/323 (20 7%) | C. 13/323 (24.3/0) | |
| | | mean+SD: 44 5+13 2 | 28 7+5 9 | $1 v_{\rm S} (1) v_$ | Common adverse events | |
| | | 111Cu1120D. 44.0110.2 | Δσe (vr) | 1 13 0. 0 0.001 | (affected more than 2%) | |
| | | | mean+SD. | PASI 100 n (%) | | |
| | | | 43.8+13.0 | 1: 78/323 (24.1%) | Nasopharynaitis, n (%) | |
| | | | | C: 14/323 (4.3%) | 1: 35/326 (10.7%) | |

Table 7.11. Secukinumab versus Etanercept

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------|----------------|-------------------------|------------|------------------------|---------------------|--------------|
| Year | Setting | | | | | |
| Reference | | | | Results | | Comment |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| | | The study also included | | l vs C: p<0.001 | C: 36/323 (11.1%) | |
| | | a control group treated | | | | |
| | | with placebo | | DLQI change (week 0 vs | Headache, n (%) | |
| | | | | 12) | 1: 30/326 (9.2%) | |
| | | | | 1: -10.4 | C: 23/323 (7.1%) | |
| | | | | C: -7.9 | | |
| | | | | | Diarrhoea, n (%(| |
| | | | | | 1: 17/326 (5.2%) | |
| | | | | | C: 11/323 (3.4%) | |
| | | | | | Pruritus. n (%) | |
| | | | | | 1: 8/326 (2.5%) | |
| | | | | | C: 8/323 (2.5%) | |
| | | | | | | |
| | | | | | Arthralgia, n (%) | |
| | | | | | I: 5/326 (1.5%) | |
| | | | | | C: 12/323 (3.7%) | |
| | | | | | lIRTIn(%) | |
| | | | | | 1. 7/326 (2.1%) | |
| | | | | | (.7/323(2.1/6)) | |
| | | | | | 0.77525 (2.270) | |
| | | | | | Back pain, n (%) | |
| | | | | | I: 8/326 (2.5%) | |
| | | | | | C: 9/323 (2.8%) | |
| | | | | | | |
| | | | | | Cough, n (%) | |
| | | | | | 1: 11/326 (3.4%) | |
| | | | | | C: 4/323 (1.2%) | |
| | | | | | Hypertension, n (%) | |
| | | | | | I: 5/326 (1.5%) | |
| | | | | | C: 5/323 (1.5%) | |
| | | | | | , , | |

| First Author Year Reference Country | Population Setting Study period | Intervention | Comparison | Analysis model Results | Adverse events | Risk of bias Comment |
|--|---------------------------------------|--------------|------------|---------------------------|---|-------------------------|
| Study design | Follow-up (FU) | | | | Nausea, n (%) | |
| | | | | | I: 8/326 (2.5%) C: 4/323 (1.2%) | |
| | | | | | Oropharyngeal pain, n | |
| | | | | | (%) I: 9/326 (2.8%) C: 4/323 (1.2%) | |

AE – adverse event; BSA – body-surface area; BMI – body mass index; DLQI – dermatology life quality index; IGA – investigator's global assessment; ITT – intention-to-treat; NRI – non-responder imputation; PASI – psoriasis area and severity index; SD – standard deviation; SE – standard error; URTI – upper respiratory tract infection

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|-------------------------|--------------------------|-------------------------|--------------------------|--------------------------|-------------------------|-----------------------|
| Year | Setting | | | | | |
| Reference | | | | Results | | Comment |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| Blauvelt A. et al. 2016 | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
| [126] | | | | ITT (all randomized | C: pooled for 45 and 90 | |
| | Inclusion criteria | Secukinumab 300 mg | Ustekinumab | patients, except one in | mg /dose regime | Acceptable |
| | Patients ≥18 years of | dose per injection. | | the intervention group | | |
| Study name | age, diagnosed with | | Treatment dose | due to problems with | IR: incidence rate per | |
| CLEAR | plaque psoriasis (≥6 | Injections at baseline, | stratified by body | informed consent) | 100 years | |
| | months), PASI score | week 1, 2, 3, and every | weight with a dose of | | | |
| RCT | ≥12, Investigator's | 4 weeks from week 4 | 45 mg of ustekinumab | Safety population: All | Any AE, n (IR) [95% CI] | 6 |
| | Global Assessment, | onward. | per injection for | patients that received | I: 286/335 (280.9) | Comment |
| | 2011 modified version | | patients ≤100 kg and 90 | at least one dose of | [249.3-315.4] | Ctudy funded by |
| | (IGA mod 2011) score 3 | n=337 | mg for patients >100 kg. | study treatment. | C: 278/336 (250.1) | Study funded by |
| | (moderate) or 4 | | | | [221.6-281.3] | Novartis Pharma |
| | (severe). BSA affected | Drop-outs n (%) | Injections at baseline, | Missing data | | |
| | ≥10% | 25/337 (7.4%) | week 4 and then every | NRI for PASI and IGA | Serious AE, n (IR) [95% | |
| | | | 12 weeks. Placebo | mod 2011 | CI] | The stratification of |
| | Randomisation was | | injections to match | | I: 30/335 (9.6) [6.5- | treatment dose based |
| | stratified by body | | secukinumab injection | | 13.7] | on body weight means |
| | weight ≤100 kg or >100 | | regime. | Results | C: 26/336 (8.5) [5.5- | that most patients in |
| | kg | | | Week 16 | 12.4] | the comparison group |
| | | | n=339 | <u>PASI≥90, n (%)</u> | | received 45 mg |
| | Baseline characteristics | | | Subjects ≤100 kg. | Death, n (%) | ustekinumab. |
| | Male (%) | | Drop-outs n (%) | I: 214/256 (83.6%) | I: 0/335 (0%) | |
| | I: 68.0% | | 41/339 (12.1%) | C: 152/252 (60.3%) | C: 1/336 (0.3%) | |
| | C: 74.3% | | | | | |
| | Race - Caucasian (%) | | | Subjects >100 kg. | Discontinued treatment | |
| | I: 88.7% | | | I: 50/78 (64.1%) | due to AE, n (%) | |
| | C: 85.0% | | | C: 40/83 (48.2%) | I: 10/335 (3.0%) | |
| | Weight (kg±SD) | | | | C: 9/336 (2.7%) | |
| | l: 87.4±19.95 | | | All subjects (both < and | | |
| | C: 87.2±22.11 | | | > 100 kg) | | |
| | BMI (kg/m²±SD) | | | I: 264/334 (79.0%) | | |

Table 7.12. Secukinumab versus Ustekinumab

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------|-----------------------|--------------|------------|--|--------------------------------|--------------|
| Year | Setting | | | | | |
| Reference | | | | Results | | Comment |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| | I: 29.1±5.87 | | | C: 193/335 (57.6%) | Infections and | |
| | C: 29.0±6.69 | | | l vs C: p <0.001 | infestations, n (IR) [95% | |
| | | | | | CI] | |
| | Study period | | | DLQI, proportion | I: 197/335 (98.4) [85.1- | |
| | | | | responders w 0 or 1, all | 113.1] | |
| | Follow-up | | | subjects | C: 194/336 (95.8) [82.8- | |
| | Head-to-head | | | I: ca 70% | 110.3] | |
| | comparison between | | | C: ca 60% | | |
| | secukinumab och | | | l vs C: p<0.01 | Most frequent AEs | |
| | ustekinumab with 16 | | | | Nasopharygitis, n (IR) | |
| | weeks as primary | | | | [95% CI] | |
| | endpoint and 52 weeks | | | Week 52 | I: 77/335 (27.1) [21.4- | |
| | as secondary. | | | <u>PASI≥90, n (%)</u> | 33.8] | |
| | | | | Subjects ≤100 kg. | C: 83/336 (31.0) [24.7- | |
| | | | | I: 201/256 (78.5%) | 38.5] | |
| | | | | C: 157/252 (62.3%) | | |
| | | | | | Headache, n (IR) [95% | |
| | | | | Subjects >100 kg. | CI] | |
| | | | | I: 49/78 (62.8%) | I: 40/335 (13.5) [9.7- | |
| | | | | C: 46/83 (55.4%) | 18.4] | |
| | | | | | C: 41/336 (14.2) [10.2- | |
| | | | | All subjects (both < and | 19.3] | |
| | | | | > 100 kg) | | |
| | | | | 1: 24//334 (74.0%) | URTI, n (IR) [95% CI] | |
| | | | | C: 203/335 (60.6%) | 1: 31/335 (10.1) [6.9- | |
| | | | | T vs C: p < 0.001 | 14.3] | |
| | | | | | C: 30/336 (9.9) [6.7- | |
| | | | | DLQI, proportion | 14.2] | |
| | | | | responders W U Or 1, all | Arthroloia n (ID) [OF0/ | |
| | | | | SUDJECTS | Artinaigia, n (ik) (95% | |
| | | | | 1. 23//331 (/1.0%) C. 107/332 (E0.3%) | | |
| | | | | C. 13//333 (33.2%) | 1. 20/000 (0.1) [0.3- 10 0] | |
| | | | | 1 vs c. µ=0.000 | 12.0] | |
| | | | | | | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------|----------------|--------------|------------|----------------|----------------------------|--------------|
| Year | Setting | | | | | |
| Reference | | | | Results | | Comment |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| | | | | | C: 28/336 (9.2) [6.1- | |
| | | | | | 13.3] | |
| | | | | | | |
| | | | | | Diarrhoea, n (IR) [95% | |
| | | | | | CI] | |
| | | | | | I: 23/335 (7.5) [4.7- | |
| | | | | | 11.2] | |
| | | | | | C: 24/336 (7.9) [5.1- | |
| | | | | | 11.8] | |
| | | | | | Deals nation of (ID) [050(| |
| | | | | | Back pain, n (IR) [95% | |
| | | | | | | |
| | | | | | 1: 22/335 (7.1) [4.4- | |
| | | | | | 10./] | |
| | | | | | C: 26/336 (8.5) [5.6- | |
| | | | | | 12.5] | |

AE – adverse event; BSA – body-surface area; BMI – body mass index; DLQI – dermatology life quality index; IGA – investigator's global assessment; ITT – intention-to-treat; NRI – non-responder imputation; PASI – psoriasis area and severity index; SD – standard deviation; SE – standard error; URTI – upper respiratory tract infection

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|---------------------------|--------------------------|-------------------------|----------------------|----------------------|-------------------------|-------------------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| Landells <i>et al</i> | Population | Intervention | Comparison | Model of analysis | Adverse events | Risk of Bias |
| 2015 | Patients 12 to 17 years | Ustekinumab 0.75 | Placebo | ITT | Patients with ≥1 AE | Acceptable |
| [127] | with moderate-to- | mg/kg for patients with | | Per protocol for AEs | I: 16/36 (44.4%) | |
| | severe plaque psoriasis | a body weight of ≤60 | n=37 | Missing data | C: 21/37 (56.8%) | Comment |
| Multicentre trial carried | (for ≥6 months) with | kg, 45 mg for patients | | NRI for PGA and PASI | | |
| out at 36 sites in | PASI≥12, PGA≥3, and | >60 to ≤100 kg, 90 mg | drop-out rate, n (%) | | Discontinued due to AE, | The study was funded |
| Canada and Europe. | BSA≥10% | dose for patients >100 | 0/37 (0%) | Results – week 12 | n | by Janssen Research & |
| | | kg | | PASI ≥75, n (%) | I: 0/36 (0%) | Development, LLC |
| RCT | Baseline characteristics | | | I: 29/36 (80.6%) | C: 0/37 (0%) | Several authors |
| | Females/Males, % | Subcutaneous injections | | C: 4/37 (10.8%) | | affiliated with Janssen |
| | I: 55.6%/44.4% | at week 0, 4, 12 week | | I vs C: p<0.001 | Infections, n (%) | Research & |
| | C: 45.9%/54.1% | | | | I: 8/36 (22.2%) | Development, LCC |
| | Body-weight (kg), | Randomised pop | | PASI ≥90, n (%) | C: 14/37 (37.8%) | |
| | mean±SD | n=36 | | I: 22/36 (61.1%) | | |
| | l: 62.0±17.1 | | | C: 2/37 (5.4%) | Patients with ≥1 SAE | |
| | C: 64.7±14.7 | Drop-out rate, n (%) | | l vs C: p<0.001 | I: 0/36 (0%) | |
| | | 1/36 (2.8%) | | | C: 0/37 (0%) | |
| | Ethnicity (Caucasian), % | | | CDLQI change from | | |
| | I: 94.4% | | | baseline, mean±SD, n | | |
| | C: 91.9% | | | I: -6.7±5.6, 32 | | |
| | | | | C: -1.5±3.2. 32 | | |
| | Study period | | | I vs C: p<0.001 | | |
| | March 2010 – January | | | | | |
| | 2014 | | | | | |
| | | | | | | |
| | Follow-up | | | | | |
| | 12 weeks placebo- | | | | | |
| | controlled phase, | | | | | |
| | through week 52 active | | | | | |
| | treatment phase, | | | | | |
| | follow-up phase | | | | | |

Table 7.14. Ustekinumab versus placebo

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|---------------------------|---------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| | through week 60. | | | | | |
| | Results from placebo- | | | | | |
| | controlled phase | | | | | |
| | reported here | | | | | |
| Lebwohl et al 2010 | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
| [128] | Reported in Leonardi et | I1: 90 mg ustekinumab | C: placebo | Per protocol | | Acceptable |
| | al 2008 [129] | I2: 45 mg of ustekiumab | | | Reported in Leonardi et | |
| Efficacy results reported | | | Randomised, n | Results | al 2008 [129] | Comments |
| in Leonardi et al 2008 | Baseline characteristics | Randomised, n | C: n=255 | Week 12 | | |
| [129] | Female/Male, % | l1: n=256 | | | | Ustekinumab produced |
| Study name | l1: 32.4%/67.6% | l2: n=255 | Subcutaneous injections | DLQI change, mean±SD, | | by Centocor, Inc. Study |
| PHOENIX I | 12: 31.4%/68.6% | Subcutaneous injection | of placebo to match | n | | supported by Centocor, |
| | C: 28.2%/71.8% | were administered at | active treatment | l1: -8.7±6.47, 249 | | Inc. |
| Multicentre trial carried | Body weight (kg), | weeks 0, 4 and every 12 | | l2: -8.0±6.87, 254 | | |
| out in the US, Canada | mean±SD | weeks thereafter | | C: -0.6±5.97, 252 | | Several of the authors |
| and Belgium. | l1: 93.8±23.9 | | | 11, 12 vs C: p<0.001 | | had financial ties/were |
| | I2: 93.7±23.8 | | | | | employed by Centocor, |
| RCT | C: 94.2±23.5 | | | SF-36 PCS score change, | | Inc. as well as other |
| | | | | mean±SD, n | | pharmaceutical |
| | Study period | | | l1: 3.2±7.6 | | companies |
| | December 2005 – | | | 12: 2.0±7.4 | | |
| | September 2007 | | | C: -0.51±7.5 | | |
| | | | | 11, 12, vs C: p<0.001 | | |
| | Follow-up | | | | | |
| | 12 weeks placebo- | | | SF-36 MCS score | | |
| | controlled phase, | | | change, mean±SD, n | | |
| | followed by active | | | l1: 2.5±9.5 | | |
| | treatment period | | | I2: 2.1±9.3 | | |
| | (weeks 12-40) where | | | C: -1.3±7.5 | | |
| | placebo group received | | | l1, l2, vs C: p<0.001 | | |
| | ustekinumab, followed | | | | | |
| | by a withdrawal period | | | | | |
| | (weeks 40–76). Results | | | | | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------------------|--------------------------|-------------------------|-------------------------|--------------------------|------------------------|---------------------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| | from placebo-controlled | | | | | |
| | phase reported here | | | | | |
| Leonardi et al 2008 | Population | Intervention | Comparison | Analysis model | Adverse Events | Risk of bias |
| [129] | Patients ≥18 years of | I1: 90 mg ustekinumab | C: placebo | ITT for efficacy | AEs - week 0–12 | Acceptable |
| | age, with a diagnosis of | I2: 45 mg of ustekiumab | | outcomes | | |
| Quality of life related | plaque psoriasis (≥6 | | Subcutaneous injections | Per protocol (≥1 dose of | Patients with ≥1 AE, n | Comment |
| outcomes reported in | months), baseline PASI | Subcutaneous injection | of placebo to match | test substance) for | (%) | |
| Lebwohl et al. 2010 | score ≥12, BSA | were administered at | active treatment | safety analyses | I1: 131/255 (51.4%) | Study funded by |
| [128] | involvement ≥10%. No | weeks 0, 4 and every 12 | | | 12: 147/255 (57.6%) | Centocor Inc. who was |
| Multicentre trial, | other form or psoriasis. | weeks thereafter | Randomised, n | Results – week 12 | C: 123/255 (48.2%) | also involved in the |
| conducted at 48 sites in | | | C: 255 | | | design of the study, |
| the US, Canada and | Baseline randomisation | Randomised, n | | PASI ≥50, n (%) | AEs leading to | carried out the analysis. |
| Belgium | stratified by | 11: 256 | Drop-out rate (week | 11: 220/256 (85.9%) | withdrawal, n (%) | Several authors have |
| | investigational site, | 12: 255 | 12), n (%) | 12: 213/255 (83.5%) | 11: 4/255 (1.6%) | been affiliated with or |
| Study name | weight (≤90 kg or >90 | | C: 12/255 (4.7%) | C: 26/255 (10.2%) | 12: 1/255 (0.4%) | have financial ties to |
| PHOENIX I | kg) | Drop-out rate (week | | I1, I2 vs C: p<0.0001 | C: 6/255 (2.4%) | Centocor inc. or other |
| | | 12), n (%) | | | | pharmaceutical |
| RCT | Baseline characteristics | 11: 11/256 (4.3%) | | PASI ≥75, n (%) | Serious AEs, n (%) | companies. |
| | Female/Male, % | 12: 2/255 (0.8%) | | 11: 170/256 (66.4%) | 11: 2/255 (0.8%) | |
| | 11: 32.4%/67.6% | | | 12: 171/255 (67.1%) | 12: 4/255 (1.6%) | |
| | 12: 31.4%/68.6% | | | C: 8/255 (3.1%) | C: 2/255 (0.8%) | |
| | C: 28.2%/71.8% | | | 11, 12 vs C: p<0.0001 | | |
| | | | | 5 1 0 L 0 0 (0 () | Common AEs | |
| | Bodyweight (kg), | | | PASI ≥90, n (%) | URTI, n (%) | |
| | mean±SD | | | 11: 94/256 (36.7%) | 11: 16/255 (6.3%) | |
| | 11: 93.8±23.9 | | | 12: 106/255 (41.6%) | 12: 18/255 (7.1%) | |
| | 12: 93.7±23.8 | | | C: 5/255 (2.0%) | C: 16/255 (6.3%) | |
| | C: 94.2±23.5 | | | 11, 12 vs C: p<0.0001 | | |
| | Chudu novied | | | DAC(100 - (0/) | Nasopharyngitis, n (%) | |
| | Study period | | | PASI100, n (%) | 11: 21/255 (8.2%) | |
| | December 2005 – | | | 11: 28/256 (10.9%) | 12: 26/255 (10.2%) | |
| | September 2007 | | | 12: 32/255 (12.5%) | C: 22/255 (8.6%) | |
| | | | | C: 0/255 (0.0%) | | |
| | | 1 | | 11, 12 vs C: p<0.0001 | 1 | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|-------------------------|-----------------------------|-------------------------|------------|--------------------------|------------------------|-----------------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| | Follow-up | | | | Arthralgia, n (%) | |
| | 12 weeks placebo- | | | | l1: 6/255 (2.4%) | |
| | controlled phase, | | | | 12: 7/255 (2.7%) | |
| | followed by active | | | | C: 7/255 (2.7%) | |
| | treatment period | | | | | |
| | (weeks 12–40), | | | | Headache, n (%) | |
| | followed by a | | | | l1: 13/255 (5.1%) | |
| | withdrawal period | | | | I2: 14/255 (5.5%) | |
| | (weeks 40-76) and a | | | | C: 6/255 (2.4%) | |
| | long term extension | | | | | |
| | period through week | | | | | |
| | 264. Efficacy results | | | | | |
| | from placebo-controlled | | | | | |
| | phase reported here. | | | | | |
| Kimball et al | Population | Intervention | | Effects from OLE-studies | Adverse events | Risk of bias |
| 2013 | | I1: 90 mg ustekinumab | | are not reported | | |
| [133] | Reported in [129] and [128] | I2: 45 mg of ustekiumab | | | Patients treated: 753 | Not assessed |
| This article is an open | | Subcutaneous injection | | | Patient years (follow- | Comment |
| lable extension (OLE) | 68.7% (n = 517) | were administered at | | | <i>up):</i> 3104.2 | Study funded by |
| from the PHOENIX I | completed | weeks 0, 4 and every 12 | | | | Janssen Research & |
| trial, [129] and [128] | study agent through the | weeks thereafter. | | | Key safety events per | Development, LLC, |
| | last Year-5 dose at or | | | | 100 patient-years of | Spring House, PA, USA |
| | before Week 244 | Number of patients in | | | follow-up through year | |
| | | safety population for | | | 5: | |
| | Follow-up | intervention at week | | | | |
| | Placebo-controlled | 244: | | | AE: 214.94 | |
| | phase 0–12 weeks | n=753 | | | | |
| | (presented in [129] and | | | | Serious AE: 5.35 | |
| | [128]), OLE for up to 5 | | | | | |
| | years presented here | | | | Discontinuation due to | |
| | | | | | AE: | |
| | | | | | 2.13 | |
| | | | 1 | | | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|----------------------------|--------------------------|-------------------------|-------------------------|-----------------------|--------------------------|-------------------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| | | | | | Infections: 82.66 | |
| | | | | | | |
| | | | | | Infections requiring | |
| | | | | | treatment: 29.41 | |
| | | | | | Serious infections: 1.03 | |
| | | | | | | |
| | | | | | Malignant neoplasms: | |
| | | | | | 0.93 | |
| | | | | | Non-melanoma skin | |
| | | | | | cancer (NMSC): 0.45 | |
| | | | | | | |
| | | | | | Other malignancies | |
| | | | | | (exklucding NMSC): | |
| | | | | | 0.48 | |
| | | | | | | |
| | | | | | Major adverse | |
| | | | | | cardiovascular event | |
| | | | | | (MACE): 0.32 | |
| T-F Tsai et al | Population | Intervention | Comparison | Analysis model | Adverse effects | Risk of bias |
| 2011 | | | | ITT for efficacy | | Acceptable |
| [131] | Patients (≥20 year of | I: Ustekinumab 45 mg. | C: placebo. | outcomes through week | AEs week 0–12 | Comments |
| Multicentre study | age with Korean or | Subcutaneous injections | Subcutaneous injections | 12. | Patients with ≥1 AE, n | |
| carried out at 13 sites in | Taiwanese ancestry), | weeks 0, 4, 16 and | week 0 and 4, crossover | Per protocol analysis | (%) | Study funded by |
| Taiwan and Korea | with moderate-to- | placebo at week 12 | to ustekinumab 45 mg | after week 12 | I: 40/61 (65.6%) | Centocor Inc., who also |
| | severe plaque psoriasis | | at week 12 and 16 | | C: 42/60 (70.0%) | provided statistical |
| Study name | and PASI score ≥12, BSA | n=61 | | Results | | analysis and writing |
| PEARL | involvement ≥10% | | n=60 | Week 12 | AE leading to | assistance |
| | | Drop-out rate (12 | | | withdrawal, n (%) | |
| RCT | Baseline characteristics | weeks), n (%) | Drop-out rate (12 | PASI ≥75 – primary | I: 0/61 (0.0%) | |
| | Female/Male, % | 4/61 (6.6%) | weeks), n (%) | endpoint, n (%) | C: 3/60 (5.0%) | |
| | I: 18.0%/82.0% | | 5/60 (8.3%) | I: 41/61 (67.2%) | | |
| | C: 11.7%/88.3% | | | C: 3/60 (1.7%) | Patients with SAE, n (%) | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------|-------------------------|--------------|------------|------------------|------------------------|--------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| | | | | I vs C: p<0.001 | I: 0/61 (0.0%) | |
| | Ethnicity, n (%) | | | | C: 2/60 (3.3%) | |
| | Taiwanese/Chinese | | | PASI ≥50, n (%) | | |
| | I: 49.2% | | | I: 51/61 (83.6%) | Common AEs | |
| | C: 50.0% | | | C: 8/60 (13.3%) | URTI, n (%) | |
| | Korean | | | I vs C: p<0.001 | I: 7/61 (11.5%) | |
| | I: 50.8% | | | | C: 7/60 (11.7%) | |
| | C: 50.0% | | | PASI ≥90, n (%) | | |
| | | | | I: 30/61 (49.2%) | Hyperglycemia, n (%) | |
| | BMI (kg/m²), n (%) | | | C: 1/60 (1.7%) | I: 5/61 (8.2%) | |
| | Normal (BMI<25) | | | I vs C: p<0.001 | C: 5/60 (8.3%) | |
| | I: 29/61 (47.5%) | | | | | |
| | C: 33/60 (55.0%) | | | PASI 100, n (%) | Nasopharyngitis, n (%) | |
| | Overweight (BMI ≥25, | | | I: 5/61 (8.2%) | I: 5/61 (8.2%) | |
| | <30) | | | C: 0/60 (0.0%) | C: 3/60 (5.0%) | |
| | I: 27/61 (44.3%) | | | l vs C: 0.024 | | |
| | C: 21/60 (35.0%) | | | | Pruritus, n (%) | |
| | Obese (BMI ≥30) | | | DLQI change from | I: 5/61 (8.2%) | |
| | I: 5/61 (8.2%) | | | baseline | C: 16/60 (26.7%) | |
| | C: 6/60 (10.0%) | | | mean±SD, n | | |
| | | | | I: -11.2±7.1, 59 | Cough, n (%) | |
| | Study period | | | C: -0.5±6.5, 60 | I: 4/61 (6.6%) | |
| | December 2008 – | | | I vs C: p<0.001 | C: 3/60 (5.0%) | |
| | March 2010 | | | | | |
| | | | | | Eosinophilia, n (%) | |
| | Follow-up | | | | I: 2/61 (3.3%) | |
| | Placebo-controlled | | | | C: 2/60 (3.3%) | |
| | phase 0–12 weeks. At | | | | | |
| | 12 weeks placebo group | | | | Psoriasis, n (%) | |
| | received active | | | | I: 2/61 (3.3%) | |
| | treatment, both I and C | | | | C: 6/60 (10.0%) | |
| | 45 mg ustekinumab. | | | | | |
| | Results from placebo- | | | | Anaemia, n (%) | |
| | | | | | I: 1/61 (1.6%) | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|----------------------------|--------------------------|--------------------------|-------------------------|-----------------------|---------------------------|-------------------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| | controlled phase | | | | C: 1/60 (1.7%) | |
| | reported here | | | | | |
| | | | | | Injection site reactions, | |
| | | | | | n (%) | |
| | | | | | I: 1/61 (1.6%) | |
| | | | | | C: 3/60 (5.0%) | |
| | | | | | Eczema, n (%) | |
| | | | | | I: 0/61 (0.0%) | |
| | | | | | C: 0/60 (0.0%) | |
| | | | | | | |
| | | | | | Abnormal nepatic | |
| | | | | | function, n (%) | |
| | | | | | 1: 0/61 (0.0%) | |
| | | | | | C: 2/60 (3.3%) | |
| | | | | | Psoriatic arthropathy n | |
| | | | | | (%) | |
| | | | | | 1: 0/61 (0.0%) | |
| | | | | | $C \cdot 3/60 (5.0\%)$ | |
| Papp et al | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
| 2008 | Patients (≥18 years old) | I1: 45 mg ustekinumab | C: placebo | ITT | | Acceptable |
| [130] | with a diagnosis of | I2: 90 mg ustekinumab | | Safety population: | AEs week 0-12 | |
| | plaque psoriasis (≥6 | | After 12 weeks patients | patients who received | | Comments |
| Multicentre study | months), with a PASI | Subcutaneous injections | were re-randomised to | ≥1 dose of substance | Patients with ≥1 AE, n | |
| carried out at 70 sites in | score of ≥12, BSA | of ustekinumab at week | active treatment (45 mg | | (%) | Study funded by |
| Europe (Austria, France, | involvement ≥10% | 0, 4 (placebo-controlled | or 90 mg ustekinumab | Results | l1: 217/409 (53.1%) | Centocor Inc., Centocor |
| Germany, Switzerland | | phase), and week 12, 16 | every 12 weeks) | Week 12 | I2: 197/411 (47.9%) | was involved in the |
| and UK) and North | Baseline characteristics | and every 12 weeks | | | C: 204/410 (49.8%) | design of the study and |
| America (Canada and | Female/Male, % | thereafter. | Randomised population | PASI ≥50, n (%) | | data analysis |
| USA). | l1: 30.8%/69.2% | | C: n=410 | l1: 342/409 (83.6%) | AEs leading to | |
| | 12: 33.3%/66.7% | Randomised population | | 12: 367/411 (89.3%) | withdrawal, n (%) | |
| Study name | C: 31.0%/69.0% | l1: n=409 | Drop-out rate (week 0- | C: 41/410 (10.0%) | l1: 1/409 (0.2%) | |
| PHOENIX 2 | Ethnicity | l2: n=411 | 12) | 11, 12 vs C: p<0.0001 | I2: 6/411 (1.5%) | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------|--------------------------|------------------------|----------------|----------------------------|--------------------------|--------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| | No information | | C: 18/410=4.4% | | C: 8/410 (2.0%) | |
| RCT | Bodyweight (kg), | Drop-out rate (week 0- | | PASI ≥75, n (%) – | | |
| | mean±SD | 12) | | primary endpoint | Serious AEs, n (%) | |
| | l1: 90.3±21.0 | I1: 6/409=1.5% | | 11: 273/409 (66.7%) | I1: 8/409 (2.0%) | |
| | I2: 91.5±21.3 | 12:9/411=2.2% | | 12: 311/411 (75.7%) | 12: 5/411 (1.2%) | |
| | C: 91.1±21.6 | | | C: 15/410 (3.7%) | C: 8/410 (2.0%) | |
| | | | | l1, l2 vs C: p<0.0001 | | |
| | Randomisation was | | | | Common adverse | |
| | stratified based by | | | PASI ≥90, n (%) | events, week 0-12 | |
| | investigational site and | | | 11: 173/409 (42.3%) | presented here | |
| | bodyweight (≤90 kg, or | | | 12: 209/411 (50.9%) | Arthralgia, n (%) | |
| | >90 kg), and history of | | | C: 3/410 (0.7%) | I1: 14/409 (3.4%) | |
| | response, intolerance, | | | 11, 12 vs C: p<0.0001 | I2: 10/411 (2.4%) | |
| | or contraindication to | | | | C: 12/204 (2.9%) | |
| | more/less than three | | | PASI 100, n (%) | | |
| | conventional therapies. | | | 11: 74/409 (18.1%) | Cough, n (%) | |
| | | | | 12: 75/411 (18.2%) | I1: 3/409 (0.7%) | |
| | Study period | | | C: 0/410 (0.0%) | 12: 4/411 (1.0%) | |
| | March 2007 – | | | 11, 12 vs C: p<0.0001 | C: 7/410 (1.7%) | |
| | September 2007 | | | | | |
| | | | | DLQI change, mean±SD; | Headache, n (%) | |
| | Follow-up | | | median [IQR], n | l1: 19/409 (4.6%) | |
| | Placebo-controlled | | | l1: -9.3±7.12, -8.00 | I2: 19/411 (4.6%) | |
| | phase week 0–12, | | | (-14.0, -4.0), 401 | C: 17/410 (4.1%) | |
| | followed by a crossover | | | I2: -10.0±6.67, -9.00 | | |
| | phase were all groups | | | (-14.0, -5.0), 402 | Injection site erythema, | |
| | received active | | | C: -0.5±5.66; -0.50 (-4.0, | n (%) | |
| | treatment (week 12– | | | 3.0), 400 | I1: 6/409 (1.5%) | |
| | 28), and a randomised | | | 11, 12 vs C: p<0.0001 | 12: 6/411 (1.5%) | |
| | dose intensification | | | | C: 1/410 (0.2%) | |
| | phase (week 28–52). | | | | | |
| | Results from placebo- | | | | Nasopharyngitis, n (%) | |
| | controlled phase | | | | I1: 30/409 (7.3%) | |
| | reported here | | | | 12: 28/411 (6.8%) | |

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|---------------------|-------------------------|--------------------------|------------|---------------------------------|-------------------------|--------------------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| | | | | | C: 29/410 (7.1%) | |
| | | | | | | |
| | | | | | URTI, n (%) | |
| | | | | | 11: 18/409 (4.4%) | |
| | | | | | 12: 12/411 (2.9%) | |
| | | · · · · | | | C: 14/410 (3.4%) | |
| Papp et al | Population | Intervention | | Analysis model | Adverse events | Risk of bias |
| 2013 | For inclusion criteria, | I1: Ustekinumab 45 mg | | All patients receiving ≥ 1 | Expressed as event | Not assessed |
| [132] | see [134] and [130] | | | dose of study drug | rates of n events/100 | |
| | | 12: Ustekinumab 90 mg | | included | patient yrs of exposure | Comment |
| OLE – after ACCEPT | Follow up | | | | to ustekinumab | Results from OLE:s were |
| [134] and PHOENIX I | 5 yrs | S.c. Injections every 12 | | | | not assessed for blas as |
| and II [130] | Deservation | weeks. | | | Adverse events | only observational data |
| | Drop-out rate | 14 | | | 11: 242.6 | of AE's were collected. |
| | 1482/311/ patients | 11: n=1319 | | | 12: 225.3 | |
| | completed 24 yrs of | 12: h=2001 | | | Serious daverse events: | |
| | treatment and follow | Total a metionatum | | | 11: 7.0 | |
| | up | Total n patient yrs | | | 12: 7.2 | |
| | 929/2117 patients | exposure to | | | AE.S reduing to | |
| | completed >5 yrs of | 11. 2776 vrs | | | | |
| | treatment and follow | 12: 5720 yrs | | | 12.2.4 | |
| | | 12. 5252 915 | | | Infections any | |
| | μμ | | | | 11.89.8 | |
| | | | | | 12.84.1 | |
| | | | | | 12.0112 | |
| | | | | | Serious AE:s occurring | |
| | | | | | >1/100 patient vrs | |
| | | | | | Serious infections | |
| | | | | | 11: 0.9 | |
| | | | | | 12: 1.2 | |
| | | | | | Cardiac disorders | |
| | | | | | 11: 1.1 | |
| | | | | | 12: 1.1 | |

| First Author Year Reference Country Study design | Population Setting Study period Follow-up (FU) | Intervention | Comparison | Analysis model Results | Adverse events | Risk of bias Comment |
|--|---|--------------|------------|---------------------------|--|-------------------------|
| | | | | | MalignanciesI1: 1.2I2: 1.1 $\underline{Common adverse events}$ $\underline{occurring \geq 5/100}$ $\underline{patient yrs}$ NasopharyngitisI1: 21.0I2: 20.6URTII1: 17.4I2: 15.4HeadacheI1: 7.5I2: 6.8ArthralgiaI1: 5.0 | |
| | | | | | 12: 4.5 | |

AE – adverse events; BSA – body surface area; CDLQI – children's dermatology life quality index; DLQI – dermatology life quality index; ITT – intention-to-treat; IQR – Interquartile range; MCS; mental component summary score; NRI – non-responder imputation; PASI – psoriasis area and severity index; PCS – physical component summary score; PGA – physician's global assessment; SD – standard deviation; SE – standard error; URTI – upper respiratory tract infection

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|-------------------------|--------------------------|-------------------------|-------------------------|-------------------------|--------------------------|-----------------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| Griffiths et al | Population | Intervention | Comparison | Analysis model | Adverse Events | Risk of bias |
| 2010 | Patients (≥18 year of | I1: 45 mg ustekinumab | C: 50 mg etanercept, | ITT for efficacy | | Acceptable |
| [134] | age), with plaque | I2: 90 mg ustekinumab | subcutaneous injections | outcomes | Results (week 0–12) | |
| | psoriasis (diagnosis ≥6 | | twice weekly for | Per protocol for safety | | Comment |
| Multicentre study | months, no other form | Subcutaneous injections | 12 weeks | outcomes | Patients with ≥1 AE, n | |
| carried out at 67 sites | of psoriasis permitted), | at 0 and 4 weeks | | | (%) | Study sponsored by |
| worldwide | with PASI score ≥12, | | C: n=347 | Results (week 12) | I1: 138/209 (66.0%) | Centocor Research and |
| | PGA score ≥3, BSA | l1: n=209 | | | 12: 240/347 (69.2%) | Development. Centocor |
| RCT | involvement ≥10% | l2: n=347 | Drop-out rate (week | PASI ≥90, n (%) | C: 243/347 (70.0) | designed the study, |
| | | | 12), n (%) | I1: 76/209 (36.4%) | | conducted the data |
| | Baseline characteristics | Drop-out rate (week | C: 11/347 (3.2%) | 12: 155/347 (44.7%) | Patients with ≥1 serious | analyses, and |
| | Female/Male% | 12), n (%) | | C: 80/347 (23.1%) | AEs, n (%) | participated in the |
| | I1: 36.4%/63.6% | I1: 8/209 (3.8%) | | l1 vs C: p<0.001 | I1: 4/209 (1.9%) | writing of the |
| | 12: 32.6%/67.4% | 12: 5/347 (1.4%) | | l2 vs C: p<0.001 | 12: 4/347 (1.2%) | manuscript |
| | C: 29.1%/70.9% | | | | C: 4/347 (1.2%) | |
| | | | | PASI ≥75, n (%) – | | |
| | Ethnicity (Caucasian), % | | | primary endpoint | AEs leading to | |
| | l1: 92.3% | | | l1: 141/209 (67.5%) | withdrawal, n (%) | |
| | 12: 89.0% | | | 12: 256/347 (73.8%) | I1: 4/209 (1.9%) | |
| | C: 91.1% | | | C: 197/347 (56.8%) | 12: 4/347 (1.2%) | |
| | | | | l1 vs C: p=0.01 | C: 8/347 (2.3%) | |
| | Bodyweight (kg), | | | I2 vs C: p<0.001 | | |
| | mean±SD | | | | Common AEs | |
| | l1: 90.8±20.9 | | | | Nasopharyngitis, n (%) | |
| | I2: 90.4±21.1 | | | | I1: 21/209 (10.0%) | |
| | C: 91.0±22.8 | | | | 12: 34/347 (9.8%) | |
| | Randomisation | | | | C: 30/347 (8.6%) | |
| | stratified according to | | | | | |
| | site and bodyweight | | | | URTI, n (%) | |
| | (<90 kg, ≥90 kg) | | | | 11: 13/209 (6.2%) | |
| | | | | | 12: 22/347 (6.3%) | |
| | Study period | | | | C: 20/347 (5.8%) | |

Table 7.14. Ustekinumab versus Etanercept

| First Author | Population | Intervention | Comparison | Analysis model | Adverse events | Risk of bias |
|--------------|-------------------------|--------------|------------|----------------|----------------------------|--------------|
| Year | Setting | | | | | Comment |
| Reference | | | | Results | | |
| Country | Study period | | | | | |
| Study design | Follow-up (FU) | | | | | |
| | March 2007 – January | | | | | |
| | 2009 | | | | Headache, n (%) | |
| | | | | | 11: 31/209 (14.8%) | |
| | Follow-up | | | | 12: 42/347 (12.1%) | |
| | Controlled phase for 12 | | | | C: 38/347 (11.0%) | |
| | weeks. Week 12-44 | | | | | |
| | treatment of patients | | | | Back pain, n (%) | |
| | with poor response | | | | 11: 14/209 (6.7%) | |
| | with ustekinumab (all | | | | 12: 15/347 (4.3%) | |
| | groups), treatment with | | | | C: 7/347 (2.0%) | |
| | ustekinumab if | | | | | |
| | response lost. Week | | | | Injection-site reaction, n | |
| | 44–64 follow-up. | | | | (%) | |
| | Results from placebo- | | | | I1: 9/209 (4.3%) | |
| | controlled phase | | | | 12: 13/347 (3.7%) | |
| | reported here | | | | C: 86/347 (24.8%) | |
| | | | | | | |

AE – adverse events; BSA – body surface area; CDLQI – children's dermatology life quality index; DLQI – dermatology life quality index; ITT – intention-to-treat; IQR – Interquartile range; MCS; mental component summary score; NRI – non-responder imputation; PASI – psoriasis area and severity index; PCS – physical component summary score; PGA – physician's global assessment; SD – standard deviation; SE – standard error; URTI – upper respiratory tract infection

| Author Year Reference Country | Study design Population Setting Perspective | Intervention versus control | Incremental cost | Incremental effect | ICER | Study quality and transferability* Further information Comments |
|--|---|-------------------------------------|--|-------------------------------------|------|---|
| Opmeer et al 2004 [137] Netherlands | RCT-based CUA/CEA Patients with moderate to severe psoriasis and no previous methotrexate or cyclosporine treatment Follow up period of 16 and 36 weeks. | Methotrexate versus cyclosporine | Week 16: \$ -521 (185*) Week 36: \$ -409 (-9*) Costs reported in USD (\$) year 1999 | No significant effect difference | NA | Quality Moderate quality Moderate transferability Comments Did not control for active treatment with UV-B therapy during trail. |
| | Societal perspective | | *indirect costs | | | Higher pharmaceutical costs then in Sweden and indirect costs not valued with the human capital method. |

Table 8. Methotrexate versus cyclosporine, economic evaluation

CA = Cost analysis; CBA = Cost-benefit analysis; CEA = Cost-effectiveness analysis; CUA = Cost-utility analysis; ICER = Incremental cost-effectiveness ratio; USD = United States Dollar

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Note: the reference list contains all references from the main report, not only of included studies. The list is given in the same order as in the main report.

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