**Chapter 3Assessment of clinical effectiveness**

This report contains reference to confidential information provided as part of the NICE appraisal process. This information has been removed from the report and the results, discussions and conclusions of the report do not include the confidential information. These sections are clearly marked in the report.

[Go to:](https://www.ncbi.nlm.nih.gov/books/NBK458358/)

**Methods for reviewing clinical effectiveness**

**Search strategies**

The literature search aimed to identify all relevant randomised controlled trials (RCTs) of CZP and SEC, and the comparators ETN, ADA, INF, GOL, APR and UST for the treatment of PsA.

The searches for CZP and SEC for PsA were not restricted by date. However, as ETN, ADA, INF, GOL, APR and UST for PsA had been subject to previous TAs, updated searches were performed based on the search dates of these previous TAs.

The search strategy was developed in MEDLINE (via Ovid) and then adapted for use in the other resources searched. The strategy included terms for PsA combined, using the Boolean operator AND, with terms for the eight treatments. No language or geographical limits were applied. A study design search filter to limit retrieval to RCTs was used where available.

Search strategies were developed by an information specialist with input from the project team. The MEDLINE search strategy was checked by a second information specialist. The searches were carried out during December 2015 and then updated on 28 April 2016 to capture more recent studies.

The following databases were searched: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), EMBASE, Health Technology Assessment (HTA) database, PubMed, and the Science Citation Index (SCI).

In addition, the following resources were searched for ongoing, unpublished or grey literature: ClinicalTrials.gov, Conference Proceedings Citation Index – Science (CPCI-S), EU Clinical Trials Register, PROSPERO and the World Health Organization’s International Clinical Trials Registry Platform portal.

As DARE ceased at the end of March 2015, additional searches for systematic reviews were carried out in MEDLINE and EMBASE to ensure that any relevant systematic reviews were identified.

Full search strategies can be found in [*Appendix 1*](https://www.ncbi.nlm.nih.gov/books/n/ukhta2156/app1/).

**Inclusion criteria**

Two reviewers independently screened all titles and abstracts. Full manuscripts of any titles/abstracts that were relevant were obtained, where possible, and the relevance of each study was assessed by two reviewers according to the inclusion criteria, described below. Any discrepancies were resolved by involving a third reviewer. Studies available only as abstracts were also included.

**Study design**

Randomised or quasi-RCTs were eligible for the review of clinical efficacy and safety. For the eligible interventions (see [*Interventions*](https://www.ncbi.nlm.nih.gov/books/NBK458358/#s3-1-2-2)), all open-label extension studies of RCTs were included. For the comparators (see [*Comparators*](https://www.ncbi.nlm.nih.gov/books/NBK458358/#s3-1-2-3)), open-label extensions were identified and listed with the main focus being on those studies that reported data relating to the longest duration of follow-up available for each individual comparator.

To evaluate the adverse effect profiles of the different biologics, the eligible study designs were systematic reviews that covered a range of diseases and large observational studies in patients with PsA.

Prospective registry studies that included PsA patients receiving biologics were eligible to provide data on treatment adherence, treatment withdrawal, and the rates and efficacy of switching to new biologics (i.e. sequential use). Potentially relevant registry studies were sought and identified, with a focus on those deemed to be most clinically relevant and appropriate to the UK setting. This decision was based on an examination of study characteristics and discussion with our clinical adviser.

Studies were also sought on the longer-term natural history of PsA in populations that have not taken a biologic therapy.

**Interventions**

Certolizumab pegol and SEC were eligible at their licensed doses (see [*Table 2*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table2/?report=objectonly)). Studies comparing these two treatments with each other were also eligible.

**Comparators**

The relevant comparators were:

* placebo
* DMARDs: MTX, sulfasalazine, leflunomide, hydroxychloroquine, azathioprine and ciclosporin
* biologic therapies: ADA, ETN, GOL, INF and UST, including any licensed biosimilars
* APR
* best supportive care (BSC).

Biologics and APR may have been used with or without concomitant DMARDs. Only studies that included treatments used at their licensed dose were eligible. Head-to-head trials of the five biologic comparators (and biosimilars) and APR were eligible, but were anticipated to be rare. Therefore, to allow comparisons of active treatments via network meta-analysis (NMA), the biologic comparators and APR could also have been compared with either placebo or a DMARD.

**Participants**

For the evaluation of the effectiveness of CZP and SEC, the included studies were of adults with active PsA for whom DMARDs had been inadequately effective.

**Outcomes**

For CZP and SEC, studies reporting any of the following outcomes were eligible:

* disease activity, using the following multidomain measures: PsARC, ACR 20, 50% improvement in the American College of Rheumatology criteria (ACR 50) and 70% improvement in the American College of Rheumatology criteria (ACR 70)
* functional capacity (assessed using HAQ-DI)
* radiographic assessment of disease progression
* response of psoriatic skin lesions (assessed using PASI)
* measures of dactylitis, enthesitis and tendonitis
* mortality
* HRQoL, assessed using EuroQol-5 Dimensions (EQ-5D) or Short Form questionnaire-36 items (SF-36)
* adverse effects of treatment, focusing on the key adverse events (AEs) identified from previous studies of biologics: malignancies, serious infections, reactivation of latent tuberculosis (TB), injection site reactions and withdrawals due to AEs.

Randomised controlled trials of comparators needed to report at least one of the following: PsARC, ACR 20/50/70, PASI 50 (50% reduction in PASI), PASI 75 (75% reduction in PASI), PASI 90 (90% reduction in PASI) or HAQ-DI score.

For patient registry studies, treatment adherence, treatment withdrawal, and the rates and efficacy of switching to new biologics (i.e. sequential use) were the key outcomes of interest, and particularly those which were identified as being useful to inform parameters in the economic model.

**Data extraction**

For SEC and CZP, data were extracted from published papers and abstracts supplemented by data from the manufacturer submissions (when they were not available from other sources). Data were extracted from previous single technology appraisal (STA) or multiple technology appraisal (MTA) reports for studies of ETN, INF, ADA, GOL, UST and APR. When missing or further information on the trials of these treatments was needed, data were extracted either from the relevant published trial reports or from reviews.[36](https://www.ncbi.nlm.nih.gov/books/NBK458358/)–[39](https://www.ncbi.nlm.nih.gov/books/NBK458358/) Some data may have been missing in the original TAs because of commercial- or academic-in-confidence restrictions; and some of these data may have subsequently been published. Data for UST at the 12-week time point were extracted from the full clinical study reports of PSUMMIT (Study of the Safety and Effectiveness of Ustekinumab in Patients With Psoriatic Arthritis) 1 and 2 trials, which were accessed via the Yale University Open Data Access (YODA) project. For APR, although only the Psoriatic Arthritis Long-term Assessment of Clinical Efficacy (PALACE) 1 trial has been published, data from the PALACE 2 and 3 trials were extracted from STA documents on NICE’s website. All data for these treatments were extracted by one reviewer and then checked for any transcription errors by a second reviewer.

For the dichotomous responder outcomes (PsARC, ACR 20/50/70 and PASI 50/75/90), intention-to-treat (ITT) baseline denominators (i.e. the number of patients randomised for each trial arm) were used, with patients assumed to be non-responders where data were missing. This explains why there is a small difference in the ADalimumab Effectiveness in Psoriatic arthritis Trial (ADEPT) denominators used between this current MTA, the previous MTA and the manufacturers’ submissions (the last two used the ‘modified ITT’ data whereby patients had to have received at least one dose of study treatment).

Data on study design, participant characteristics, efficacy outcomes and quality were extracted by one reviewer using a standardised data extraction form and independently checked by a second reviewer for the SEC and CZP trials. Disagreements were resolved through consensus. For the comparator treatments, most of the data were copied (from previous reports) by one reviewer and then checked for any transcription errors by a second reviewer.

Attempts were made, where possible, to contact authors for missing data. Data from studies with multiple publications were extracted and reported as a single study. For the open-label extension studies of comparator treatments, only the data relating to the latest time point were extracted. Data were also extracted from the manufacturers’ submissions when they were not available from other sources.

**Quality assessment**

The quality of the RCTs was assessed using a modified version of the Cochrane risk-of-bias tool, which incorporated an assessment of baseline imbalance.[40](https://www.ncbi.nlm.nih.gov/books/NBK458358/) The assessments of baseline imbalance were made based on evidence from a systematic review of predictors of treatment response to anti-TNFs.[41](https://www.ncbi.nlm.nih.gov/books/NBK458358/) The review identified several possible such predictors in patients with PsA, although none was identified as being conclusive owing to the limited number of studies and the heterogeneity of response measures. We looked at baseline CRP concentration, age and sex. The characteristics of young age, male sex and high CRP concentration may be predictive of a better response. Risk-of-bias assessments were performed by one reviewer and checked independently by a second reviewer. Any disagreements were resolved through consensus or by involvement of a third reviewer if necessary. Open-label extension studies were less formally evaluated. This was based on assessing imputation methods, the patient withdrawal criteria used and the clinical relevance of any treatment stopping/changing rules.

**Methods of data synthesis**

The study characteristics and quality assessment results were tabulated and summarised narratively. Where possible, the clinical effectiveness data for the PsARC, ACR, PASI and HAQ-DI outcomes were synthesised using Bayesian NMA methods (see [*Chapter 4*](https://www.ncbi.nlm.nih.gov/books/n/ukhta2156/s4/)). For other outcomes, or for studies not included in the NMAs, studies were either summarised narratively or pooled using pairwise meta-analysis methods.

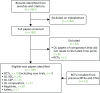
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**Quantity and quality of the identified evidence**

A total of 1761 records were retrieved from the original December 2015 electronic database searches. The searches were updated on 28 April 2016, with a further 200 records available for screening. After screening titles and abstracts, full copies of 182 papers were assessed for inclusion in the review.

Two RCTs were excluded at the abstract stage for using unlicensed dosages (50 mg of ETN twice weekly,[42](https://www.ncbi.nlm.nih.gov/books/NBK458358/) and 20 and 40 mg of APR[43](https://www.ncbi.nlm.nih.gov/books/NBK458358/)). Two RCTs were excluded at the full-paper stage: one did not report subgroup results for PsA[44](https://www.ncbi.nlm.nih.gov/books/NBK458358/) and the other included only patients who were naive to MTX.[45](https://www.ncbi.nlm.nih.gov/books/NBK458358/) The FUTURE [Efficacy at 24 Weeks and Long Term Safety, Tolerability and Efficacy up to 2 Years of Secukinumab (AIN457) in Patients With Active PsA] 1 trial of SEC was excluded from the RCT short-term efficacy review as it used an unlicensed, very high, loading dose. It was, however, included as an open-label extension study as the impact of the initial high loading dose would probably be negligible at later time points.[46](https://www.ncbi.nlm.nih.gov/books/NBK458358/) Fifty open-label studies of comparator treatments were excluded as they did not relate to the latest (longest) duration of follow-up.

Details of the numbers of other eligible full publications or conference abstracts that relate to open-label studies of the included RCTs and patient registry or safety studies are presented in [*Figure 1*](https://www.ncbi.nlm.nih.gov/books/NBK458358/figure/fig1/?report=objectonly).

[](https://www.ncbi.nlm.nih.gov/books/NBK458358/figure/fig1/?report=objectonly)

[**FIGURE 1**](https://www.ncbi.nlm.nih.gov/books/NBK458358/figure/fig1/?report=objectonly)

Flow chart showing the number of studies identified and eligible for inclusion. OL, open label.

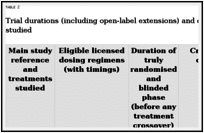
[Go to:](https://www.ncbi.nlm.nih.gov/books/NBK458358/)

**Characteristics of the randomised controlled trials included in the systematic review of short-term efficacy**

Of the 19 included RCTs, 17 were placebo controlled: one of CZP,[47](https://www.ncbi.nlm.nih.gov/books/NBK458358/) three of SEC (two of which were reported in one publication),[48](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[49](https://www.ncbi.nlm.nih.gov/books/NBK458358/) one of GOL,[50](https://www.ncbi.nlm.nih.gov/books/NBK458358/) two of INF,[51](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[52](https://www.ncbi.nlm.nih.gov/books/NBK458358/) two of ETN,[53](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[54](https://www.ncbi.nlm.nih.gov/books/NBK458358/) three of ADA,[55](https://www.ncbi.nlm.nih.gov/books/NBK458358/)–[57](https://www.ncbi.nlm.nih.gov/books/NBK458358/) two of UST[58](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[59](https://www.ncbi.nlm.nih.gov/books/NBK458358/) and three of APR.[60](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[61](https://www.ncbi.nlm.nih.gov/books/NBK458358/) The FUTURE 1 trial of SEC was excluded from the RCT short-term efficacy review as it used an unlicensed, and very high, loading dose.[46](https://www.ncbi.nlm.nih.gov/books/NBK458358/)

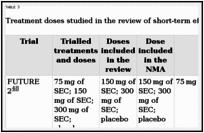
Two trials compared active treatments: one compared SEC with UST[62](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[63](https://www.ncbi.nlm.nih.gov/books/NBK458358/) and one compared INF, ETN and ADA.[64](https://www.ncbi.nlm.nih.gov/books/NBK458358/)

Most studies were conducted mainly in Europe and North America. All but two[53](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[64](https://www.ncbi.nlm.nih.gov/books/NBK458358/) were multicentre trials. Details of the trial durations, different phases and the dosing regimens of the main interventions studied are presented in [*Table 2*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table2/?report=objectonly). Details of all interventions studied are presented in [*Table 3*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table3/?report=objectonly). For some trials we excluded individual treatment arms from the systematic review (see [*Table 3*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table3/?report=objectonly)). This was as a result of the doses not being licensed or recommended in the populations studied. Some included trials were excluded from the NMAs because of the populations being different from the other trial populations (see [*Table 3*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table3/?report=objectonly)).

[](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table2/?report=objectonly)

[**TABLE 2**](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table2/?report=objectonly)

Trial durations (including open-label extensions) and dosing regimens of key interventions studied

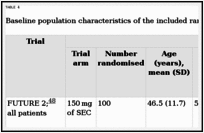
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[**TABLE 3**](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table3/?report=objectonly)

Treatment doses studied in the review of short-term efficacy

The design of many trials typically included a fully blinded, placebo-controlled phase followed by an ‘early escape’ crossover phase (from placebo to an active treatment) for non-responders, then finally crossover to active treatment for the remaining placebo participants. Non-response in this context related to failure to achieve prespecified minimum improvements (ranging between 5% and 20%) in tender joint count (TJC) and swollen joint count (SJC). All the trials using an early escape design ran for 16 weeks before patients were eligible for early escape. Trials then entered open-label extension phases (see [*Long-term effectiveness*](https://www.ncbi.nlm.nih.gov/books/NBK458358/#s3-5)).

[*Table 4*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table4/?report=objectonly) describes the population characteristics of the included trials. Where available, this includes subgroup characteristics for patients who had never previously taken a biologic (i.e. biologic-naive populations) and patients who *had* previously taken a biologic (i.e. biologic-experienced populations). Biologic-experienced patients were available only for the more recent trials (those of SEC, CZP, UST and APR); in the earlier trials such patients were not eligible to participate. Trial sample sizes varied, with earlier trials tending to be smaller than more recent trials. Variation in sample size was also evident within treatments: the two trials of ETN had populations of 60 and 205,[53](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[54](https://www.ncbi.nlm.nih.gov/books/NBK458358/) and the three trials of ADA had populations of 100, 207 and 315.[55](https://www.ncbi.nlm.nih.gov/books/NBK458358/)–[57](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[67](https://www.ncbi.nlm.nih.gov/books/NBK458358/) The duration of PsA ranged from 3 to 12 years across trials; the shortest durations (reported as medians) came from the UST PSUMMIT trials[58](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[59](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[66](https://www.ncbi.nlm.nih.gov/books/NBK458358/) and the longest (reported as means) came from the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT).[51](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[52](https://www.ncbi.nlm.nih.gov/books/NBK458358/) The duration of psoriasis ranged from 11 to 23 years, although this information was not available for the FUTURE 2[48](https://www.ncbi.nlm.nih.gov/books/NBK458358/) SEC and RAPID-PsA[47](https://www.ncbi.nlm.nih.gov/books/NBK458358/) (Certolizumab Pegol in Subjects With Adult Onset Active and Progressive Psoriatic Arthritis) CZP trials. Although not reported in all trials, baseline CRP concentration levels were difficult to interpret as they appeared to have slightly skewed distributions, with means (range 10–31 mg/l) being generally higher than medians (range 7–15 mg/l).

[](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table4/?report=objectonly)

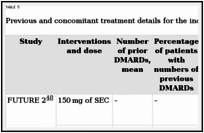
[**TABLE 4**](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table4/?report=objectonly)

Baseline population characteristics of the included randomised trials

Notwithstanding this limited heterogeneity, many key patient characteristics were broadly similar across trials, including mean ages (which ranged from 45 to 51 years), the proportion of male participants (around 50% for most trials), and TJCs and SJCs (TJC, range 18–29; SJC, range 9–18); an exception was the three-arm head-to-head trial, which had notably lower TJC and SJC.[64](https://www.ncbi.nlm.nih.gov/books/NBK458358/) The population in this trial, along with the PsA populations from the large SEC psoriasis trials,[49](https://www.ncbi.nlm.nih.gov/books/NBK458358/) also had markedly higher baseline PASI scores than the other trials (typically around two to three times higher). The FUTURE 2 SEC trial had slightly higher baseline PASI scores than the other trials, most notably in the 150 mg treatment arm. The PsA populations from two of the SEC psoriasis trials[49](https://www.ncbi.nlm.nih.gov/books/NBK458358/) also had lower baseline HAQ-DI scores (range 0.5–0.8 units) than the other trials (range 0.9–1.6 units). In light of these differences, the characteristics of the PsA patients in the SEC psoriasis trials were deemed to be too dissimilar to the other trials to be included in the NMAs. There were three of these psoriasis trials: Efficacy of Response and Safety of Two Fixed Secukinumab Regimens in Psoriasis (ERASURE), Full Year Investigative Examination of Secukinumab vs. Etanercept Using Two Dosing Regimens to Determine Efficacy in Psoriasis (FIXTURE) and Efficacy of Secukinumab Compared to Ustekinumab in Patients with Plaque-type Psoriasis (CLEAR; baseline data were not available for the PsA patients in CLEAR). To be eligible for the ERASURE, FIXTURE and CLEAR trials, patients had to have moderate–severe psoriasis based on a PASI score of > 12 units and BSA involvement of ≥ 10%.[49](https://www.ncbi.nlm.nih.gov/books/NBK458358/) In the trials only of patients with PsA, the proportion of patients with at least moderate psoriasis (i.e. PASI-evaluable patients, defined as a BSA involvement of ≥ 3%) ranged between 41% and 87%.

In the FUTURE 2 (SEC)[48](https://www.ncbi.nlm.nih.gov/books/NBK458358/) and RAPID-PsA (CZP)[47](https://www.ncbi.nlm.nih.gov/books/NBK458358/) trials, the biologic-experienced and biologic-naive subgroups were broadly similar except that the biologic-experienced subgroups tended to have slightly higher TJCs and SJCs, and slightly longer durations of PsA.

All the trials of ETN, INF, ADA and GOL and one UST trial[58](https://www.ncbi.nlm.nih.gov/books/NBK458358/) (nine in total) excluded patients who had previously received an anti-TNF, so their populations comprised entirely biologic-naive patients ([*Table 5*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table5/?report=objectonly)). In the remaining trials, where reported, the proportion of biologic-experienced patients ranged from 15% to 58%. Of the trials that allowed recruitment of biologic-experienced patients, the RAPID-PsA trial[47](https://www.ncbi.nlm.nih.gov/books/NBK458358/) was more selective than the FUTURE 2,[48](https://www.ncbi.nlm.nih.gov/books/NBK458358/) PSUMMIT 2[59](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[66](https://www.ncbi.nlm.nih.gov/books/NBK458358/) and PALACE trials.[60](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[61](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[65](https://www.ncbi.nlm.nih.gov/books/NBK458358/) RAPID-PsA[47](https://www.ncbi.nlm.nih.gov/books/NBK458358/) was the only trial that excluded patients with primary failure of a previous anti-TNF (primary failure was defined as no response within the first 12 weeks of treatment with the anti-TNF). (See [*Appendix 2*](https://www.ncbi.nlm.nih.gov/books/n/ukhta2156/app2/), which details the eligibility criteria for all trials.) The results for the RAPID-PsA biologic-experienced subgroup may therefore be somewhat inflated when compared with the other trials reporting results for this subgroup.

[](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table5/?report=objectonly)

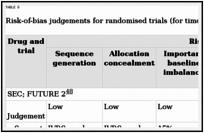
[**TABLE 5**](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table5/?report=objectonly)

Previous and concomitant treatment details for the included studies

**Risk-of-bias assessments**

The proportion of patients who took concomitant MTX ranged from 44% to 70%; most trials allowed concomitant MTX although the FIXTURE and ERASURE psoriasis trials[49](https://www.ncbi.nlm.nih.gov/books/NBK458358/) did not. The reporting of data on the number of previous DMARDs used was limited, although it appeared that most patients had tried one or two DMARDs.

The results of the risk-of-bias assessments are presented in [*Table 6*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table6/?report=objectonly). All except one[57](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[67](https://www.ncbi.nlm.nih.gov/books/NBK458358/) of the trials included in the NMAs were judged as being at low overall risk of bias. Only one trial[64](https://www.ncbi.nlm.nih.gov/books/NBK458358/) was rated as being at high overall risk of bias for all outcomes, which was primarily due to lack of blinding. However, blinding would have been both difficult and impractical as the trial compared INF, ETN and ADA.[64](https://www.ncbi.nlm.nih.gov/books/NBK458358/) All the other trials were appropriately blinded. Across the trials the randomisation methods were well reported; only the head-to-head trial had unclear judgements for both sequence generation and allocation concealment.[64](https://www.ncbi.nlm.nih.gov/books/NBK458358/) The only chance imbalance of note occurred in the PSUMMIT 2 trial, in which median CRP concentration levels were higher in the 45-mg group (13 mg/l) than in the placebo group (8.5 mg/l).[59](https://www.ncbi.nlm.nih.gov/books/NBK458358/) Two of the three SEC trials in patients with psoriasis and PsA had overall judgements as being at unclear risk of bias.[49](https://www.ncbi.nlm.nih.gov/books/NBK458358/) This was because PsA subgroup data were being assessed and no details were available on missing outcome data. IMPACT 2[52](https://www.ncbi.nlm.nih.gov/books/NBK458358/) was rated as being at high risk of bias for the PASI 75 outcome, as last observation carried forward (LOCF) was used for missing data (instead of the more conservative non-responder imputation).

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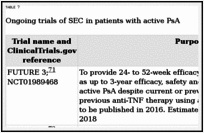
[**TABLE 6**](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table6/?report=objectonly)

Risk-of-bias judgements for randomised trials (for time points before early escape crossover)

**Short-term efficacy of secukinumab**

The clinical effectiveness evidence identified for SEC consisted of four Phase III RCTs: FUTURE 2, ERASURE, FIXTURE and CLEAR.[48](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[49](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[62](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[63](https://www.ncbi.nlm.nih.gov/books/NBK458358/) The FUTURE 2 trial[48](https://www.ncbi.nlm.nih.gov/books/NBK458358/) was of patients with PsA and the ERASURE,[49](https://www.ncbi.nlm.nih.gov/books/NBK458358/) FIXTURE[49](https://www.ncbi.nlm.nih.gov/books/NBK458358/) and CLEAR trials[62](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[63](https://www.ncbi.nlm.nih.gov/books/NBK458358/) were trials of patients with psoriasis and reported subgroup data for patients who also had PsA. The FUTURE 2 trial[48](https://www.ncbi.nlm.nih.gov/books/NBK458358/) provides the main evidence for SEC. FUTURE 1[46](https://www.ncbi.nlm.nih.gov/books/NBK458358/) studied a non-licensed, very high, loading dose (10 mg/kg) followed by a 150-mg maintenance dose. Although this trial was therefore not eligible to contribute data to the review of efficacy of SEC, nor to be included in the evidence synthesis, it has been used to provide supportive evidence on SEC as, unlike FUTURE 2, it reports data on radiographic progression of joint damage (see [*Long-term effectiveness*](https://www.ncbi.nlm.nih.gov/books/NBK458358/#s3-5)). FUTURE 2[48](https://www.ncbi.nlm.nih.gov/books/NBK458358/) and ERASURE[49](https://www.ncbi.nlm.nih.gov/books/NBK458358/) compared 150 or 300 mg of SEC with placebo; FIXTURE[49](https://www.ncbi.nlm.nih.gov/books/NBK458358/) compared 150 or 300 mg of SEC with ETN (100 mg/week) and placebo; and CLEAR[62](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[63](https://www.ncbi.nlm.nih.gov/books/NBK458358/) compared 300 mg of SEC with 45 or 90 mg of UST (dosing was as per licence, 45 mg in patients weighing ≤ 100 kg and 90 mg for patients weighing > 100 kg).

There are three relevant ongoing trials for which results are not yet available ([*Table 7*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table7/?report=objectonly)).

[](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table7/?report=objectonly)

[**TABLE 7**](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table7/?report=objectonly)

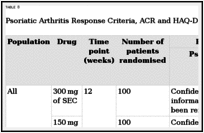
Ongoing trials of SEC in patients with active PsA

As previously discussed, the baseline characteristics of the ERASURE, FIXTURE and CLEAR[49](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[62](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[63](https://www.ncbi.nlm.nih.gov/books/NBK458358/) subgroup populations were different to the baseline characteristics of the other trials. The patients in these trials had much higher baseline PASI scores and notably lower baseline HAQ-DI scores than the other trials, suggesting that these patients had more severe psoriasis and less severe arthritis symptoms (see [*Table 4*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table4/?report=objectonly)).

The FUTURE 2[48](https://www.ncbi.nlm.nih.gov/books/NBK458358/) and CLEAR[62](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[63](https://www.ncbi.nlm.nih.gov/books/NBK458358/) trials were judged as being at a low overall risk of bias with an unclear risk of overall judgements for ERASURE[49](https://www.ncbi.nlm.nih.gov/books/NBK458358/) and FIXTURE[49](https://www.ncbi.nlm.nih.gov/books/NBK458358/) (see [*Table 6*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table6/?report=objectonly)).

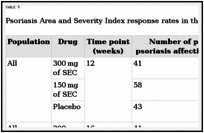
**FUTURE 2 trial**

[*Tables 8*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table8/?report=objectonly) and [*9*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table9/?report=objectonly) show FUTURE 2 trial[48](https://www.ncbi.nlm.nih.gov/books/NBK458358/) results for the key review outcomes for the full-trial population across the 12-, 16- and 24-week time points. Results for the biologic-naive and biologic-experienced subgroups are presented in [*Tables 10*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table10/?report=objectonly) and [*11*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table11/?report=objectonly). The corresponding relative risks (RRs) for the dichotomous outcomes were calculated by the Evidence Review Group (ERG) and are presented in [*Table 12*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table12/?report=objectonly).

[](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table8/?report=objectonly)

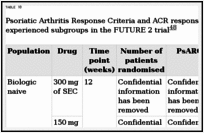
[**TABLE 8**](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table8/?report=objectonly)

Psoriatic Arthritis Response Criteria, ACR and HAQ-DI responses in the FUTURE 2 trial

[](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table9/?report=objectonly)

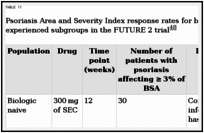
[**TABLE 9**](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table9/?report=objectonly)

Psoriasis Area and Severity Index response rates in the FUTURE 2 trial

[](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table10/?report=objectonly)

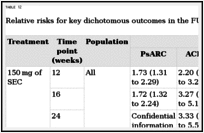
[**TABLE 10**](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table10/?report=objectonly)

Psoriatic Arthritis Response Criteria and ACR response rates for biologic-naive and biologic-experienced subgroups in the FUTURE 2 trial

[](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table11/?report=objectonly)

[**TABLE 11**](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table11/?report=objectonly)

Psoriasis Area and Severity Index response rates for biologic-naive and biologic-experienced subgroups in the FUTURE 2 trial

[](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table12/?report=objectonly)

[**TABLE 12**](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table12/?report=objectonly)

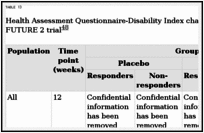
Relative risks for key dichotomous outcomes in the FUTURE 2 trial: 150 or 300 mg of SEC vs. placebo

**Efficacy at 12–24 weeks in the full-trial population**

For the whole-trial population, SEC was associated with statistically significant improvements in all outcomes at all time points. Patients taking SEC were around six times more likely to be ACR 50 responders – an outcome of particular clinical importance to patients – than patients taking placebo. An increase in RRs is apparent when looking across the PsARC, ACR 20, ACR 50 and ACR 70 columns in [*Table 12*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table12/?report=objectonly). These increases in RR are likely to be a consequence of the different placebo rates, with higher rates for the lower threshold outcomes (see the placebo rates in [*Table 8*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table8/?report=objectonly)). The lower threshold outcomes (such as PsARC and ACR 20) appear to underestimate efficacy because the RRs tend to be diluted by the high placebo response rates. This association of higher placebo responses with lower relative efficacy was also noted *across* trials by outcome in the evidence synthesis and is discussed in [*Chapter 4*](https://www.ncbi.nlm.nih.gov/books/n/ukhta2156/s4/).

FUTURE 2[48](https://www.ncbi.nlm.nih.gov/books/NBK458358/) trial patients taking 150 or 300 mg of SEC were also around six to seven times more likely to be PASI 50 responders than patients taking placebo. Efficacy was also demonstrated for the higher PASI thresholds (PASI 75 and PASI 90), with the 300-mg group having only slightly higher RRs than the 150-mg group.

All three study arms showed improvements in physical function as assessed using HAQ-DI change from baseline scores; HAQ-DI assesses a patient’s ability to perform eight categories of activities of daily living. Patients taking SEC had greater reductions in HAQ-DI scores than patients taking the placebo (see [*Table 8*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table8/?report=objectonly)). At 24 weeks, the difference when compared with placebo (–0.25 units) was statistically significant for 300 mg (*p* = 0.004), but the difference of –0.17 units for 150 mg did not quite reach statistical significance (*p* = 0.055).[48](https://www.ncbi.nlm.nih.gov/books/NBK458358/) The manufacturer also submitted HAQ-DI results based on PsARC responder status ([*Table 13*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table13/?report=objectonly)). These results show (confidential information has been removed).

[](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table13/?report=objectonly)

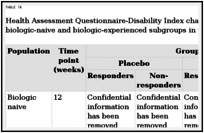
[**TABLE 13**](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table13/?report=objectonly)

Health Assessment Questionnaire-Disability Index changes based on PsARC responder status in the FUTURE 2 trial

**Efficacy in the biologic-naive and biologic-experienced subgroups**

[*Table 12*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table12/?report=objectonly) also presents RRs for the subgroups based on patients’ previous use of biologics. These subgroup results are difficult to interpret for several reasons. Some of the subgroup sample sizes were particularly small: there were no placebo responders (PRs) for some outcomes in the biologic-experienced subgroup and the RR confidence intervals (CIs) were therefore extremely wide. The PASI results are effectively based on subgroups (previous biologic status) of a subgroup (patients with psoriasis covering ≥ 3% of BSA). Placebo response rates also differed across subgroups (see [*Evaluating the secukinumab and certolizumab pegol trial results in comparison with other treatments*](https://www.ncbi.nlm.nih.gov/books/NBK458358/#s3-4)). Similar subgroup issues were also seen for CZP (see [*Efficacy in the RAPID-PsA biologic-naive and biologic-experienced subgroups*](https://www.ncbi.nlm.nih.gov/books/NBK458358/#s3-3-8)).

The manufacturer also submitted HAQ-DI results based on PsARC responder status for the biologic-naive and biologic-experienced population ([*Table 14*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table14/?report=objectonly)). Again, comparisons between the two subgroups is difficult as (confidential information has been removed).

[](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table14/?report=objectonly)

[**TABLE 14**](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table14/?report=objectonly)

Health Assessment Questionnaire-Disability Index changes based on PsARC responder status for biologic-naive and biologic-experienced subgroups in the FUTURE 2 trial

**Other efficacy results**

*Efficacy of secukinumab with or without concomitant methotrexate*

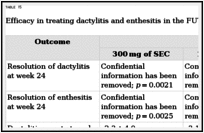
Just under half of the patients in FUTURE 2[48](https://www.ncbi.nlm.nih.gov/books/NBK458358/) took concomitant MTX. In exploratory post hoc analyses, SEC was found to be similarly efficacious whether or not patients were taking concomitant MTX.[48](https://www.ncbi.nlm.nih.gov/books/NBK458358/) For ACR 50, response rates were statistically significantly higher in the 300- and 150-mg groups than in the placebo group for both the concomitant MTX subgroup (*p* = 0.001 and *p* = 0.006, respectively) and the no concomitant MTX subgroup (*p* = 0.007 and *p* < 0.0001, respectively). Similar statistically significant differences were also reported for the ACR 20 and 70 thresholds.[48](https://www.ncbi.nlm.nih.gov/books/NBK458358/)

*Efficacy of secukinumab in the one prior DMARD subgroup*

Data were presented in the manufacturer’s submission at week 24 for efficacy in the one prior DMARD subgroup. (Confidential information has been removed.)

*Efficacy in treating dactylitis and enthesitis*

At week 24, relative to placebo treatment with both 150 and 300 mg of SEC statistically significantly improved the resolution of both dactylitis (as measured via the Leeds Dactylitis Index; LDI) and enthesitis (as measured via the Leeds Enthesitis Index; LEI) ([*Table 15*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table15/?report=objectonly)).

[](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table15/?report=objectonly)

[**TABLE 15**](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table15/?report=objectonly)

Efficacy in treating dactylitis and enthesitis in the FUTURE 2 trial

*Health-related quality of life*

Up to week 24, improvement in the EQ-5D overall health state (as measured by a visual analogue scale; VAS) was higher in both SEC groups (150 and 300 mg) than in the placebo group. (Confidential information has been removed.)

At week 24, self-reported quality of life and physical functioning, as measured by SF-36 Physical Component Summary score, was found to have improved more in the SEC groups than in the placebo group (SEC 150 mg, 6.39 points; SEC 300 mg, 7.25 points; placebo, 1.95 points).

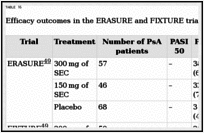
*Mortality*

No deaths were reported during the trial.

**ERASURE and FIXTURE trials**

As the focus of the ERASURE and FIXTURE trials[49](https://www.ncbi.nlm.nih.gov/books/NBK458358/) was on patient populations with psoriasis (subgroups of which also had PsA), fewer outcomes that were relevant to this assessment were evaluated. Patients recruited into in the ERASURE and FIXTURE trials had more severe psoriasis but lower baseline HAQ-DI scores than the patients recruited into the FUTURE 2 trial and into the other trials included in the systematic review (see [*Table 4*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table4/?report=objectonly)). The FIXTURE trial was one of the very few identified in the systematic review that compared different biologics (SEC with ETN).

[*Table 16*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table16/?report=objectonly) and [*Figure 2*](https://www.ncbi.nlm.nih.gov/books/NBK458358/figure/fig2/?report=objectonly) (in which data from the ERASURE and FIXTURE trials have been pooled) illustrate SEC’s superiority over placebo for the PASI outcomes. In the FIXTURE trial at 12 weeks, 300 mg of SEC was statistically significantly more effective than 50 mg of ETN twice weekly in terms of patients achieving a PASI 75 response (RR 1.86, 95% CI 1.24 to 2.81) and a PASI 90 response (RR 2.42, 95% CI 1.20 to 4.88). Changes from baseline in the HAQ-DI scores were greater in SEC- and ETN-treated patients in ERASURE and FIXTURE trials than with placebo.

[](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table16/?report=objectonly)

[**TABLE 16**](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table16/?report=objectonly)

Efficacy outcomes in the ERASURE and FIXTURE trials at 12 weeks

[FIGURE 2. Forest plot of the efficacy of 300 mg of SEC vs.](https://www.ncbi.nlm.nih.gov/books/NBK458358/figure/fig2/?report=objectonly)

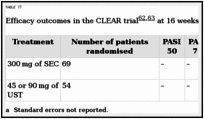
[**FIGURE 2**](https://www.ncbi.nlm.nih.gov/books/NBK458358/figure/fig2/?report=objectonly)

Forest plot of the efficacy of 300 mg of SEC vs. placebo for PASI 75 at 12 weeks in PsA patients with moderate–severe psoriasis. df, degrees of freedom; M–H, Mantel–Haenszel.

**CLEAR trial**

The CLEAR trial,[62](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[63](https://www.ncbi.nlm.nih.gov/books/NBK458358/) which compared SEC with UST, was similar to the ERASURE and FIXTURE trials[49](https://www.ncbi.nlm.nih.gov/books/NBK458358/) with respect to the population studied (patients with more severe psoriasis than those recruited into the FUTURE 2 trial) and the limited data assessed and reported (in the CLEAR trial only PASI 90 and HAQ-DI scores were reported for the subgroup of patients with PsA).

At 16 weeks, patients treated with 300 mg of SEC had a better PASI 90 response rate than patients receiving 45 or 90 mg of UST, although the difference was not statistically significant (RR 1.23, 95% CI 0.98 to 1.55; *p* = 0.08). Patients treated with 300 mg of SEC had a greater improvement in HAQ-DI score than patients receiving 45 or 90 mg of UST ([*Table 17*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table17/?report=objectonly)).

[](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table17/?report=objectonly)

[**TABLE 17**](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table17/?report=objectonly)

Efficacy outcomes in the CLEAR trial, at 16 weeks for the subgroup of PsA patients

**Summary**

The results of the FUTURE 2 trial[48](https://www.ncbi.nlm.nih.gov/books/NBK458358/) demonstrated the short-term efficacy of SEC in treating PsA. When considering the whole-trial population, SEC was associated with statistically and clinically significant improvements in all key outcomes. Patients taking SEC were around six times more likely to be ACR 50 responders – a key clinical outcome to patients – than patients taking placebo. Clinically important improvements in activities of daily living (assessed using the HAQ-DI) were also evident in patients taking SEC, particularly in patients who were PsARC responders. However, when the trial population was split into subgroups based on previous biologic experience, the resulting RRs for the biologic-experienced subgroup became difficult to interpret. This was attributable to both the low numbers of placebo patients and the differences in placebo response rates across subgroups (see [*Evaluating the secukinumab and certolizumab pegol trial results in comparison with other treatments*](https://www.ncbi.nlm.nih.gov/books/NBK458358/#s3-4)). Although SEC is efficacious in both subgroups, it is not possible to make robust conclusions about any difference in the efficacy of SEC across these subgroups. Similar efficacy across the ACR outcomes was evident in subgroups of patients based on presence or absence of concomitant MTX, although limited data and analyses were available specifically for the one prior DMARD group. Treatment with SEC resulted in statistically significant improvements in HRQoL measures and in the resolution of both dactylitis and enthesitis.

Results from the trials of patients with more severe psoriasis demonstrated SEC’s superiority over placebo in terms of psoriasis (as measured by the PASI) and function (as measured by the HAQ-DI) outcomes. SEC was also found to be significantly more effective than ETN in improving psoriasis (assessed using PASI 75 and PASI 90). However, the populations studied in these trials had quite severe psoriasis and less functional impairment (lower baseline HAQ-DI scores) than other trial populations. Their results should not therefore be generalised to more typical PsA populations.

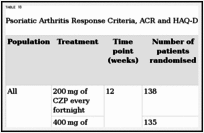
**Short-term efficacy of certolizumab pegol**

One eligible RCT of CZP was identified. RAPID-PsA[47](https://www.ncbi.nlm.nih.gov/books/NBK458358/) compared 200 or 400 mg of CZP against placebo up to 24 weeks. The trial was dose blinded to 48 weeks and then open label to 216 weeks. Placebo patients who failed to achieve a 10% improvement from baseline in both swollen and tender joints at week 14 and 16 were re-randomised to active treatment at week 16. At week 24, all the remaining placebo patients were re-randomised to receive 200 or 400 mg of CZP. The RAPID-PsA[47](https://www.ncbi.nlm.nih.gov/books/NBK458358/) trial was judged as being at low overall risk of bias (see [*Table 6*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table6/?report=objectonly)).

Compared with the other PsA trials, the RAPID-PsA trial was more selective in recruiting biologic-experienced patients; patients with primary failure of a previous anti-TNF were excluded (primary failure was defined as no response within the first 12 weeks of treatment with the anti-TNF).

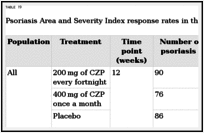
There are no UCB Pharma-sponsored ongoing studies of CZP in patients with PsA.

[*Tables 18*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table18/?report=objectonly) and [*19*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table19/?report=objectonly) show the RAPID-PsA trial results[47](https://www.ncbi.nlm.nih.gov/books/NBK458358/) for the key review outcomes for the full-trial population across the 12-, 16- and 24-week time points. ACR 20 results, split into subgroups according to the number of previous DMARDs taken by patients, are presented in [*Table 20*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table20/?report=objectonly). Results for the biologic-naive and biologic-experienced subgroups are presented in [*Tables 21*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table21/?report=objectonly)*–*[*24*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table24/?report=objectonly). The corresponding RRs for the dichotomous outcomes were calculated by the ERG and are presented in [*Table 25*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table25/?report=objectonly).

[](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table18/?report=objectonly)

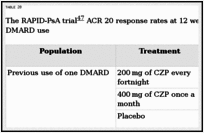
[**TABLE 18**](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table18/?report=objectonly)

Psoriatic Arthritis Response Criteria, ACR and HAQ-DI responses in the RAPID-PsA trial

[](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table19/?report=objectonly)

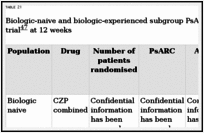
[**TABLE 19**](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table19/?report=objectonly)

Psoriasis Area and Severity Index response rates in the RAPID-PsA trial

[](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table20/?report=objectonly)

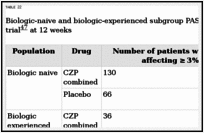
[**TABLE 20**](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table20/?report=objectonly)

The RAPID-PsA trial ACR 20 response rates at 12 weeks for subgroups of previous DMARD use

[](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table21/?report=objectonly)

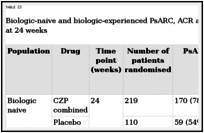
[**TABLE 21**](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table21/?report=objectonly)

Biologic-naive and biologic-experienced subgroup PsARC, ACR and HAQ-DI results in the RAPID-PsA trial at 12 weeks

[](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table22/?report=objectonly)

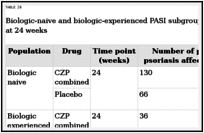
[**TABLE 22**](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table22/?report=objectonly)

Biologic-naive and biologic-experienced subgroup PASI response rates in the RAPID-PsA trial at 12 weeks

[](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table23/?report=objectonly)

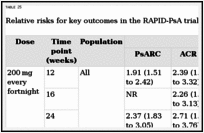
[**TABLE 23**](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table23/?report=objectonly)

Biologic-naive and biologic-experienced PsARC, ACR and HAQ-DI subgroup results from the RAPID-PsA trial at 24 weeks

[](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table24/?report=objectonly)

[**TABLE 24**](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table24/?report=objectonly)

Biologic-naive and biologic-experienced PASI subgroup results from the RAPID-PsA trial at 24 weeks

[](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table25/?report=objectonly)

[**TABLE 25**](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table25/?report=objectonly)

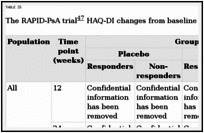
Relative risks for key outcomes in the RAPID-PsA trial: 200 or 400 mg of CZP vs. placebo

**Efficacy at 12–24 weeks in the RAPID PsA full-trial population**

For the full-trial population, the RRs in [*Table 25*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table25/?report=objectonly) are for comparisons of the different CZP regimens (200 mg every 2 weeks or 400 mg every 4 weeks) with placebo, across the 12-, 16- and 24-week time points and across the PsARC, ACR and PASI outcomes. For the subgroup analyses (based on previous biologic status), combined data from the two CZP arms were used to calculate RRs.

For the full-trial population, when compared with placebo, CZP was associated with statistically significant improvements in all outcomes at all time points (for which data were available). Patients taking CZP were around three times more likely to be ACR 50 responders than patients taking placebo. Similar to the pattern seen with the SEC FUTURE 2 trial[48](https://www.ncbi.nlm.nih.gov/books/NBK458358/) results, an increase in RRs is apparent as the outcome thresholds (for achieving a response) increase across the PsARC, ACR and PASI outcomes (see [*Table 25*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table25/?report=objectonly)). Again, these increases are likely to be a consequence of the different placebo rates, with higher rates of placebo response in the lower threshold outcomes.

The RAPID-PsA trial[47](https://www.ncbi.nlm.nih.gov/books/NBK458358/) patients taking CZP were around two-and-a-half times more likely to be PASI 50 responders than patients taking placebo. Efficacy was also demonstrated in the results for the higher PASI thresholds. Improvements in physical function, as assessed using HAQ-DI change from baseline scores, were also seen, with the difference being reported as being statistically significant (*p* < 0.001) at 24 weeks.[47](https://www.ncbi.nlm.nih.gov/books/NBK458358/) The manufacturer also submitted HAQ-DI results based on PsARC responder status ([*Table 26*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table26/?report=objectonly)). (Confidential information has been removed.)

[](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table26/?report=objectonly)

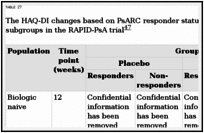
[**TABLE 26**](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table26/?report=objectonly)

The RAPID-PsA trial HAQ-DI changes from baseline based on PsARC responder status

**Efficacy in the RAPID-PsA biologic-naive and biologic-experienced subgroups**

[*Table 25*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table25/?report=objectonly) presents RRs for subgroups based on patients’ previous use of biologics. When comparing results for all outcomes across subgroups the efficacy of CZP *appears* somewhat better in the biologic-experienced subgroup than in the biologic-naive subgroup; this trial evidence is contrary to evidence from large patient registries suggesting that effectiveness may decrease with each new anti-TNF taken (see [*Drug survival and anti-tumour necrosis factor switching*](https://www.ncbi.nlm.nih.gov/books/NBK458358/#s3-6-1)). The differences between subgroups observed in the RAPID-PsA trial[47](https://www.ncbi.nlm.nih.gov/books/NBK458358/) are likely to have been influenced by two factors. First, there is a problem with sample size, with low numbers of placebo patients and PRs in the biologic-experienced subgroup. There is therefore considerable uncertainty about these estimates, which is reflected in the very wide CIs. Second, there is a notable difference in placebo response rates between the two subgroups (see [*Table 21*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table21/?report=objectonly) and [*Evaluating the secukinumab and certolizumab pegol trial results in comparison with other treatments*](https://www.ncbi.nlm.nih.gov/books/NBK458358/#s3-4)). Furthermore, as detailed previously in [*Characteristics of the randomised controlled trials included in the systematic review of short-term efficacy*](https://www.ncbi.nlm.nih.gov/books/NBK458358/#s3-3), the RAPID-PsA trial excluded patients with primary failure of a previous biologic, so the subgroups were not as different as they could have been (other trials did not exclude primary failures).

The manufacturer also submitted HAQ-DI results based on PsARC responder status for the biologic-naive and biologic-experienced populations ([*Table 27*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table27/?report=objectonly)). (Confidential information has been removed.)

[](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table27/?report=objectonly)

[**TABLE 27**](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table27/?report=objectonly)

The HAQ-DI changes based on PsARC responder status for biologic-naive and biologic-experienced subgroups in the RAPID-PsA trial

**Other efficacy results**

**Efficacy of certolizumab pegol with or without concomitant methotrexate**

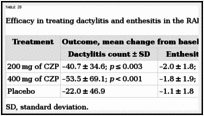
Results were not reported for subgroups based specifically on MTX use, although results were reported based on concomitant use of a DMARD (which was mostly MTX). Concomitant DMARD use did not seem to affect ACR 20 (57% with vs. 50% without) or PsARC (68% with vs. 73% without) response rates to CZP (combined dose) at week 12.[47](https://www.ncbi.nlm.nih.gov/books/NBK458358/)

**Efficacy of certolizumab pegol in the one prior DMARD subgroup**

When compared with placebo, at weeks 12 and 24, CZP was associated with statistically significantly better ACR 20 response rates (*p* < 0.001); 207 patients who had received one prior DMARD were included in the analysis.[47](https://www.ncbi.nlm.nih.gov/books/NBK458358/) Data in the manufacturer’s submission showed that (confidential information has been removed).

**Efficacy in treating dactylitis and enthesitis**

At week 24, patients treated with CZP achieved statistically significant improvements in dactylitis (assessed using the LDI) when compared with placebo-treated patients; statistically significant improvements in enthesitis, as assessed using the LEI, were also seen in the CZP group ([*Table 28*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table28/?report=objectonly)).

[](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table28/?report=objectonly)

[**TABLE 28**](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table28/?report=objectonly)

Efficacy in treating dactylitis and enthesitis in the RAPID-PsA trial

**Health-related quality of life**

At week 12, EQ-5D VAS scores were higher in CZP-treated groups (confidential information has been removed).

In addition, at week 24, there was a significant improvement with pooled CZP in all domains of the SF-36, including both the physical (confidential information has been removed) and mental components (confidential information has been removed), regardless of the dose regimen and prior TNF inhibitor status. (Confidential information has been removed.)

**Mortality**

Two deaths were reported during the 24 weeks: one was in the 200-mg group and one was in the 400-mg group. The trial investigators considered both deaths to be unrelated to study medication.

**Summary**

The results of the RAPID-PsA trial[47](https://www.ncbi.nlm.nih.gov/books/NBK458358/) demonstrated the short-term efficacy of CZP in treating PsA. When considering the full-trial population, CZP was associated with statistically significant improvements in all key outcomes. When the trial population was split into subgroups based on previous biologic experience, the results became difficult to compare (as was seen in the FUTURE 2 trial). The small number of placebo patients in the biologic-experienced subgroup coupled with higher placebo response rates in the biologic-naive subgroup meant that it was not possible to make reliable conclusions about the difference in the efficacy of CZP across these subgroups. Furthermore, patients with primary failure of a previous biologic were excluded from the RAPID-PsA trial, so estimates of efficacy may have been slightly inflated when comparisons were made with other trials that recruited biologic-experienced patients (e.g. FUTURE 2[48](https://www.ncbi.nlm.nih.gov/books/NBK458358/) and PSUMMIT 2[59](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[66](https://www.ncbi.nlm.nih.gov/books/NBK458358/)). Similar efficacy across the ACR and PsARC outcomes was seen in subgroups of patients based on presence or absence of a concomitant DMARD and (confidential information has been removed). Treatment with CZP resulted in statistically significant improvements in HRQoL measures and in the resolution of both dactylitis and enthesitis.

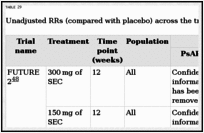
[Go to:](https://www.ncbi.nlm.nih.gov/books/NBK458358/)

**Evaluating the secukinumab and certolizumab pegol trial results in comparison with other treatments**

In order to more fully evaluate the clinical efficacy of SEC and CZP, the trial results of these two newer biologics need to be compared with each other and with the results of the older biologics (and APR). However, this is not straightforward for two reasons. First, there is variation across trials with respect to previous biologic use.

* The populations recruited to clinical trials have changed over time, with earlier trials excluding biologic-experienced patients and later trials including such patients.
* The RAPID-PsA trial was more selective than the FUTURE 2,[48](https://www.ncbi.nlm.nih.gov/books/NBK458358/) PSUMMIT 2[59](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[66](https://www.ncbi.nlm.nih.gov/books/NBK458358/) and PALACE trials[60](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[61](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[65](https://www.ncbi.nlm.nih.gov/books/NBK458358/) in recruiting its biologic-experienced patients: only in RAPID-PsA were patients with primary failure of a previous biologic excluded (see [*Characteristics of the randomised controlled trials included in the systematic review of short-term efficacy*](https://www.ncbi.nlm.nih.gov/books/NBK458358/#s3-3)).

Second, placebo response rates have increased markedly over time across the trials included in this review. This issue is key when interpreting RRs because, although RRs are easy to interpret clinically, their ceilings (maximum values) are limited by baseline response rates. For example, in the FUTURE 2 trial[48](https://www.ncbi.nlm.nih.gov/books/NBK458358/) the placebo response rate for PsARC was (confidential information has been removed) in the biologic-naive subgroup. This high rate meant that the maximum possible RR would be (confidential information has been removed); this maximum result is lower than some of the *actual* RRs for other biologics presented in [*Table 29*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table29/?report=objectonly), which compares unadjusted RRs across the trials in the NMAs. Comparisons between treatments using odds ratios (ORs) and that adjust for the varying placebo rates were therefore necessary (see [*Chapter 4*](https://www.ncbi.nlm.nih.gov/books/n/ukhta2156/s4/)).

[](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table29/?report=objectonly)

[**TABLE 29**](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table29/?report=objectonly)

Unadjusted RRs (compared with placebo) across the trials included in the evidence synthesis

Examination of the trial baseline characteristics across trials offers no clear reason as to why placebo response rates in biologic trials have increased over time. The PsARC placebo response rates increased most markedly from 2013 onwards, starting with the PSUMMIT trials.[60](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[61](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[65](https://www.ncbi.nlm.nih.gov/books/NBK458358/) One theory is that patient and clinician expectations have increased over time (i.e. more caution and lower expectations when the first biologics were trialled, and more confidence about the likely benefits in more recent trials). Subjective patient- and clinician-reported outcomes such as PsARC and ACR may be prone to such expectation effects. This theory might also explain why, within trials, higher placebo response rates are observed in the biologic-naive subgroups than in biologic-experienced subgroups, where treatment expectations might be lower. Coupled with this is the trend – beginning with the PSUMMIT trials – for increases in the number of active treatment arms offered in trials: typically there was one active arm in the early trials and two or more active arms in more recent trials (e.g. the FUTURE 2 SEC trial had three active treatment arms: 75, 150 and 300 mg). Patients in the more recent trials might therefore also be more confident and optimistic about the likelihood that they are receiving an active treatment.

Ideally the different treatments would be compared in head-to-head trials. However, only one trial identified in the systematic review compared two or more biologics directly in a PsA population. The Atteno *et al.* trial[64](https://www.ncbi.nlm.nih.gov/books/NBK458358/) compared INF, ETN and ADA. It reported that patients on INF and ADA showed the greatest improvement in terms of PASI (statistically significantly better than ETN), whereas patients on ETN showed the greatest improvement in TJC (statistically significantly better than INF and ADA) and HAQ-DI (statistically significantly better than ADA). However, the reliability of this study’s results are limited somewhat by its small size (100 patients were randomised in total). This trial also did not report its methods clearly (see [*Table 6*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table6/?report=objectonly)), and was rated as being at high risk of bias (although blinding would be difficult to achieve in such a trial). Finally, by reporting results only at the 52-week time point, the results of this trial could not be included in our NMAs.

[Go to:](https://www.ncbi.nlm.nih.gov/books/NBK458358/)

**Long-term effectiveness**

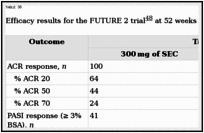
**Open-label extension studies**

**Long-term efficacy of secukinumab**

The Novartis submission to NICE for the appraisal in 2016 reported long-term data for both FUTURE 1[46](https://www.ncbi.nlm.nih.gov/books/NBK458358/) (to 104 weeks) and FUTURE 2[48](https://www.ncbi.nlm.nih.gov/books/NBK458358/) (to 52 weeks) trials. Although the FUTURE 1 trial[46](https://www.ncbi.nlm.nih.gov/books/NBK458358/) was not eligible for the systematic review of efficacy because it initiated the randomised phase of the study with a non-licensed high loading dose (10 mg/kg), it did use a 150-mg maintenance dose and so can be considered to provide useful long-term data. Importantly, this trial reported radiographic efficacy outcomes (at 2 years); the FUTURE 2 trial[48](https://www.ncbi.nlm.nih.gov/books/NBK458358/) did not report radiographic efficacy outcomes.

*FUTURE 2*

Of the FUTURE 2 trial [48](https://www.ncbi.nlm.nih.gov/books/NBK458358/) patients originally randomised to 150 or 300 mg of SEC, by week 52, 22 (11%) had withdrawn for any reason, 10 of whom withdrew as a result of an AE or loss of efficacy. In the FUTURE 2 trial,[48](https://www.ncbi.nlm.nih.gov/books/NBK458358/) most of the dichotomous data reported in the submission used non-responder imputations for missing data; a mixed-effects repeated measures model was used for continuous outcomes. There were no stopping rules up to week 52, so non-responding patients could keep taking SEC thus allowing the possibility of achievement of much later responses than would be viable in the NHS. For time points a*fter* week 52, the protocol stated that subjects who are deemed not to be benefiting from the study treatment based on lack of improvement or worsening of their symptoms should discontinue the study. However, results for post-week 52 time points are not yet available. Results for key review outcomes at week 52 are presented in [*Table 30*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table30/?report=objectonly). The outcomes suggest that SEC continues to be an effective treatment for PsA at this later time point.

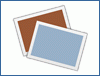
[](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table30/?report=objectonly)

[**TABLE 30**](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table30/?report=objectonly)

Efficacy results for the FUTURE 2 trial at 52 weeks

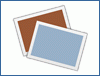
*Longer-term efficacy in FUTURE 2 trial patients who were responders at 16 weeks*

In the NHS, patients will typically be allowed 16 weeks to achieve a response, after which SEC may be stopped in non-responding patients. The Assessment Group (AG) requested results specifically for patients who are responders at 16 weeks to inform what happens to this group of patients in the longer term. The results ([*Figures 3*](https://www.ncbi.nlm.nih.gov/books/NBK458358/figure/fig3/?report=objectonly) and [*4*](https://www.ncbi.nlm.nih.gov/books/NBK458358/figure/fig4/?report=objectonly)) indicate that for the lower threshold outcomes – such as ACR 20 and PASI 50 – response rates remain high from week 16 to week 52. As the outcome thresholds increase, response rates become more variable over time and there is generally a greater decrease in response rates than the lower threshold outcomes. Around 70% of patients on 150 mg still achieve an ACR 50 response at week 52, and around 55% still achieve an ACR 70 (see [*Figure 3*](https://www.ncbi.nlm.nih.gov/books/NBK458358/figure/fig3/?report=objectonly)); the corresponding results for PASI 75 and PASI 90 are around 85% and around 70%, respectively (see [*Figure 4*](https://www.ncbi.nlm.nih.gov/books/NBK458358/figure/fig4/?report=objectonly)).

[](https://www.ncbi.nlm.nih.gov/books/NBK458358/figure/fig3/?report=objectonly)

[**FIGURE 3**](https://www.ncbi.nlm.nih.gov/books/NBK458358/figure/fig3/?report=objectonly)

Long-term response rates in the FUTURE 2 trial SEC patients who were (a) ACR 20, (b) ACR 50 or (c) ACR 70 responders at 16 weeks. (Confidential information has been removed.)

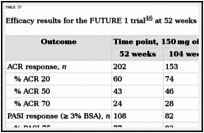
[](https://www.ncbi.nlm.nih.gov/books/NBK458358/figure/fig4/?report=objectonly)

[**FIGURE 4**](https://www.ncbi.nlm.nih.gov/books/NBK458358/figure/fig4/?report=objectonly)

Long-term response rates in the FUTURE 2 trial SEC patients who were (a) PASI 50, (b) PASI 75 or (c) PASI 90 responders at 16 weeks. (Confidential information has been removed.)

*FUTURE 1*

Of the FUTURE 1 trial[46](https://www.ncbi.nlm.nih.gov/books/NBK458358/) patients originally randomised to receive 75 or 150 mg of SEC or placebo, 15% had withdrawn at week 52 for any reason, of which 6% of withdrawals were the result of an AE or loss of efficacy.[46](https://www.ncbi.nlm.nih.gov/books/NBK458358/) At week 104, 79% of patients remained in the study. Here, we report only on the long-term efficacy of 150 mg of SEC. Results at 52 weeks are similar to those seen in the FUTURE 2 trial;[48](https://www.ncbi.nlm.nih.gov/books/NBK458358/) observed data were also available at 2 years ([*Table 31*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table31/?report=objectonly)).

[](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table31/?report=objectonly)

[**TABLE 31**](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table31/?report=objectonly)

Efficacy results for the FUTURE 1 trial at 52 weeks and 104 weeks

*Radiographic progression of joint damage*

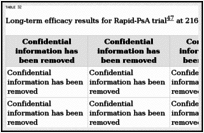
In the FUTURE 1 trial,[46](https://www.ncbi.nlm.nih.gov/books/NBK458358/) at week 52 the observed population comprised 189 of the 202 patients randomised to 150 mg; this group had a mean Sharp/van der Heijde change from baseline score of 0.37 points. At 104 weeks, 85% of patients treated with 150 mg of SEC had no radiographic progression – defined as a change in Sharp/van der Heijde score of ≤ 0.5 units – between baseline and week 104. This result was based on the observed population (*n* = 166).

*Long-term efficacy of certolizumab pegol*

The UCB Pharma submission reported long-term efficacy data for the RAPID-PsA trial[47](https://www.ncbi.nlm.nih.gov/books/NBK458358/) at time points up to around 4 years (216 weeks). By week 96, 20% of the 273 patients originally randomised to CZP had withdrawn from the study; 13.5% of the total cohort had withdrawn as a result of an AE or loss of efficacy. Non-responder imputations were used for dichotomous outcomes and LOCF was used for most of the continuous outcomes (except for radiographic progression).

At week 96 the ACR 20, 50 and 70 response rates were 64%, 50% and 35%, respectively,[74](https://www.ncbi.nlm.nih.gov/books/NBK458358/) and were (confidential information has been removed). PASI 75 and 90 response rates were 53% and 44% at week 96;[74](https://www.ncbi.nlm.nih.gov/books/NBK458358/) and (confidential information has been removed).

(Confidential information has been removed.) The improvement in HAQ-DI score from baseline was maintained (confidential information has been removed). Efficacy results for the overall population together with the biologic-naive and biologic-experienced subgroups are presented in [*Table 32*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table32/?report=objectonly).

[](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table32/?report=objectonly)

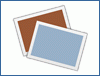
[**TABLE 32**](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table32/?report=objectonly)

Long-term efficacy results for Rapid-PsA trial at 216 weeks

(Confidential information has been removed.)

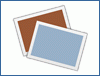
*Longer-term efficacy in patients who were responders at 12 weeks*

In the NHS, patients will typically be allowed 12 weeks to achieve a response, after which CZP may be stopped in non-responding patients. The AG requested results specifically for patients who are responders at 12 weeks to inform what happens to this group of patients in the longer term. The response rates at 1 year are similar to those seen with SEC. Later results show that, across outcomes, around two-thirds (of responders at 12 weeks) remain responders at 4 years ([*Figures 5*](https://www.ncbi.nlm.nih.gov/books/NBK458358/figure/fig5/?report=objectonly) and [*6*](https://www.ncbi.nlm.nih.gov/books/NBK458358/figure/fig6/?report=objectonly)).

[](https://www.ncbi.nlm.nih.gov/books/NBK458358/figure/fig5/?report=objectonly)

[**FIGURE 5**](https://www.ncbi.nlm.nih.gov/books/NBK458358/figure/fig5/?report=objectonly)

Long-term response rates in the RAPID-PsA trial CZP patients who were (a) ACR 20, (b) ACR 50 or (c) ACR 70 responders at 12 weeks. (Confidential information has been removed.)

[](https://www.ncbi.nlm.nih.gov/books/NBK458358/figure/fig6/?report=objectonly)

[**FIGURE 6**](https://www.ncbi.nlm.nih.gov/books/NBK458358/figure/fig6/?report=objectonly)

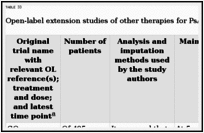
Long-term response rates in the RAPID-PsA trial CZP patients who were (a) PASI 50, (b) PASI 75 or (c) PASI 90 responders at 12 weeks. (Confidential information has been removed.)

*Radiographic progression of joint damage*

At week 96, the modified total Sharp score (mTSS) non-progressor rate (non-progression defined as mTSS change from baseline of ≤ 0.5 points) was 87%. This was based on observed data for the combined CZP groups: 218 of the 273 randomised. For patients randomised to CZP (combined group), the mean level of progression was 0.14 points [standard error (SE) 0.09 points], which is below the 0.5-point non-progression cut-off point. Subgroup analyses indicated that patients (randomised to CZP) with a baseline mTSS of > 3.5 points had a slightly greater radiographic progression at week 96 than patients with a baseline mTSS of ≤ 3.5 points [mean 0.24 points (SE 0.19 points) for a mTSS of > 3.5 vs. mean 0.07 points (SE 0.04 points) for a mTSS of ≤ 3.5 points].

**Efficacy of other therapies**

Methods and result details relating to the latest time point for which long-term data were available for GOL, ETN, ADA, INF, UST and APR are presented in [*Table 33*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table33/?report=objectonly).

[](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table33/?report=objectonly)

[**TABLE 33**](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table33/?report=objectonly)

Open-label extension studies of other therapies for PsA

The Golimumab – A Randomized Evaluation of Safety and Efficacy in Subjects with Psoriatic Arthritis Using a Human Anti-TNF Monoclonal Antibody (GO-REVEAL) study[75](https://www.ncbi.nlm.nih.gov/books/NBK458358/) reported results at 5 years using the originally randomised ITT groups. Across the groups the proportion of responders ranged from 63% to 70% for ACR 20, from 43% to 51% for ACR 50 and from 61% to 72% for PASI 75. Mean changes from baseline in the modified Sharp/van der Heijde score ranged from 0.1 to 0.3 units. Clinically important improvements in HAQ-DI scores (a decrease of ≥ 0.3 units) were seen for 52–58% of randomised patients. The use of concomitant MTX at baseline did not affect ACR 20 or PASI 75, but did appear to reduce radiographic progression when a comparison was made with patients who did not use concomitant MTX at baseline. Although some method details were not fully clear, it appeared that the data imputations used were not conservative enough. For example, it seems that LOCF was used for patients who stopped treatment as a result of an AE (so a patient responding well to treatment but who discontinued treatment early in the study as a result of an AE was counted as a responder at 5 years). In addition, it was unclear whether or not there were any stopping rules – such as how long non-responders were allowed to remain on treatment – which raises further uncertainties about the study’s applicability to clinical practice.

The follow-up for the Mease *et al.* ETN trial[54](https://www.ncbi.nlm.nih.gov/books/NBK458358/) extended to 2 years and consisted of three phases: the 24-week initial randomised phase, an optional 24-week maintenance therapy phase (according to randomised assignment) and a 48-week open-label phase. Most results were given as percentages and it was not fully clear what the denominator was for some results. Several results were presented only as graphs. Very few data were provided on reasons for withdrawal from the study and HAQ-DI results were not reported. The ACR response results were similar to those seen in the GO-REVEAL trial (at 5 years), although the proportions of PASI 75 responders were markedly lower.

The ADEPT ADA trial[78](https://www.ncbi.nlm.nih.gov/books/NBK458358/) was extended to 2.75 years for radiographic progression outcomes and to 2 years for other outcomes. The ACR 50 results were similar to those seen for the ETN and GOL open-label studies. PASI 75 results were only presented in a graph; the response was around 60% (*n* = 128), which is similar to the GO-REVEAL trial’s PASI 75 result at 5 years. Non-responders could increase their dose from 40 mg every other week (the recommended dose) to 40 mg weekly; this occurred in 54 (19%) patients. The use of LOCF imputation for missing data for the ACR, PASI and PsARC outcomes is different (potentially much less conservative) from the imputations used in the placebo-controlled phase, where non-responder imputations were used. This is likely to have inflated the response rates in the open-label phase. The results for HAQ-DI remained very stable throughout the 2 years. These open-label HAQ-DI results are similar to the placebo-controlled, fully blinded 24-week phase in which HAQ-DI scores remained the same between week 12 and week 24 in both the ADA and the placebo groups.

The UST PSUMMIT 1 trial[80](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[81](https://www.ncbi.nlm.nih.gov/books/NBK458358/) was extended to 108 weeks, with efficacy data evaluated at 100 weeks. The change from baseline Sharp/van der Heijde radiographic progression scores varied across the three treatment groups. The change from baseline HAQ-DI results ranged between –0.36 and –0.45 units, similar to the ADA study results.

For INF, IMPACT[79](https://www.ncbi.nlm.nih.gov/books/NBK458358/) was extended to 98 weeks. The data for all patients were summarised as one group (as for the ADA open-label study). At 98 weeks, 46% and 34% were ACR 20 and ACR 50 responders, respectively. The mean change in the modified Sharp/van der Heijde score was 1.2 units, which is similar to the results in the UST PSUMMIT 1.[80](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[81](https://www.ncbi.nlm.nih.gov/books/NBK458358/) However, the result was based on 41% of the initial 104 patients. The authors also acknowledged that the 2-year radiographic progression result may have reflected non-linear progression of damage, with more damage occurring in earlier disease stages. Mean changes from baseline were not available for the HAQ-DI.

For APR, the PALACE 1 trial[61](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[82](https://www.ncbi.nlm.nih.gov/books/NBK458358/) was extended to 2 years. There were no separate results for the patients at 104 weeks who were in the placebo group at the beginning of the trial. In the 30-mg group, at 2 years 40% of patients were ACR 20 responders and 30% were PASI 75 responders. The HAQ-DI result may be an overestimate, as it was based on data from patients remaining in the study at 2 years (i.e. observed data). No data were reported on any radiographic progression outcomes.

*Summary*

The uncontrolled nature of open-label extension studies means that it is often very difficult to determine the magnitude of effects that can be ascribed only to active treatment; results should generally be viewed with much more caution than the results of the earlier randomised controlled study phases. Furthermore, it is not straightforward to compare long-term results across different treatments because of the variation in outcomes and time points reported. There is also variation in the methodological approaches used for analyses and for imputing missing data. Additionally, most studies did not report whether or not there were any treatment stopping rules, and it is likely that the decisions made regarding continuation of treatment were not reflective of those used in the NHS, limiting the applicability of many of these results. For example, in the open-label ADEPT[78](https://www.ncbi.nlm.nih.gov/books/NBK458358/) non-responders after 12 weeks had their dose doubled – the opposite of what would be expected in practice (when treatment with ADA would have been stopped).

With these caveats in mind, the results relating specifically to those patients who were responders at 12 or 16 weeks appear to be the most clinically relevant and useful (for the dichotomous outcomes), although such data were available only for CZP and SEC (confidential information has been removed).

The available data on disease progression based on radiographic assessments of joint damage indicate that, after 2 years of treatment, CZP effectively reduces disease progression, with results being similar to those observed in the open-label studies of the other anti-TNFs. For SEC, fewer result details were available at 2 years, although the results also indicated effective reduction in radiographic disease progression.

For long-term HAQ-DI results, missing data were often imputed using LOCF, which is not the most conservative of approaches for this outcome. Notwithstanding this, the results suggest that HAQ-DI gains remain stable in PsA patients treated with biologics. The 2-year open-label HAQ-DI results from ADEPT were similar to the placebo-controlled, fully blinded 24-week phase in which HAQ-DI scores remained the same between week 12 and week 24 in both the ADA and the placebo groups. This stability of HAQ-DI scores over time was also seen in the open-label studies of CZP (data up to 4 years) and SEC (data to 1 year).

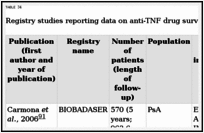
Withdrawal rates as a result of AEs or loss of efficacy were low in both the FUTURE 2[48](https://www.ncbi.nlm.nih.gov/books/NBK458358/) (5% at 52 weeks) and RAPID-PsA[47](https://www.ncbi.nlm.nih.gov/books/NBK458358/) trials (around 10% at 52 weeks).

[Go to:](https://www.ncbi.nlm.nih.gov/books/NBK458358/)

**Review of anti-tumour necrosis factor patient registry studies**

**Drug survival and anti-tumour necrosis factor switching**

The database of references, which resulted from the searches for RCTs, was also screened to identify registries containing PsA patients and the corresponding publication output. The results of this search were supplemented by separate searches for the output of the identified patient registries reporting information on their PsA cohorts. A library of 165 potentially relevant studies was assembled and screened fully, from which there were 12 studies[83](https://www.ncbi.nlm.nih.gov/books/NBK458358/)–[93](https://www.ncbi.nlm.nih.gov/books/NBK458358/) reporting data on drug survival and switching of anti-TNF treatments. The populations of all 12 studies were defined as having clinically diagnosed PsA. These studies are presented in [*Table 34*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table34/?report=objectonly).

[](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table34/?report=objectonly)

[**TABLE 34**](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table34/?report=objectonly)

Registry studies reporting data on anti-TNF drug survival and switching

These studies were all retrospective analyses of prospective patient registers from primarily European countries (10 studies[83](https://www.ncbi.nlm.nih.gov/books/NBK458358/)–[86](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[88](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[90](https://www.ncbi.nlm.nih.gov/books/NBK458358/)–[94](https://www.ncbi.nlm.nih.gov/books/NBK458358/)), along with one Australian study[89](https://www.ncbi.nlm.nih.gov/books/NBK458358/) and another from the USA.[87](https://www.ncbi.nlm.nih.gov/books/NBK458358/) The majority of patients in each of the registries had been treated with ETN, ADA or INF; two of the studies named other anti-TNF-α treatments, GOL and CZP, but neither had sufficient data to provide individual drug survival information for these.

Drug survival was reported in a number of ways: as the number of patients remaining on treatment at a given time point; as the proportion of patients remaining on treatment at each time point; or as the median duration patients remained on treatment.

Treatment withdrawal rates in patients who had switched anti-TNFs were reported in three studies.[83](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[94](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[95](https://www.ncbi.nlm.nih.gov/books/NBK458358/) The Danish Database for Biological Therapies (DANBIO) registry[94](https://www.ncbi.nlm.nih.gov/books/NBK458358/) reported up to three sequential anti-TNFs, with 548 patients who had switched treatment once, and 189 patients who had switched treatment twice. The UK’s British Society for Rheumatology Biologics Register (BSRBR)[83](https://www.ncbi.nlm.nih.gov/books/NBK458358/) also reported drug survival rates for its population of 178 one-time switchers over 2 years, whereas the 95 switchers in the Norwegian Antirheumatic Drug Register (NOR-DMARD)[95](https://www.ncbi.nlm.nih.gov/books/NBK458358/) were followed for 3 years.

For the first course of anti-TNF treatment, the proportion of patients remaining on treatment ranged from 60% to 88% at 1 year, from 57% to 81% at 2 years and from 55% to 73% at 3 years. Three studies reported first anti-TNF drug survival rates for ≥ 5 years: (1) the BSRBR study,[84](https://www.ncbi.nlm.nih.gov/books/NBK458358/) in which 47% of patients were still on the initial anti-TNF treatment at 5 years; (2) the Southern Sweden Antirheumatic Therapy Group study,[85](https://www.ncbi.nlm.nih.gov/books/NBK458358/) which reported 5-year survival of around 40%; and (3) the study conducted by another Swedish registry, Antirheumatic Therapies In Sweden,[86](https://www.ncbi.nlm.nih.gov/books/NBK458358/) which reported 6-year first anti-TNF drug survival of 37% and 8-year survival of 32%.

The median first anti-TNF survival time across all anti-TNFs was reported as 2.5–2.9 years.[87](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[88](https://www.ncbi.nlm.nih.gov/books/NBK458358/) One study reported this separately by anti-TNF: ETN, 2.62 years; ADA, 4.21 years; and INF, 1.92 years.[89](https://www.ncbi.nlm.nih.gov/books/NBK458358/)

Drug survival was consistently lower in patients who switched anti-TNF than in those who did not. The DANBIO[94](https://www.ncbi.nlm.nih.gov/books/NBK458358/) register had the largest population of switchers; the median drug survival for a first anti-TNF was 2.2 (95% CI 1.9 to 2.5) years, whereas median drug survival for a second anti-TNF was 1.3 years (95% CI 1.0 to 1.6 years) (*n* = 548), and was 1.1 years (95% CI 0.7 to 1.5 years) (*n* = 189) for those on a third anti-TNF.

There is some evidence suggesting that drug survival varies between types of anti-TNF; both the Australian Rheumatology Association Database register and the BSRBR study report rates for individual therapies, and both indicate that ADA and ETN are associated with considerably higher survival rates than INF. Two studies reported the impact of concomitant MTX or other DMARDs.[85](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[87](https://www.ncbi.nlm.nih.gov/books/NBK458358/) One reported a small increase in drug survival at 1 year (from 65% to 80%), but this effect was diminished at 3 years (from 55% to 60%) and 5 years (from 37.5% to 40%).[85](https://www.ncbi.nlm.nih.gov/books/NBK458358/) The other study reported that median drug survival time for anti-TNF-α monotherapy was 30.8 months, compared with 32.4 months for combination therapy (anti-TNF + MTX or DMARD).[87](https://www.ncbi.nlm.nih.gov/books/NBK458358/)

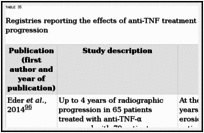
Reasons for discontinuation of treatment varied widely between studies, due in part to the inconsistency of observation period duration. Across all registries, between 20% and 35% of patients withdrew from treatment because of a lack of efficacy and, generally, a smaller proportion withdrew as a result of AEs. The frequency of occurrence of AEs was linked to the types of anti-TNF used and whether or not patients received concomitant MTX, which was generally found to reduce AE frequency when MTX subgroups were analysed.

Only one study reported an analysis of response rates; this was based on the 3-month response rates from the NOR-DMARD (*n* = 439).[90](https://www.ncbi.nlm.nih.gov/books/NBK458358/) A retrospective comparison of response rates in switchers and non-switchers found that switchers had a lower response rate to the first anti-TNF: for ACR 50, 30.5% compared with 40%. In addition, the response to the second anti-TNF was lower than to the first: 22.5% (compared with 30.5%, although this difference was not statistically significant). The same pattern was seen for ACR 20 and 70 and, for the latter, the difference reached statistical significance.

In summary, across all relevant studies, those patients who switched treatment had a shorter median drug survival time, also showing a continuously smaller proportion of patients remaining on each subsequent treatment option. This may reflect a lack of improvement in treatment response after switching biologic; however, there are limited direct data on the effect of sequential treatments on relevant outcome measures. The proportion of patients withdrawing from treatment because of a lack of effect also seems to increase with the number of times a patient switches anti-TNF therapy. The registry data suggest that, although patients can benefit from a second (or further) anti-TNF, the expected benefit from anti-TNFs diminishes after switching, with a reduced chance of response and reduced drug survival.

**Effect of anti-tumour necrosis factors on radiographic progression and Health Assessment Questionnaire-Disability Index score**

Four patient registry studies that provided longitudinal data on the effect of anti-TNFs on HAQ-DI scores were identified, one of which also reported on radiographic progression. The results of these are presented in [*Table 35*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table35/?report=objectonly).

[](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table35/?report=objectonly)

[**TABLE 35**](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table35/?report=objectonly)

Registries reporting the effects of anti-TNF treatment on HAQ-DI and radiographic progression

One study[96](https://www.ncbi.nlm.nih.gov/books/NBK458358/) reported on radiographic progression; a comparison of anti-TNF and MTX found an inhibitory effect of anti-TNF on radiographic progression over 4 years of observation. Radiographic progression was measured in terms of newly forming erosions and change in a modified Steinbrocker score; radiographic progression according to both measures was significantly more prevalent in the MTX group at each follow-up assessment.

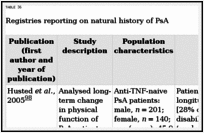
Four studies[88](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[90](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[96](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[97](https://www.ncbi.nlm.nih.gov/books/NBK458358/) reported on disease progression in terms of HAQ-DI score for between 6 months and 5 years at varying frequency. Eder *et al.*[96](https://www.ncbi.nlm.nih.gov/books/NBK458358/) compared HAQ-DI score change in 70 patients treated with MTX and 65 patients on an anti-TNF, finding no significant difference in HAQ-DI score between the groups at the two assessments at up to 4 years from baseline. The HAQ-DI score was measured in 658 patients receiving anti-TNFs for 5 years in the largest cohort[88](https://www.ncbi.nlm.nih.gov/books/NBK458358/) (the DANBIO register). The baseline mean HAQ-DI score was 1.0 unit, decreasing to 0.3 units by 3 years, and increasing to 0.5 units at 5 years. This suggests sustained long-term improvement of functional status during anti-TNF treatment, although the number of patients at each time point after the 6-month assessment decreased significantly. Therefore, the trend of improving HAQ-DI scores observed in this study is potentially due to a higher attrition of patients, with greater functional impairment skewing the data. The third study on HAQ-DI change is from the NOR-DMARD,[90](https://www.ncbi.nlm.nih.gov/books/NBK458358/) and showed an improvement in HAQ-DI score from 0.7 units at baseline to 0.39 units at 3 months, and 0.38 units at 6 months. This study also found no significant difference in HAQ-DI response in patients receiving MTX compared with those on biologics alone. The BSRBR[97](https://www.ncbi.nlm.nih.gov/books/NBK458358/) study followed an initial cohort of 562 patients on biologics for 18 months. This group of patients appears to have had more advanced disease (12 years since onset) and poorer functional status than those in the other included studies, with a median baseline HAQ-DI score of 1.88 units (95% CI 1.38 to 2.25 units). There is a 0.63-unit decrease in HAQ-DI score between baseline and 6 months of treatment, representing what the authors describe as a clinically important improvement. The median HAQ-DI score then increases to and remains at 1.38 units (95% CI 0.63 to 2.00 units) at both the 12- and 18-month assessments. Disease duration at the time of treatment initiation in the BSRBR study was more than twice that in two of the aforementioned studies on the HAQ-DI, showing that significant improvements in functional status are achievable using anti-TNF therapy in advanced cases of PsA.

Treatment with anti-TNFs appears to yield significant improvement in radiographic progression and long-term HAQ-DI score change in patient registry studies, although it is not clear to what extent the treatment is responsible for the reduction in mean cohort HAQ-DI score over time. Estimation of HAQ-DI score change using measures more robust to attrition bias or profiling those lost to follow-up based on disease severity would have given a truer representation of HAQ-DI score change in these cohorts. The paucity of radiographic data in these registry studies is perhaps surprising given the significance of radiographic damage as a measure of disease progression and treatment effects. This lack of published data may be because few of these registries were set up to record PsA-specific outcomes, and there has historically been little consensus on a method for objectively taking and scoring joint radiographs in this disease. It may be that HAQ-DI was usually preferred as an acceptable and standardised proxy for assessing bone erosion and, as a patient-reported outcome measure, can be cheaply and routinely recorded without the need for specialist assessment.

[Go to:](https://www.ncbi.nlm.nih.gov/books/NBK458358/)

**Review of the natural history of psoriatic arthritis: registry and cohort study data**

A total of four publications[33](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[98](https://www.ncbi.nlm.nih.gov/books/NBK458358/)–[100](https://www.ncbi.nlm.nih.gov/books/NBK458358/) analysing patterns of natural disease progression in registries or long-term cohort data were found and are shown in [*Table 36*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table36/?report=objectonly). These were reviewed in order to gain an understanding of the manner in which disease progresses in patients who do not receive anti-TNF therapy, despite being eligible for treatment. Owing to the now ubiquitous nature of anti-TNFs and only recent recognition of PsA as a separate and distinct form of arthritis, information on the long-term uncontrolled progression of the disease is scarce. Two of the studies[33](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[100](https://www.ncbi.nlm.nih.gov/books/NBK458358/) found in the literature search were different analyses of the same data set derived from the Norfolk Arthritis Register (NOAR): one was a 2-year prospective cohort study[99](https://www.ncbi.nlm.nih.gov/books/NBK458358/) and the other a retrospective analysis of a Canadian single-site patient registry.[98](https://www.ncbi.nlm.nih.gov/books/NBK458358/)

[](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table36/?report=objectonly)

[**TABLE 36**](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table36/?report=objectonly)

Registries reporting on natural history of PsA

The studies explore changes in functional disability in terms of HAQ-DI score and bone erosion as measures of disease activity and progression over time. There is a great deal of variability between the three cohorts under observation in terms of both baseline characteristics and patterns of disease. It should be noted that disease classification of the NOAR cohort[99](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[100](https://www.ncbi.nlm.nih.gov/books/NBK458358/) was performed retrospectively and both studies analysing the 79 patients emphasise that they are unlikely to be representative of PsA patients, preferring instead to refer to them as having polyarthritis plus psoriasis. The Morgan *et al.*[100](https://www.ncbi.nlm.nih.gov/books/NBK458358/) study analysed the change in median cohort HAQ-DI score over 5 years in 79 patients, finding an increase of 0.125 units over the observation period, indicating a small increase of 0.025 units in HAQ-DI score every year. The patients in this analysis may or may not have been treated with DMARDs over this period. The analysis in Rodgers *et al.*[33](https://www.ncbi.nlm.nih.gov/books/NBK458358/) includes only those patients who had previously received two or more DMARDs at each time point, finding an annual HAQ-DI score change of –0.060 units per year over the first 2 years (*n* = 24), and an annual increase of 0.077 units over years 3 to 5 (*n* = 52). This represents a faster progression of disease than that found in the Morgan *et al.*[100](https://www.ncbi.nlm.nih.gov/books/NBK458358/) study, but is inconsistent and derived from a small cohort of varying size.

A prospective cohort study of progression in early arthritis carried out by Kane *et al.*[99](https://www.ncbi.nlm.nih.gov/books/NBK458358/) found that HAQ-DI score changed from 0.71 units at baseline to 0.4 units at 1 year and remained as such until the end of the 2-year observation period, representing a decrease of 0.31 units. This decrease is likely to be explained by the increase in uptake of DMARDs, as 12% of patients were receiving DMARD treatment at baseline, compared with 59% at 1 year and 56% at 2 years. This was the only study that recorded radiographic progression, finding consistent increases across all measures between baseline and 2 years, despite the simultaneous drop in HAQ-DI score. The Sharp erosion score increased from 1.2 units at baseline to 3 units at 2 years, demonstrating how HAQ-DI score change may not reflect progressive radiographic damage, particularly during early disease.

The study by Husted *et al.*[98](https://www.ncbi.nlm.nih.gov/books/NBK458358/) was the longest and largest study of natural history of PsA, with 341 patients included and observed for up to 10 years. This study found that the patient population exhibited several patterns of disease progression, rather than just universal consistent deterioration over time. Patients were assigned to one of three disability states based on their HAQ-DI score. These were as follows: ‘no disability’ (a HAQ-DI score of < 0.5 units), ‘moderate disability’ (a HAQ-DI score of 0.5–1.5 units) and ‘severe disability’ (a HAQ-DI score of 1.51–3.0 units). The transition of patients between groups was recorded over the course of the observation period to ascertain the direction of change in their symptoms. Forty-six per cent remained in the same disability group over the course of the study, with 28% of these in the no disability state, 12% in the moderate state and 6% in the severely disabled state. A total of 26.7% of patients made a single transition between disability groups, reflecting steady improvement or deterioration, and 27.3% experienced two or more transitions between disability states. Although this methodology may reveal broad patterns of disease progression, it appears to be insensitive to change within groups and weights HAQ-DI score change near thresholds more highly (e.g. a patient with a baseline HAQ-DI score at the lower end of a Markov group can experience a significant worsening of their disability without progressing into the next group). Mean HAQ-DI score change between consecutive assessments was 0.55 units (± 0.32 units) for those moving from a lower to a higher state and –0.57 units (± 0.36 units) for those moving to a lower state, with assessments being on average 1.29 years apart. In those patients who did not move between groups, the mean HAQ-DI score change was –0.002 units (± 0.215 units). A more complete picture of patterns of disease progression would have been possible had there been more Markov states. The mean HAQ-DI change for the majority of patients at any one time was effectively zero, but this may conceal significant within-group changes in either direction. Greater age was associated with a slower improvement in HAQ-DI score in those in the moderate and severe disability groups, and disability worsened more slowly in males than in females. Time since PsA diagnosis was related to more frequent transition between disability states, and there was no association between PASI score and transition between disability states. In summary, this study indicates that functional disability (as measured via the HAQ-DI) in PsA is generally stable over time in the majority of patients, but there are groups who exhibit patterns of more rapidly worsening or improving symptoms at certain periods, with some experiencing fluctuating deterioration and improvement over time.

Owing to the paucity of observational data on natural history of PsA, it is difficult to produce accurate estimates of yearly disease progression rates without anti-TNF therapy. None of the included studies can claim to provide accurate long-term estimates on uncontrolled disease progression. It is clear from the largest cohort that functional disability deteriorates over time, but the course of HAQ-DI progression is not constant or predictable. Therefore, it is unclear if an average rate of HAQ-DI change is a useful statistic, as this change is neither constant nor generalisable to the patient population. The Kane *et al.* study[99](https://www.ncbi.nlm.nih.gov/books/NBK458358/) does show that, despite reductions in functional disability in early-stage disease under DMARD therapy, radiographic progression continues to occur, which theoretically will ultimately result in worsening disability in the long term; however, because of the lack of large and long-term observational studies, HAQ-DI change over time in uncontrolled PsA is yet to be properly measured.

[Go to:](https://www.ncbi.nlm.nih.gov/books/NBK458358/)

**Review of adverse effects of certolizumab pegol, secukinumab and comparators**

**Randomised trials of certolizumab pegol or secukinumab for psoriatic arthritis**

**Secukinumab: FUTURE 2**

During the 16-week placebo-controlled period, AEs were reported in 54% and 58% of patients in the pooled SEC and placebo groups, respectively. The most frequently reported AEs up to 16 weeks in any SEC group (vs. placebo) were upper respiratory tract infection [(confidential information has been removed) vs. 7%], nasopharyngitis [(confidential information has been removed) vs. 8%], headache [(confidential information has been removed) vs. 4%], nausea [(confidential information has been removed) vs. 4%], diarrhoea [(confidential information has been removed) vs. 3%] and urinary tract infection [(confidential information has been removed) vs. 4%]. Rates of infections and infestations were similar across treatment groups (27% on any SEC dose vs. 31% placebo), and no cases of active TB were reported.

The majority of AEs that occurred up to week 16 were mild [(confidential information has been removed) of AEs on any SEC dose and (confidential information has been removed) on placebo] or moderate [(confidential information has been removed) AEs on any SEC dose and (confidential information has been removed) on placebo] in severity. Severe AEs were reported in five patients (1.7% of pooled SEC population), compared with none in patients on placebo. Around 3% of patients in the SEC groups reported non-fatal serious adverse events (SAEs), compared with 2% on placebo. More patients in the placebo group than in the pooled SEC group discontinued study treatment as a result of an AE (confidential information has been removed).

**Certolizumab pegol: RAPID-PsA**

During the 24-week period, the incidence of drug-related AEs was 26% in the pooled CZP group and 27% in the placebo group and they were mostly of mild intensity (51% pooled CZP vs. 54% placebo) or moderate intensity (30% pooled CZP vs. 36% placebo). The incidence of serious AEs was 6.6% in the pooled CZP group and 4.4% in the placebo group. The incidence of SAEs was 5.8% in the CZP 200 mg group and 9.6% in the CZP 400 mg group.

(Confidential information has been removed.) The most common serious AEs were infections (confidential information has been removed).

**Open-label extensions of randomised controlled trials of certolizumab pegol and secukinumab**

**Secukinumab: FUTURE 2**

By the 52-week time point, the most common AEs experienced in patients receiving 300 mg were infection and infestations (79 cases per 100 patient-years), upper respiratory tract infection (18 per 100 patient-years) and nasopharyngitis (14 per 100 patient-years). The rate of discontinuation as a result of AEs in patients who received at least one dose of 150 mg of SEC was 2%. No deaths were reported.

**Secukinumab: FUTURE 1**

At week 104, 79% of patients remained in the open-label extension study. Infections and infestations were the most common AEs reported, occurring at a rate of 68 per 100 patient-years. Malignant or unspecified tumours occurred at a rate of 0.3 per 100 patient-years, and major adverse cardiac event rates occurred at a rate of 0.7 per 100 patient-years. No cases of active TB or suicide were reported. At week 52 the rate of discontinuation as a result of AEs was 3.9%.

**Pooled safety analysis of plaque psoriasis and psoriatic arthritis trials**

A conference abstract reported a pooled safety analysis for seven Phase III SEC trials: five plaque psoriasis trials {ERASURE, FIXTURE, SCULPTURE [Efficacy and Safety of Subcutaneous Secukinumab (AIN457) for Moderate to Severe Chronic Plaque-type Psoriasis Assessing Different Doses and Dose Regimens], FEATURE (First Study of Secukinumab in Pre-filled Syringes in Subjects With Chronic Plaque-type Psoriasis: Response at 12 Weeks) and JUNCTURE (Judging the Efficacy of Secukinumab in Patients With Psoriasis Using AutoiNjector: a Clinical Trial Evaluating Treatment Results)} and two PsA trials (FUTURE 1 and FUTURE 2).[101](https://www.ncbi.nlm.nih.gov/books/NBK458358/) All trials except FUTURE 2 contributed data up to (at least) 52 weeks; FUTURE had data up to 24 weeks. A total of 3928 patients received at least one dose of SEC (3225 patient-years of exposure; mean exposure 299.8 days for SEC and 105.7 days for placebo). Exposure-adjusted incidence rates per 100 patient-years for SEC and placebo were, respectively, 241 and 329 for AEs, 8 and 10 days for SAEs, and 93 and 94 for infections/infestations. Around 3% of patients treated with SEC discontinued treatment as a result of an AE. Nasopharyngitis and upper respiratory tract infections were the most commonly reported events.

Four deaths occurred in patients treated with SEC (one intracranial haemorrhage, one cardiorespiratory arrest, one alcohol intoxication and one of unknown cause); all the deaths were deemed unrelated to the SEC according to the investigators. There were two (0.05%) cases of suicidality with SEC: one attempted suicide and one case of suicidal ideation.

**Certolizumab pegol: RAPID-PsA**

In the open-label extension study, 393 patients had been exposed to CZP by week 96 (total exposure 606 patient-years). At week 96, the incidence of overall treatment-emergent AEs was 87.8% (345/393 patients; 330 per 100 patient-years). The rate of SAEs was 17% (67 patients; 14.5 per 100 patient-years). Around 4% of patients reported a serious infection (16 cases; 3.3 per 100 patient-years) and 14.2% of patients reported an upper respiratory tract infection (56 patients; 13.7 per 100 patient-years), with no cases of active TB. Malignancies were reported in 1% of patients (four patients; 0.7 per 100 patient-years).

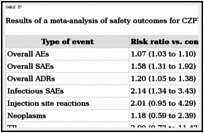
By 96 weeks, 9.2% of patients had experienced an AE leading to withdrawal and six patients (1.5%) had experienced an AE leading to death (two cardiac disorders, one sudden death, one case of breast cancer, one case of sepsis and one lymphoma). According to the investigator, neither cardiac events was considered to be related to the study medication.

**Reviews of safety outcomes for other biologics**

Six relevant reviews of AEs were identified from the searches. The key results for three of these reviews[33](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[102](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[103](https://www.ncbi.nlm.nih.gov/books/NBK458358/) have been summarised in a recently published HTA journal publication of a MTA of anti-TNFs for ankylosing spondylitis and non-radiographic axial spondyloarthritis.[104](https://www.ncbi.nlm.nih.gov/books/NBK458358/)

The Cochrane systematic review and NMA of AEs of nine biologics in adults with any disease (except human immunodeficiency virus infection/acquired immunodeficiency syndrome) used data from 160 RCTs (*n* = 48,676) and 46 open-label extension studies (*n* = 11,954).[102](https://www.ncbi.nlm.nih.gov/books/NBK458358/) The most frequently studied disease in the included trials was RA. When compared with control treatments, only INF and CZP were statistically significantly associated with AEs. INF was associated with higher rates of total AEs [number needed to harm 13, 95% credible interval (CrI) 8 to 505] and withdrawals because of AEs (number needed to harm 10, 95% CrI 5 to 30). CZP was associated with higher rates of serious infections (number needed to harm 12, 95% CrI 4 to 79) and SAEs (number needed to harm 18, 95% CrI 9 to 162). An individual patient data meta-analysis (*n* = 22,904 from 74 RCTs) examining short-term cancer risk associated with ETN, INF and ADA found no increase in risk of cancers excluding non-melanoma skin cancer (RR 0.99, 95% CI 0.61 to 1.68) when considering all three anti-TNFs together.[103](https://www.ncbi.nlm.nih.gov/books/NBK458358/) However, a doubling in the risk of non-melanoma skin cancer was found, with 332 events per 100,000 person-years in the control group and 655 events per 100,000 person-years in the anti-TNF group [hazard ratio (HR) 2.02, 95% CI 1.11 to 3.95]. NICE TA199[33](https://www.ncbi.nlm.nih.gov/books/NBK458358/) included a review of studies (including both randomised and non-randomised studies) of the adverse effects of ETN, INF and ADA. The rates of SAEs covered a broadly similar range across the three anti-TNFs. However, all estimates were derived from a highly heterogeneous group of studies in terms of patients, study design and treatment regimens so reliable estimates of the relative rate of SAEs for each anti-TNF could not be made.[33](https://www.ncbi.nlm.nih.gov/books/NBK458358/)

Of the three more recent reviews identified,[105](https://www.ncbi.nlm.nih.gov/books/NBK458358/)–[107](https://www.ncbi.nlm.nih.gov/books/NBK458358/) two were reported only as conference abstracts.[105](https://www.ncbi.nlm.nih.gov/books/NBK458358/),[106](https://www.ncbi.nlm.nih.gov/books/NBK458358/) A Danish guideline panel performed a NMA of SAEs from 87 RCTs (*n* = 27,333) of biologics for inflammatory arthritis (RA, PsA and spondyloarthritis).[105](https://www.ncbi.nlm.nih.gov/books/NBK458358/) The conference abstract reported the odds of a SAE to be statistically significantly higher for CZP than for placebo (OR 1.6, 95% CI 1.19 to 2.16). Treatment with CZP was also statistically significantly more likely to result in SAEs than treatment with GOL (OR 2.02, 95% CI 1.26 to 3.25), ETN (OR 1.70, 95% CI 1.15 to 2.51) or ADA (OR 1.44, 95% CI 1.02 to 2.02). The other conference abstract reported a 2014 systematic review and meta-analysis on the safety profile of CZP in patients with an immune-mediated inflammatory disease.[106](https://www.ncbi.nlm.nih.gov/books/NBK458358/) The review identified 18 RCTs with 6992 participants; the results, presented in [*Table 37*](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table37/?report=objectonly), also highlight the increased risk of SAEs associated with CZP (compared with ‘control’), particularly the risk of infectious SAEs.

[](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table37/?report=objectonly)

[**TABLE 37**](https://www.ncbi.nlm.nih.gov/books/NBK458358/table/table37/?report=objectonly)

Results of a meta-analysis of safety outcomes for CZP

A review published in 2012 examined the safety of anti-TNFs for treating psoriasis and PsA and focused mainly on data from European patient registries of biologics used across a range of diseases (mostly RA).[107](https://www.ncbi.nlm.nih.gov/books/NBK458358/) It was (at least) partly funded by Pfizer, the manufacturer of ETN, and it did not appear to be systematic in its methods of selection, critical appraisal and synthesis of the included studies. It concluded that the safety profile of monoclonal antibodies (INF and ADA) seems generally less favourable than that of ETN, particularly in terms of infections, cancer and hepatotoxicity. The conclusion for infections appeared largely to be based on a BSRBR analysis, specifically on lower respiratory tract infections, even though a previous BSRBR study reported no difference in the risk of infection between ADA, ETN and INF.[108](https://www.ncbi.nlm.nih.gov/books/NBK458358/) The conclusion for cancer appeared to be based on an analysis of a small number (38) of lymphomas in a case–control study derived from the French Registry of Infections and Lymphoma in Patients Treated With TNF-α Antagonists (the data were collected between 2004 and 2006).[109](https://www.ncbi.nlm.nih.gov/books/NBK458358/) The conclusion for hepatotoxicity was based on a very small number of case reports.

**Recent large observational studies**

One recent observational study on the safety of biologics in patients with PsA was identified. It was an Israeli retrospective cohort study based on a health services database, which reported on 3128 patients between 2002 and 2013. The study examined the association between traditional DMARDs or anti-TNFs and infection by the herpes zoster virus (shingles). There were 182 cases of herpes zoster infection in 20,096 person-years. The risk of herpes zoster infection significantly increased in patients treated with a combination of an anti-TNF and a traditional DMARD, but did not increase significantly with each of these types of therapy alone.[110](https://www.ncbi.nlm.nih.gov/books/NBK458358/)

**Summary**

Safety assessments of new treatments can sometimes be limited in systematic reviews of RCTs because of the small number of trials and relatively short follow-up durations for which data are available. Where available, safety data from trials relating to the same treatment for other indications are therefore sometimes evaluated. For this review, more data from trials of other patient populations were available for CZP than for SEC. The results from three systematic reviews[105](https://www.ncbi.nlm.nih.gov/books/NBK458358/)–[107](https://www.ncbi.nlm.nih.gov/books/NBK458358/) (which looked specifically at AEs) suggested that CZP was associated with statistically significantly more SAEs and serious infections than placebo. SEC was not included in these systematic reviews of AEs, probably as a result of the limited availability of data at the time. Although the safety data for SEC appear promising, the fairly small number of trials for which data are currently available means there is still some uncertainty regarding its safety.

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