# Certolizumab pegol and secukinumab for treating active psoriatic arthritis following inadequate response to disease-modifying antirheumatic drugs: a systematic review and economic evaluation

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## Scientific summary

### Treating active psoriatic arthritis: certolizumab pegol and secukinumab

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# Scientific summary

## Background

Psoriatic arthritis (PsA) is a chronic, immune-mediated inflammatory arthritis, closely associated with psoriasis of the skin and nails, that typically affects joints in the hands, feet and spine. It can cause joint damage so early diagnosis and treatment is important. Current practice typically involves early use of non-steroidal anti-inflammatory drugs followed by disease-modifying antirheumatic drugs (DMARDs), if necessary. When conventional disease-modifying antirheumatic drugs (cDMARDs) are ineffective, biologic therapies may be used; for example, anti-tumour necrosis factor (TNF) biologics such as etanercept [(ETN); ENBREL®; Pfizer Inc., New York City, NY, USA)], infliximab [(INF) REMICADE®; Merck Sharp & Dohme, Kenilworth, NJ, USA], adalimumab [(ADA) HUMIRA®; AbbVie Inc., North Chicago, IL, USA] and golimumab [(GOL) SIMPONI®; Merck Sharp & Dohme, Kenilworth, NJ, USA] are approved by the National Institute for Health and Care Excellence (NICE) for patients who have had an inadequate response to two or more DMARDs. Ustekinumab [(UST) STELARA®; Janssen Pharmaceuticals, Inc., Horsham, PA, USA], which is an anti-interleukin (IL)-12/23 – a different kind of biologic therapy to anti-TNFs - is also recommended as a possible treatment, specifically when DMARDs have not worked well enough, provided that treatment with anti-TNFs is not suitable, or the patient has had an anti-TNF before. NICE does not specifically recommend switching anti-TNF treatments other than the guidance for UST and switching decisions can vary depending on local guidelines. The newer biologics, secukinumab [(SEC) COSENTYX®; Novartis International AG, Basel, Switzerland; an anti-IL-17] and certolizumab pegol [(CZP) CIMZIA®; UCB Pharma, Brussels, Belgium; an anti-TNF], have not previously been appraised by NICE for treating PsA.

## Objective

To determine the clinical effectiveness and cost-effectiveness of CZP and SEC within their marketing authorisations for treating active PsA in adults in whom DMARDs have been inadequately effective.

## Methods

For the systematic review of clinical efficacy, randomised controlled trials (RCTs) were eligible, including open-label extensions. Adverse events (AEs) data were sought from existing safety reviews of biologics. Patient registry studies (of patients taking biologics) and studies of natural history of disease (in patients not taking biologics) were also sought. Eligible studies were of adults with PsA. The treatments of interest were SEC and CZP with the relevant comparators being ETN, INF, ADA, GOL, UST, apremilast (APR; Otezla®, Celgene Corporation, Summit, NJ, USA) and placebo.

Fourteen databases (including MEDLINE and EMBASE) were searched for relevant studies from inception to April 2016 for CZP and SEC studies; update searches were run to identify new comparator studies. Clinical effectiveness data from RCTs were synthesised using Bayesian network meta-analysis (NMA) methods to formally investigate the relative efficacy of SEC and CZP compared with the other active comparators. Analyses were conducted on four outcomes: Psoriatic Arthritis Response Criteria (PsARC); Health Assessment Questionnaire-Disability Index (HAQ-DI), conditional on PsARC response; Psoriasis Area and Severity Index (PASI); and American College of Rheumatology improvement criteria. Results from other studies were summarised narratively.

### *Methods of cost-effectiveness review*

A systematic review was undertaken to identify published evidence on the cost-effectiveness of CZP and SEC in PsA. This also includes the company submissions (CSs) from Novartis (SEC) and UCB Pharma (CZP). The systematic review also includes a broader assessment of published decision-analytic models for relevant comparators INF, ETN, ADA, GOL and UST. The differences in the model structures and assumptions used across the studies were examined to identify any important differences in approaches and areas of remaining uncertainty.

### *Methods of economic modelling*

A de novo decision-analytic model was developed to estimate the cost-effectiveness of SEC and CZP compared with other relevant comparators including ETN, INF, ADA, GOL, UST and best supportive care (BSC) for the treatment of adult PsA. A different set of comparators are defined according to each subpopulation of interest. Here BSC includes the use of cDMARDs. The cost-effectiveness model takes the form of a lifetime (40 years) Markov cohort model, developed using the R programming language (The R Foundation for Statistical Computing, Vienna, Austria). Outcomes are expressed using quality-adjusted life-years (QALYs). The parameters of the model were obtained from published literature, manufacturers' reported data and the results of the evidence synthesis. Probabilistic sensitivity analysis (PSA) was used to explore decision uncertainty.

Although the model shares a number of important characteristics with the previous York model [Rodgers M, Epstein D, Bojke L, Yang H, Craig D, Fonseca T, *et al.* Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis: a systematic review and economic evaluation. *Health Technol Assess* 2011;**15**(10)], several significant changes have also been implemented. These include:

- incorporation of subsequent biologic treatments following primary lack of response or secondary failure
- three subpopulations specified in the NICE scope for this appraisal
- three subgroups according to the level of concomitant psoriasis.

### *Results of the clinical effectiveness review*

Nineteen eligible RCTs were included in the systematic review of short-term efficacy. Most studies were well conducted and were rated as being at low risk of bias.

#### Short-term efficacy in pivotal randomised controlled trials

Four eligible trials were of SEC and one was of CZP. Results from the pivotal RCTs of SEC and CZP demonstrated their short-term efficacy. Both therapies were associated with statistically significant improvements in all key clinical outcomes. At 3 months, patients taking SEC (150 or 300 mg) were around six times more likely to show 50% improvement in the American College of Rheumatology criteria (ACR 50) – an important clinical outcome to patients – than patients taking placebo. Patients taking CZP were around three times more likely to be ACR 50 responders than placebo patients. Clinically important improvements in activities of daily living (as assessed using HAQ-DI) were also evident for both therapies, particularly in patients who were PsARC responders. Both SEC and CZP also significantly improved measures of health-related quality of life and the resolution of enthesitis and dactylitis.

However, when the populations from these two trials were split into subgroups based on previous biologic experience, the results for the biologic-experienced subgroups became difficult to interpret. This was because of the low numbers of placebo-treated patients (and placebo events) and the differences in placebo response rates across subgroups. A further complication is that the evidence for CZP does not include patients who failed to respond to a first anti-TNF. Although SEC and, probably, CZP are efficacious in both subgroups, it is not possible to make robust conclusions about any difference in efficacy of these drugs across these subgroups.

Subgroup results from PsA patients recruited to trials of patients with quite severe psoriasis suggested that SEC may be particularly efficacious in treating the psoriasis symptoms of PsA.

### Short-term efficacy compared with other therapies from network meta-analyses

The trials identified to inform a comparison of SEC and CZP with other therapies were performed across a 15-year period and variation in the placebo response was evident for some important outcomes: larger placebo response rates were seen in the more recent trials. There was also important variation across trials with regard to patients' previous use of a biologic therapy: subgroups of biologic-experienced patients were recruited only in more recent trials. The NMAs were therefore performed on the biologic-naive and biologic-experienced subpopulations separately, and included models that adjusted for, and explored, the different rates of placebo response across trials.

Across all outcomes, the NMA results for the biologic-naive subpopulation indicated that, although SEC and CZP were effective, their relative effectiveness compared with ETN, ADA, GOL and INF and with each other was uncertain (the rankings of treatment varied with outcome and analysis). However, both agents did seem consistently more effective than APR. The results indicate that SEC and INF are the most effective in terms of PASI response.

Only SEC and UST could be included in the analyses of the biologic-experienced subpopulation. The results showed that, across all outcomes analysed, both SEC and UST were significantly more effective than placebo. Most of the results suggested SEC may be better than UST. However, the patient numbers in this subpopulation were quite low; the results were therefore uncertain (with wide overlapping credible intervals).

### Long-term efficacy

Results from open-label trial extension studies that radiographically assessed joint damage indicated that, after 2 years of treatment, CZP effectively reduced disease progression with the benefits appearing similar to those observed in the open-label studies of the other biologics. Fewer result details were available for SEC at 2 years, although the results also indicated effective reduction in radiographic disease progression. Meaningful treatment comparisons of longer-term data for other outcomes were difficult to undertake as a result of the variation in both time points assessed and in methodological approaches used for data analyses. (Confidential information has been removed.)

### Results from other studies

Patient registry studies suggested that, although patients benefit from a second or further anti-TNFs, the expected benefit from anti-TNFs diminishes after switching, with a reduced chance of response and reduced drug survival. The paucity of observational data on the natural history of PsA meant that it was difficult to produce accurate estimates of yearly disease progression rates in patients not receiving anti-TNF therapy.

The results from three systematic reviews of AEs suggested that CZP was associated with statistically significantly more serious AEs and serious infections than placebo. Although the safety data for SEC appear promising, there is still some uncertainty regarding the safety of this drug.

## *Results of the cost-effectiveness evaluation*

### Cost-effectiveness reported in existing published studies and manufacturer submissions

No previously published cost-effectiveness studies of SEC or CZP for PsA were identified. The companies submitted de novo analyses for SEC (Novartis) and CZP (UCB Pharma).

For the broader set of comparators, the systematic search of published literature identified nine studies that met the inclusion criteria for the cost-effectiveness review, including seven UK studies, only one of which was not directly related to a previous NICE technology appraisal (TA). All of these models employed similar model structures to that originally proposed by Rodgers *et al.* [Rodgers M, Epstein D, Bojke L, Yang H, Craig D, Fonseca T, *et al.* Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis: a systematic review and economic evaluation. *Health Technol Assess* 2011;**15**(10)] for TA199 (the previous York model). The main differences between these models are in relation to the comparators and associated evidence base, which has altered since TA199, rather than in terms of major structural differences. The choice of optimal treatment, ETN, is consistent across the published models.

The manufacturers' models are the only studies that directly assess the decision problem in relation to the new interventions [i.e. the positioning of SEC and CZP across the pathway for PsA (biologic-naive and biologic-experienced populations)]. Both have a similar structure to the previous York model. However, there are a number of key differences, including the comparators included in each of the subpopulations; clinical evidence used and the methods employed in the evidence synthesis; the source of cost data for HAQ-DI and PASI data; and the rate of withdrawal for patients who have initially responded to biologic therapy and baseline characteristics in terms of HAQ-DI and particularly PASI scores. Neither submission reports a list price analysis, instead reporting results using confidential Patient Access Scheme prices.

## Cost-effectiveness results from de novo modelling

The de novo model, which addressed many of the issues of earlier published models, generated incremental cost-effectiveness ratios (ICERs) for three subpopulations according to the position in the pathway of treatment and three subgroups according to severity of psoriasis:

- For subpopulation 1 (one prior DMARD): in the moderate–severe subgroup, the pairwise ICERs for CZP and 300 mg of SEC compared with BSC are £20,870 and £26,064 per QALY, respectively. In the fully incremental analysis, the ICER for 300 mg of SEC compared with CZP is £134,783; therefore, CZP is likely to be the optimal treatment. In the mild–moderate psoriasis group, the pairwise ICERs for CZP and 150 mg of SEC compared with BSC are £23,052 and £21,772 per QALY, respectively. In the fully incremental analysis, CZP is dominated by 150 mg of SEC and, therefore, 150 mg of SEC is likely to be the optimal treatment. In the no concomitant psoriasis subgroup, pairwise ICERs for 150 mg of SEC and CZP compared with BSC are £23,928 and £24,774 per QALY, respectively. In the fully incremental analysis, the ICER for CZP compared with 150 mg of SEC is £346,785 and, therefore, 150 mg of SEC is likely to be the optimal treatment.
- For subpopulation 2 (two or more prior DMARDs): in the moderate–severe subgroup, the pairwise ICERs for CZP and 300 mg of SEC compared with BSC are £21,564 and £29,569 per QALY, respectively. In the fully incremental analysis, 300 mg of SEC is dominated and CZP is extendedly dominated. Of the remaining non-dominated alternatives, ETN is likely to be the optimal treatment, with an ICER of £21,215 compared with GOL. For the mild–moderate psoriasis subgroup, the pairwise ICERs for CZP and 150 mg of SEC compared with BSC are £24,103 and £22,032 per QALY, respectively. In the fully incremental analysis, CZP and GOL are dominated and ADA is extendedly dominated. Of the remaining non-dominated alternatives, ETN is likely to be the optimal treatment, with an ICER of £23,256 per QALY compared with 150 mg of SEC. For the no concomitant psoriasis subgroup, the individual pairwise ICERs for CZP and 150 mg of SEC compared with BSC are £24,103 and £22,032 per QALY, respectively. ETN is likely to be the optimal treatment in this subgroup with an ICER of £23,883 compared with BSC (fully incremental analysis).
- For subpopulation 3 (biologic experienced): in the moderate–severe subgroup, the individual pairwise ICER for 300 mg of SEC compared with BSC is £36,013. In the fully incremental analysis, the ICER for UST versus BSC is £21,684 per QALY and the ICER for 300 mg of SEC is £85,013 per QALY. In the mild–moderate subgroup the pairwise ICER for 300 mg of SEC compared with BSC is £40,639. In the fully incremental analysis, the ICER for UST versus BSC is £24,510 per QALY and the ICER for 300 mg of SEC versus UST is £97,713 per QALY. In the no concomitant subgroup the pairwise ICER for 300 mg of SEC compared with BSC is £44,774. In the fully incremental analysis, the ICER for UST versus BSC is £26,797 per QALY and the ICER for 300 mg of SEC versus UST is £111,927 per QALY.

The model also explores a number of uncertainties through the use of scenario analysis, and found that:

- The optimal treatment in subpopulation 2 was sensitive to the choice of evidence synthesis model.
- In the contraindicated subgroup (subpopulation 4), UST appears to be the most cost-effective treatment in patients with moderate–severe psoriasis (ICER of £19,969 compared with BSC); however, in those with mild–moderate psoriasis or no concomitant psoriasis, 150 mg of SEC appears to be the most cost-effective treatment (ICERs of £19,349 and £22,334 compared with BSC for these two subgroups, respectively).

- In the biologic-experienced subgroup including only secondary failures, CZP seems to be cost-effective compared with BSC, with ICERs of £16,573, £19,113 and £20,973 for the moderate–severe, mild–moderate and no concomitant psoriasis group, respectively.
- The optimal treatment is not sensitive to the use of biosimilar prices for ETN and INF.
- In subpopulation 1, the optimal treatment is consistent across the two scenarios for baseline HAQ-DI score, base-case assumption (1.22) and using a subpopulation-specific baseline HAQ-DI score.
- In subpopulations 2 and 3, aside from the use of the Poole *et al.* (Poole CD, Lebmeier M, Ara R, Rafia R, Currie CJ. Estimation of health care costs as a function of disease severity in people with psoriatic arthritis in the UK. *Rheumatology* 2010;**49**:1949–56) HAQ-DI costs, the optimal treatment is consistent across all scenarios (subpopulation-specific baselines and alternative withdrawal rates).

The PSA demonstrated that, despite the ICERs being broadly consistent between the deterministic analysis and the means of the PSA, there is considerable decision uncertainty regarding the optimal treatment, at both £20,000 and £30,000 per QALY thresholds.

## Discussion

The key strengths of the systematic review are the rigorous methods used and the breadth of the types of study included. The updated York model confers several advantages over current published cost-effectiveness studies, namely the inclusion of the three subpopulations according to the position in the pathway of treatment, the explicit consideration of the severity of concomitant psoriasis and the modelling of subsequent treatments following primary non-response or secondary failure. The York model also facilitates a more consistent basis for evaluating CZP and SEC by ensuring comparability of methods and inputs.

## Conclusions

The NMA results for the biologic-naive subpopulation indicated that, although SEC and CZP were effective across all outcomes after 3 months' therapy, their relative effectiveness compared with other biologics and with each other was uncertain. The results of the economic model indicated that CZP and SEC may be an effective use of NHS resources, depending on the subpopulation (based on prior treatments) and subgroup (according to psoriasis severity). There were a number of limitations to the assessment, mostly driven by data availability issues.

## Suggested research priorities

Adequately powered trials are needed to better inform the efficacy of biologics in biologic-experienced populations. Further research is required to better elucidate the impact of biologics on radiographic disease progression and HAQ-DI in the long term.

## Study registration

This study is registered as PROSPERO CRD42016033357.

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