Certolizumab pegol (CIMZIA®) for the treatment of rheumatoid arthritis

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Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of certolizumab pegol (CZP) for adults with active rheumatoid arthritis (RA) that have not responded adequately to treatment with conventional disease modifying anti-rheumatic drugs (DMARDs) including methotrexate (MTX), in accordance with the licensed indication, based upon the evidence submission from the manufacturer to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. The outcome measures included American College of Rheumatology (ACR) 20, 50 and 70 response rates and quality of life measures after 3 months and 6 months of treatment. The ERG examined the submission's search strategies and considered they appeared comprehensive and that it was unlikely that relevant studies would have been missed. Only English language studies were considered in the submission and non-English language studies relevant to the decision problem may possibly have been ignored. The ERG analysed the first submitted economic model so as to itemise in detail clarification points that were brought to the attention of the manufacturer. In response the manufacturer submitted a modified cost-effectiveness analysis. The ERG undertook further analysis of this second model and other additional submitted evidence. The clinical evidence was derived from two multicentre blinded randomised controlled trials (RCTs) comparing CZP + MTX to placebo + MTX (the RAPID 1 and RAPID 2 trials). RAPID 1 lasted 52 weeks with 982

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patients and RAPID 2 24 weeks with 619 patients. Evidence for clinical effectiveness of CZP in monotherapy came from the 24-week FAST4WARD trial with 220 patients that compared CZP (400 mg every 4 weeks) versus placebo. The three key RCTs demonstrated statistically significant superiority of CZP + MTX versus placebo + MTX and of CZP versus placebo with respect to a variety of outcomes including ACR 20, ACR 50 and ACR 70 measures and quality of life measures at 3 and 6 months. On the basis of results from the indirect comparison meta-analyses, the manufacturer suggested that CZP may be at least as effective as other 'biological' DMARD (bDMARD) comparators and, in a few ACR measures at 3 and 6 months, more effective. CZP is an effective therapy for adult RA patients whose disease has failed to respond adequately to cDMARDs including MTX or who are intolerant of MTX. The cost-effectiveness of CZP relative to other bDMARDs is unclear because the economic modelling undertaken may have ignored relevant effectiveness data and potential differences between trial populations, and so may have included effectiveness results that were biased in favour of CZP; underestimated uncertainty in the relative effectiveness of compared DMARDs; and ignored the potential influence of differences between bDMARDs with regard to adverse events and their related costs and health impacts. The NICE guidance issued in October 2009 states that: the Committee is minded not to recommend certolizumab pegol as a treatment option for people with RA; and the Committee recommends that NICE asks the manufacturer of CZP for more information on the clinical effectiveness and cost-effectiveness of CZP for the treatment of people with RA. On receipt of this information and details of a patient access scheme NICE issued final guidance recommending CZP, under certain criteria, as a treatment option for people with RA.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor.[1] Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of the Institute.

This paper presents a summary of the ERG report for the STA submission that considered the clinical effectiveness and cost-effectiveness of certolizumab pegol (CZP) for adults with active rheumatoid arthritis (RA) that has not responded adequately to treatment with conventional disease modifying anti-rheumatic drugs (cDMARDs) including methotrexate (MTX).[2] CZP is a 'biological' DMARD (bDMARD) whose effectiveness could be compared to cDMARDs or to other bDMARDs administered within their licensed indications.

Description of the underlying health problem

This section is taken from the NICE scope for this STA.

Rheumatoid arthritis is a chronic, disabling autoimmune disease characterised by inflammation of the synovial tissue of the peripheral joints, which causes swelling, stiffness, pain and progressive joint destruction. For a small proportion of people, inflammatory disease outside the joints (e.g. eye and lung disease, vasculitis) can also pose a significant problem. RA is heterogeneous, it is usually a chronic relapsing condition which has a pattern of flare-ups followed by periods of lower disease activity, but in a minority of cases the disease is constantly progressive. Most patients with RA develop damage to affected joints, with the amount of damage ranging from mild to severe. RA has a severe impact on quality of life and it is estimated that 40% of people with RA will stop working within 5 years of diagnosis.

Rheumatoid arthritis is three times more prevalent in women than in men. It can develop at any age, but usually starts between 40 and 60 years of age. RA affects 1% of the population, or approximately 400,000 people in England and Wales. Of these, approximately 15% have severe disease.

People with RA are usually treated in an outpatient setting rather than in primary care. There is no cure, and treatment aims to improve quality of life and to prevent or reduce joint damage.

Treatment for RA usually includes: non-steroidal anti-inflammatory agents (NSAIDs) which reduce pain, fever and joint swelling/inflammation; and DMARDS which slow the disease process and reduce joint damage. Corticosteroids may also be used to control inflammation. DMARDs are usually started soon after diagnosis. MTX and sulfasalazine are two commonly used DMARDs. NICE guidance recommends the use of a TNF (tumour necrosis factor)-α inhibitor (adalimumab, etanercept and infliximab; types of bDMARD) after the failure of two cDMARDs such as MTX and sulfasalazine. NICE guidance recommends the use of rituximab (a bDMARD that depletes B cells) after the failure of a TNF inhibitor, but does not recommend the use of abatacept after the failure of a TNF inhibitor.

Scope of the evidence review group report

The scope for this STA was to address the clinical effectiveness and cost-effectiveness of CZP relative to cDMARDs and to bDMARDs for the treatment of adults with active RA whose disease had not responded adequately to cDMARDs including MTX. The STA was initiated prior to the granting of formal marketing authorisation. The anticipated marketing authorisation for CZP specified a dose regimen of 400 mg administered subcutaneously on weeks 0, 2 and 4, followed by 200 mg every other week. CZP is indicated for use in 'combination' therapy with MTX or as 'monotherapy' (without MTX) for patients intolerant of MTX. The acquisition cost of CZP is £357.50 per 200-mg syringe, excluding VAT (value added tax).

The key sources of evidence on clinical effectiveness of CZP in combination therapy came from two multicentre blinded randomised controlled trials (RCTs) comparing CZP + MTX to placebo + MTX [the RA Prevention of Structural Damage (RAPID) 1[3] and RAPID 2[4] trials]. RAPID 1 lasted 52 weeks with 982 patients and RAPID 2 24 weeks with 619 patients. Evidence for clinical effectiveness of CZP in mono-therapy came from the 24-week FAST4WARD trial[5] with 220 patients that compared CZP (400 mg every 4 weeks) versus placebo. There were no head-to-head trials that compared the effectiveness of CZP to the other bDMARDs. To estimate the relative clinical effectiveness between bDMARDs the manufacturer undertook indirect comparison meta-analyses (ICMs)[6] using the results from various placebo-controlled trials of bDMARDs.

The manufacturer submitted a de novo economic model that was used to estimate the cost per quality-adjusted life-year (QALY) gained from CZP in comparison with anti-TNF agents (adalimumab, etanercept and infliximab) or with rituximab. Model inputs for clinical effectiveness of the different bDMARDs were derived from results from ICMs and based on the American College of Rheumatology (ACR) 20, 50 and 70 response rates[7] after 3 months and 6 months of treatment. The estimated ACR response rates in the absence of bDMARD treatment were single point values (no associated uncertainty) and were obtained by simple aggregation of the rates reported across the control arms of the included trials.

Health-related quality of life (HRQoL) utilities for the first 6 months of treatment were obtained by regression analysis of the relationship between ACR response and European Quality of Life-5 Dimensions (EQ-5D) scores observed for European patients participating in CZP trials. Utilities while continuing on treatment and utility after cessation of treatment were obtained by converting Health Assessment Questionnaire measures using a published algorithm proposed by Brennan *et al*.[8] Costs were mainly obtained from standard sources.

Methods

The ERG report comprised a critical review of the evidence for the clinical effectiveness and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE as part of the STA process.

Owing to the central importance of the RAPID 1, RAPID 2 and FAST4WARD studies, these were formally fully appraised by the ERG, taking advantage of responses to requests for clarification from the manufacturer.

The ERG examined the submission's search strategies and considered they appeared comprehensive and that it was unlikely that relevant studies would have been missed. Only English language studies were considered in the submission and non-English language studies relevant to the decision problem may possibly have been ignored.

The ERG critically appraised the submitted ICM with focus on the validity of selection of studies for inclusion, the reproducibility of results and the exploration of heterogeneity. The ERG considered the relative merits of alternative approaches to the ICM submitted.

The ERG analysed the first submitted economic model so as to itemise in detail clarification points that were brought to the attention of the manufacturer. In response the manufacturer submitted a modified cost-effectiveness analysis. The ERG undertook further analysis of this second model and other additional submitted evidence.

Results

Summary of submitted clinical evidence

The three key RCTs demonstrated statistically significant superiority of CZP + MTX versus placebo + MTX and of CZP versus placebo with respect to a variety of outcomes including ACR 20, ACR 50 and ACR 70 measures and quality of life measures at 3 and 6 months.

On the basis of results from the ICMs, the manufacturer suggested that CZP may be at least as effective as other bDMARD comparators and, in a few ACR measures at 3 and 6 months, more effective. These ICM estimates were associated with considerable uncertainty. Some evidence was presented that CZP inhibits progression of structural damage to joints.

Summary of submitted cost-effectiveness evidence

The inputs for the first model were modified in the second model submitted. Some modifications were introduced in response to NICE's requests for clarification, others depended on new results obtained from unprompted reanalyses of trial data undertaken by the manufacturer. The main changes made were exclusion of adverse events, exact calculation of discontinuation rates and modified annual utility decrement upon cessation of bDMARD treatment. The main results from the second model are shown in *Table 1*. The submission also included an economic analysis encompassing a proposed patient access scheme. At the time, this scheme was not approved by the Department of Health (DoH) and as such it was not considered in the first appraisal meeting.

Commentary on the robustness of submitted evidence

In the three CZP trials there were large numbers of early patient withdrawals from the control arms that were imposed for lack of a rapidly established clinical effectiveness response.

In the RAPID 1 trial, of 199 patients receiving placebo + MTX, 63% had withdrawn by week 16 and 78% by the end of the trial; this compared to 21% and 35%, respectively, of patients receiving CZP. In RAPID 2, 87% of patients in the placebo + MTX arm had withdrawn by the end of the trial (week 24). In the FAST4WARD mono-therapy trial, 54% of control arm patients had withdrawn by week 12 and 74% by the end of the trial at 24 weeks.

The high withdrawal rates at early phases of the CZP trials, especially seen in the control arms,

TABLE 1 *Base-case results from the manufacturer's second economic model using indirect comparison effectiveness analysis*

	Mean cost (£)	Mean QALYs	ICER
Combination therapy			
CZP + MTX	89,158	6.654	–
Etanercept + MTX	86,165	6.589	46,192
Adalimumab + MTX	86,034	6.412	12,937
Rituximab + MTX	82,940	6.362	21,345
Infliximab + MTX	95,599	6.196	CZP dominates
Monotherapy			
CZP	85,424	6.305	–
Etanercept	85,941	6.435	(3991)[a]
Adalimumab	84,201	6.09	5687

CZP, certolizumab pegol; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life-years.
a ICER for etanercept compared with CZP.

necessitated that estimates of effectiveness at later time points required many 'last observations' to be carried forward, and somewhat compromised the robustness of these estimates.

Owing to a lack of head-to-head trials of different bDMARDs, the manufacturer undertook random effects ICMs to gain an estimate of their relative clinical effectiveness.

The effectiveness of CZP relative to other bDMARDs was based on ACR 20, ACR 50 and ACR 70 outcomes measured at 12 and 24 weeks in various trials analysed by ICM. The robustness of these comparisons was potentially compromised by the high withdrawal rates in the CZP trials relative to those observed in the other included trials.

For combination therapy ACR responses at 24 weeks, the ICM included 10 trials [two with CZP (RAPID 1 and 2), three with adalimumab, two with infliximab and one each with etanercept, rituximab and tocilizumab]. Seven trials were used for responses at 12 weeks [two with CZP (RAPID trials), two with etanercept and one each with adalimumab, infliximab and tocilizumab]. For monotherapy ACR responses at 12 and 24 weeks, the ICM included four trials (two with adalimumab and one each with CZP and etanercept).

The reported results from the ICMs (odds ratios) were associated with considerable uncertainty and there were some errors in the reported values for ACR 70. Of the 85 indirect comparisons made between pairs of bDMARDs, only four reached statistical significance. Two of these were for superiority of CZP at 24 weeks in the ACR 20 outcome.

Several aspects of the ICMs reported by the manufacturer were a cause of concern:

(a) The inclusion and exclusion of studies for the ICM did not appear to be systematic.
(b) The inclusion of data from the included studies lacked some consistency.
(c) There was a possibility that relevant information from several excluded studies, including an unpublished industry sponsored randomised trial of CZP + MTX versus MTX + placebo (study C87014), could have been used in the ICM.
(d) There was insufficient consideration and exploration of underlying heterogeneity amongst the studies included for ICM.
(e) The development of effectiveness input for the economic analysis included data for a bDMARD comparator omitted from the subsequent economic analysis, raising the issue of whether data for other omitted bDMARDs should also have been included.
(f) The development of clinical effectiveness input for the economic analysis used a point estimate derived by aggregation across trial control arms and sacrificed some of the strengths of randomisation and underestimated associated uncertainty.

The validity of ICM rests on an assumption of exchangeability between trials such that the placebo arms of the trials are interchangeable. The submission lacked an assessment or discussion of clinical or statistical heterogeneity amongst the trials used for ICM and did not comment on whether baseline characteristics of participants were similar across these RCTs. As such there was no consideration of potential sources of non-comparability of the placebo-controlled arms of the trials.

The ERG undertook an analysis of the heterogeneity amongst the control arms of the studies used in the estimation of effectiveness for the 24-week ACR 20 outcome for combination therapy. This choice was made because it involved the largest number of studies and the largest number of events. The results are shown in *Figure 1*. Data for four study level variables (chosen by the ERG) are also included in the figure.

The control rate in the two CZP RCTs was the lowest amongst the 10 trials, and the I^2 statistic indicated considerable heterogeneity. When the two CZP studies were omitted from the analysis, the I^2 statistic was reduced to 70% and the pooled estimate increased to 28%.

The four study level variables that were looked at as potential contributors to the observed heterogeneity were: entry level MTX dose as a potential indicator of treatment intensity and population differences; percentage withdrawals for the ACR 20 outcome as indicator of completeness of data; duration of RA; and number of previous DMARDs trialed as indicators of possible population differences. For each of these variables the two CZP RCTs were at the extreme of the distributions. The brief examination of heterogeneity amongst the studies used for ICMs indicated that an indirect comparison or mixed-

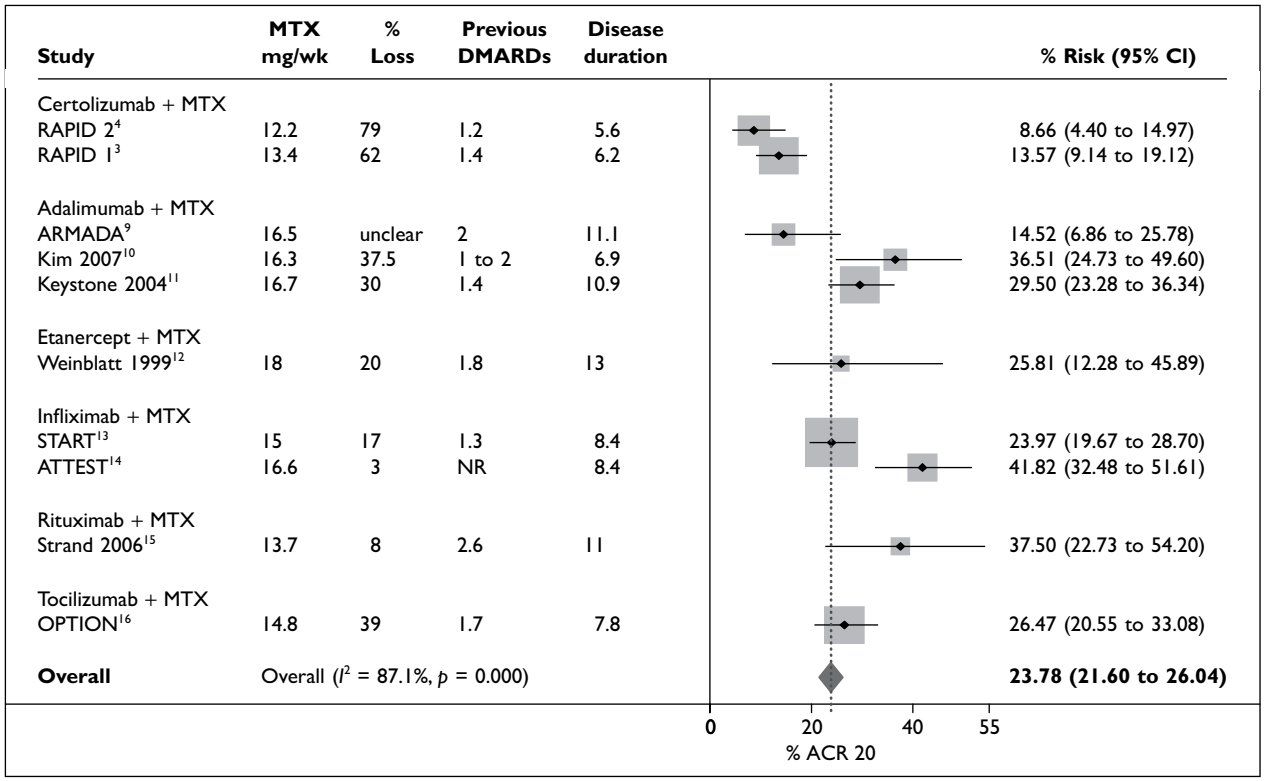

FIGURE 1 *Risk of ACR 20 in placebo plus MTX arms of trials used for ICM at 6 months. ACR, American College of Rheumatology; CI, confidence interval; DMARDs, disease modifying anti-rheumatic drugs; MTX, methotrexate.*

treatment analysis with methods that allow for differences in control rate or baseline risk (similar to the Bayesian analyses undertaken by Nixon *et al.*[17]) probably represents the preferred choice of methodology for the decision problem.

Regarding the economic model, the robustness of quality of life and health-utility inputs was difficult to determine through lack of detail of how many patients were given HRQoL questionnaires and what response rates were elicited. It was not clear how this uncertainty might affect the estimates of cost-effectiveness generated by the model.

Adverse event costs as well as their related health outcomes were not included in the revised model although they were included in the original submission. There was a lack of information to justify this revision, so it was unclear what sources of data were used in this exercise. An assumption of no difference in adverse effects between drugs (CZP, infliximab, adalimumab, etanercept, rituximab) may on average be shown to be reasonable, but on the basis of the submitted information the assumption cannot be considered to be evidence based.

Conclusions

Certolizumab pegol is an effective therapy for adult RA patients whose disease has failed to respond adequately to cDMARDs including MTX or who are intolerant of MTX.

A reasonable interpretation of the results is that there is little convincing evidence that CZP is more or less effective than the comparators examined.

Patients with RA may respond differently to different bDMARDs and effectiveness of a bDMARD for a specific patient is currently unpredictable; an increase in the variety of available bDMARDs might potentially increase the overall proportion of patients responsive to these drugs.

The cost-effectiveness of CZP relative to other bDMARD is unclear because the economic modelling undertaken may have ignored relevant effectiveness data and potential differences between trial populations, and so may have included effectiveness results that were biased in favour of CZP; underestimated uncertainty in

the relative effectiveness of compared DMARDs; and ignored the potential influence of differences between bDMARDs with regard to adverse events and their related costs and health impacts.

Summary of NICE guidance issued as a result of the STA

At the time of drafting this report, the guidance appraisal consultation document issued by NICE in October 2009 states that:

1.1 The Committee is minded not to recommend certolizumab pegol as a treatment option for people with rheumatoid arthritis (RA).

1.2 The Committee recommends that NICE asks the manufacturer of certolizumab pegol for more information on the clinical effectiveness and cost-effectiveness of certolizumab pegol for the treatment of people with RA. This information should be made available for the second Appraisal Committee meeting, and should cover the following issues:

Estimation of the clinical effectiveness of certolizumab pegol relative to other TNF-α inhibitors for the treatment of RA, including consideration of uncertainty around the estimate. In order to clarify this issue the Committee requests:

- provision of a mixed-treatment comparison (MTC) analysis, rather than an indirect comparison meta-analysis
- details of potentially relevant studies, including study C87014, that were excluded from the analysis
- provision of data from the C87014 trial and an assessment of the impact on the incremental cost-effectiveness ratios (ICERs) when the American College of Rheumatology (ACR) response for certolizumab pegol in combination with methotrexate is calculated using data from the C87014 plus the RAPID 1 and 2 trials.

Clarification of how the original economic model was revised:

- further justification of why a utility decrease of 0.037 per year after assessment of clinical response at 6 months was assumed in the original model, but a utility increase of 0.0402 per year was assumed in the revised model
- further details of how the assumed utility decrease of 0.0025 per year when treatment is discontinued was derived
- clarification and a full breakdown of the direct and indirect costs included in the model, including an explanation of why the mean cost for the intervention and comparators differed between the original and revised models, and an explanation of how these changes relate to costs associated with adverse events
- clarification of how incorporating an estimated relationship between ACR 20, 50 and 70 would affect cost effectiveness in the revised model.

Provision of an incremental cost-effectiveness analysis:

- comparing certolizumab pegol with other TNF-α inhibitors (that is, not including rituximab)
- including univariate sensitivity analysis exploring the effect of lowering the estimate for the cost of administering infliximab in line with the range of costs used in previous appraisals
- including a comparison of all treatments with full reporting of results of probabilistic sensitivity analysis, including but not limited to presentation of cost-effectiveness acceptability curves, with all treatments plotted and a scatter plot of all treatments on the same cost-effectiveness plane.

The manufacturer responded to the ACD with a new submission that incorporated a MTC that included the industry sponsored CZP study C87014 and two additional studies previously excluded from the ICMs. The major change to the economic analysis was the introduction of a DOH-approved patient access scheme (PAS) that considerably reduced the initial cost of CZP treatment by making early treatment syringes free of charge.

The MTC more faithfully reflected the inherent uncertainty in the estimates of relative effectiveness of the compared DMARDs (*Figure 2*) and the PAS improved the cost-effectiveness of CZP treatment. The main new cost-effectiveness results submitted are summarised in *Table 2*.

The final appraisal document for this technology was issued by NICE shortly before this article was sent to press. The appraisal document states:

TABLE 2 *Manufacturer's revised cost effectiveness results incorporating mixed-treatment comparison of effectiveness and DOH-approved patient access scheme*

	Mean cost (£)	Mean QALYs	ICER
Combination therapy			
CZP + MTX	85,583	6.654	–
Etanercept + MTX	86,165	6.589	CZP dominates
Adalimumab + MTX	86,034	6.412	CZP dominates
Rituximab + MTX	82,940	6.362	9072
Infliximab + MTX	95,599	6.196	CZP dominates
Monotherapy			
CZP	81,849	6.305	–
Etanercept	85,941	6.435	(31,582)[a]
Adalimumab	84,201	6.09	CZP dominates

CZP, certolizumab pegol; ICER, incremental cost-effectiveness ratio; MTX, methotrexate; QALYs, quality-adjusted life-years.
a ICER for etanercept compared with CZP.

			INDIRECT	MTC
ACR 20 odds ratio				
CZP + MTX	vs	Placebo + MTX	**10.57**	**11.12**
CZP + MTX	vs	Adalimumab + MTX	**2.17**	**2.18**
CZP + MTX	vs	Etanercept + MTX	**1.56**	**1.54**
CZP + MTX	vs	Infiximab + MTX	**3.64**	**3.82**
CZP + MTX	vs	Rituximab + MTX	**2.41**	**2.46**
CZP + MTX	vs	Toclizumab + MTX	**2.70**	**2.85**
ACR 50 odds ratio				
CZP + MTX	vs	Placebo + MTX	**9.08**	**10.01**
CZP + MTX	vs	Adalimumab + MTX	**1.35**	**1.35**
CZP + MTX	vs	Etanercept + MTX	**0.49**	**0.32**
CZP + MTX	vs	Infiximab + MTX	**2.74**	**2.98**
CZP + MTX	vs	Rituximab + MTX	**1.75**	**1.84**
CZP + MTX		Toclizumab + MTX	**1.40**	**1.51**
ACR 70 odds ratio				
CZP + MTX	vs	Placebo + MTX	**10.18**	**12.76**
CZP + MTX	vs	Adalimumab + MTX	**1.61**	**1.85**
CZP + MTX	vs	Etanercept + MTX	**0.89**	**0.43**
CZP + MTX		Infiximab + MTX	**3.10**	**3.78**
CZP + MTX	vs	Rituximab + MTX	**1.85**	**1.89**
CZP + MTX	vs	Toclizumab + MTX	**0.72**	**0.83**

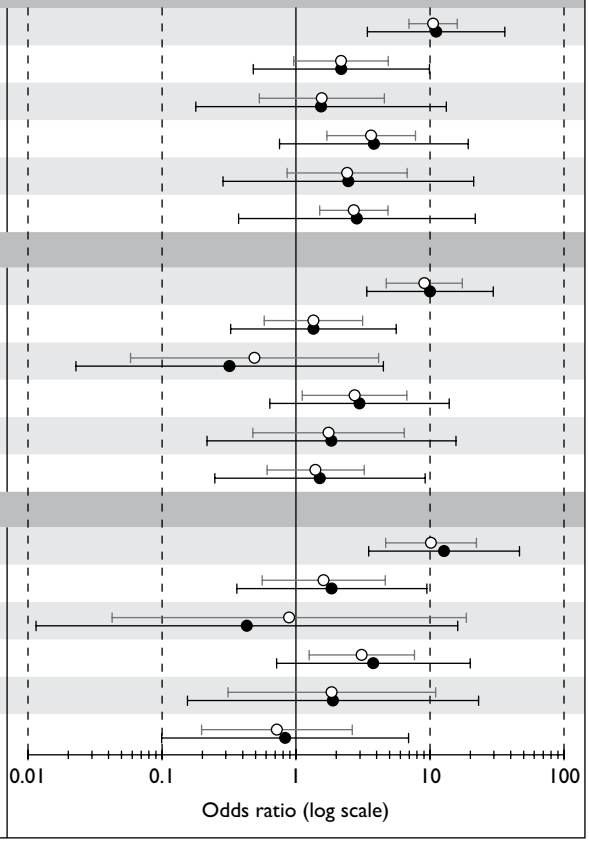

FIGURE 2 *Manufacturer's results for ICM (hollow symbol) and MTC (solid symbol) with associated uncertainty: ACR 20, 50, 70 outcomes. ACR, American College of Rheumatology; CZP, certolizumab pegol; MTC, mixed-treatment comparison; MTX, methotrexate.*

Cetolizumab pegol is recommended as an option for the treatment of people with rheumatoid arthritis only if:

- certolizumab pegol is used as described for other tumour necrosis factor (TNF) inhibitor treatments in 'Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis (NICE technology appraisal guidance 130) and
- the manufacturer provides the first 12 weeks of certolizumab pegol (10 pre-loaded 200-mg syringes) free of charge to all patients starting treatment.

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