Certolizumab pegol (CDP870) for rheumatoid arthritis in adults (Review)

Ruiz Garcia V, Jobanputra P, Burls A, Cabello JB, Gálvez Muñoz JG, Saiz Cuenca ESC, Fry-Smith A

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[Intervention Review]

Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

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ABSTRACT

Background

TNF-alpha inhibitors have been shown to reduce the risk of joint damage and improve physical function and quality of life in people with rheumatoid arthritis (RA). This is the first Cochrane review of certolizumab pegol, a new TNF-alpha inhibitor.

Objectives

To assess the effectiveness and safety of certolizumab pegol (CDP870) in patients with RA who have not responded well to conventional disease modifying anti-rheumatic drugs (DMARDs).

Search methods

We searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2009, Issue 3), MEDLINE (1966 to November 2009), EMBASE (1966 to November 2009), Scopus (January 2004 to November 2009), TOXLINE (until November 2009), Web of Knowledge (until November 2009); websites of the US Food and Drug Administration (FDA) and European Medicines Evaluation Agency (EMEA) (until November 2009), and reference lists of articles.

Selection criteria

Randomised controlled trials that compared certolizumab pegol with any other agent including placebo or methotrexate (MTX) in adult RA patients with active rheumatoid arthritis despite current or prior treatment with conventional DMARDs, such as methotrexate (MTX).

Data collection and analysis

Two authors independently assessed search results, trial quality and extracted data.

Main results

Five trials were included. We included in the analysis 2394 people for effectiveness and 2094 people for safety. The duration of follow-up was from 12 to 52 weeks, and the range of doses of certolizumab pegol were from 50 to 400 mg subcutaneously (sc). In three trials the control was placebo plus methotrexate (MTX) and in two trials it was just placebo. Significant improvements were observed at 24 weeks with the approved dose of 200 mg certolizumab pegol: American College of Rheumatology (ACR) 50% improvement: risk ratio (RR) 6.01 (95% CI 3.84 to 9.40) with an absolute benefit of 29% (95% CI 25% to 34%), number needed to treat to benefit (NNTB) of 4 (3 to 5) and the Health Assessment Questionnaire (HAQ) mean difference (MD) - 0.39 (95% CI -0.45 to -0.32) (scale 0 to 3). At 52 weeks the results were quite similar: ACR 50% improvement RR 5.27 (95% CI 3.19 to 8.71), HAQ mean difference (MD) - 0.42 (95% CI -0.52 to -0.32). Serious adverse events were more frequent for certolizumab pegol 200 mg, Peto OR 2.02 (95% CI 1.24 to 3.30). The most common adverse events with certolizumab pegol 200 mg were: upper respiratory tract infections, Peto OR 2.21 (95% CI 1.15 to 4.25); hypertension, Peto OR 2.81 (95% CI 1.38 to 5.75); and nasopharyngitis, Peto OR 2.71 (95% CI 1.30 to 5.66).

Authors' conclusions

With an overall high grade of evidence this review revealed an improvement of clinical results (ACR50, 28 joint disease activity score (DAS-28) remission and HAQ scores) with certolizumab pegol. Adverse events were more frequent with certolizumab; there was a statistically significant increase in the number of serious adverse events, infections and hypertension.

PLAIN LANGUAGE SUMMARY

Certolizumab pegol for adults with rheumatoid arthritis

This summary of a Cochrane review presents what we know from research about the effect of certolizumab pegol on adult people with rheumatoid arthritis:

The review shows that in people with rheumatoid arthritis who did not respond well to conventional treatments such as methotrexate (MTX):

- certolizumab pegol probably improves pain, function and other symptoms of rheumatoid arthritis;

- certolizumab pegol probably reduces disease activity;

- certolizumab pegol probably reduces joint damage as seen on the x-ray;

- side effects probably were more frequent in patients treated with certolizumab pegol.

What is rheumatoid arthritis and what is certolizumab?

When you have rheumatoid arthritis, your immune system, which normally fights infection, attacks the lining of your joints. This makes your joints swollen, stiff and painful. There is no cure for rheumatoid arthritis at present, so the treatments aim to relieve pain and stiffness, and improve your ability to move.

A new group of biologics has increased the number of treatment options. Certolizumab pegol belongs to this group. It is prescribed as self injection.

Best estimate of what happens to people with rheumatoid arthritis who take certolizumab pegol:

ACR 50 (number of tender or swollen joints, and other outcomes such as pain and disability)

- 29 more people out of 100 experienced improvement in the symptoms of their rheumatoid arthritis after 6 months with certolizumab pegol 200 mg sc (29% absolute improvement)

- 35 people out of 100 experienced improvement in the symptoms of their rheumatoid arthritis

- 6 people out of 100 who took a placebo experienced improvement

Remission (absence of clinical signs of inflammation)

- 9 more people out of 100 experienced remission in the symptoms of their rheumatoid arthritis after 6 months with certolizumab pegol 200 mg sc (12% absolute improvement)

- 11 people out of 100 experienced remission of their rheumatoid arthritis

- 1 person out of 100 who took a placebo experienced improvement

Serious adverse events (can include a serious infections or tuberculosis)

-5 more people out of 100 experienced serious adverse events related and not related to their rheumatoid arthritis after 6 months with certolizumab pegol 200 mg sc (5% absolute improvement)

-10 people out of 100 experienced serious adverse events related and not related to their rheumatoid arthritis

- 5 people out of 100 who took a placebo experienced serious adverse events

Limited data regarding safety of certolizumab pegol use, especially in the long term, is available.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Summary of findings Certolizumab pegol 200 mg sc (with or without MTX) versus Placebo (with or without MTX) for rheumatoid arthritis in adults

Patient or population: patients with rheumatoid arthritis in adults
Settings: adults (18 years old or more) who have persistent disease activity despite current or previous use of conventional disease modifying anti-rheumatic drugs (DMARDs)
Intervention: Summary of findings Certolizumab pegol 200 mg sc (with or without MTX) versus Placebo (with or without MTX)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Summary of findings Certolizumab pegol 200 mg sc (with or without MTX) versus Placebo (with or without MTX)				
ACR 50% improvement Follow-up: mean 24 weeks	**58 per 1000**	**349 per 1000** (223 to 545)	**RR 6.01** (3.84 to 9.4)	965 (2 studies)	⊕⊕⊕⊕ **high**	Absolute risk difference= 29%(95% CI 25% to 34%). Relative percent change= 455% (345% to 593%). NNTB= 4 (3 to 5)
HAQ change from baseline Scale from: 0 to 3. Follow-up: mean 24 weeks	The mean haq change from baseline in the control groups was **1.6** [1]	The mean HAQ change from baseline in the intervention groups was **0.39 lower** (0.45 to 0.32 lower)		965 (2 studies)	⊕⊕⊕⊕ **high**	Absolute risk difference = - 13%(95% CI -11% to -15%). Relative percent change= -24%(-28% to -20%). NNTB=4 (3 to 5)[2]
Serious adverse events Follow-up: mean 24 weeks	**46 per 1000**	**89 per 1000** (56 to 137)	**OR 2.02** (1.24 to 3.3)	964 (2 studies)	⊕⊕⊕⊕ **high**	Absolute risk difference= 5.2%(95% CI 2.3% to 7%). Relative percent change= 101% (-45% to 179%). NNTH= 24 (11 to 96)

Proportion of patients achieving DAS <2.6 (Remission) Follow-up: mean 24 weeks	**12 per 1000**	**45 per 1000** (28 to 73)	**OR 3.88** (2.33 to 6.45)	957 (2 studies)	⊕⊕⊕⊕ **high**	Absolute risk difference= 9%(95% CI 7% to 12%). Relative percent change= 892% (583% to 1687%). NNTB= 31 (17 to 65)
Radiological changes: Erosion Scores (ES) Scale from: 0 to 230. Follow-up: mean 24 weeks	The mean radiological changes: erosion scores (es) in the control groups was **23.1** [1]	The mean Radiological changes: Erosion Scores (ES) in the intervention groups was **0.67 lower** (0.96 to 0.38 lower)		859 (2 studies)	⊕⊕⊕⊕ **high**	Absolute risk difference= -0.29%(95% CI -0.42% to -0.17%). Relative percent change =- 2.90 %(-4. 16% to -1.65 %)
All Withdrawals:	**715 per 1000**	**279 per 1000** (257 to 307)	**RR 0.39** (0.36 to 0.43)	2107 (5 studies)	⊕⊕⊕⊕ **high**	All doses of certolizumab vs placebo 24-52 weeks. Absolute risk difference= 45% (95% CI 49% to 41%). Relative percent change= 61% (64% to 57%). NNTH= 3 (3 to 4)
Withdrawals due to adverse events Follow-up: 24-52 weeks	**23 per 1000**	**43 per 1000** (26 to 71)	**OR 1.93** (1.15 to 3.23)	2071 (4 studies)	⊕⊕⊕⊕ **high**	All doses certolizumab vs placebo. Absolute risk difference= 2.%(95% CI 1% to 4%). Relative percent change= 117% (15% to 310%). NNTH= 51 (19 to 393)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] From RAPID2 trial
[2] RAPID1 used to calculate NNT

BACKGROUND

Rheumatoid arthritis (RA) is a chronic illness which typically causes asymmetrical arthritis. The arthritis causes pain, swelling and stiffness of affected joints. Affected joints may become irreversibly damaged if disease persists. Patients commonly experience fatigue and show changes in the blood, such as anaemia, and an acute phase reaction. In some patients organs such as the skin (as rheumatoid nodules), lungs (pleural inflammation and alveolitis), heart (pericarditis), blood vessels (vasculitis) and the eyes (dry eyes or inflammation) may be affected. RA occurs throughout the world. Important genetic influences are recognised, in particular genes linked to activation of the immune system (Barton 2009), however environmental factors such as an urban versus a rural environment and smoking are also associated with an increased risk of RA (Edwards 2005). People of all ages are affected but the disease begins most commonly between the ages of 40 and 70 years. Three times as many women as men are affected and the population prevalence in Western countries is between 0.5 and 1%. The incidence of RA rises with increasing age (Doran 2002) and RA is associated with reduced life expectancy, particularly due to cardiovascular disease (Meune 2009) but in early years also due to pulmonary disease and lymphoma (Young 2007). Significant functional limitations occur in 15% of patients five years after disease onset and around a third of those in paid work experience work disability (Young 2000). In Spain, RA causes around 10% of total disability and 5% of transitory disability (Carmona 2002) including occupational disability (Doeglas 1995).

The objective of treatment in early disease is to induce remission, and at all stages of disease to control symptoms of joint pain and stiffness, improve function and quality of life and minimise the risk of structural damage by reducing inflammation. These objectives may be met and the prognosis improved by timely use of disease modifying anti-rheumatic drugs (DMARDs), such as methotrexate (Landewe 2003).

RA is characterised by immunological activation of many cell types and a network of cytokines, particularly tumour necrosis factor alpha (TNF-alpha) (Brennan 2008). Inhibitors of TNF-alpha have been a major development in the treatment of RA. Randomised trials have shown that these drugs are highly effective in patients with RA who have not responded well to conventional DMARDs. TNF-alpha inhibitors have been shown to reduce the risk of joint damage, improve physical function and quality of life (Chen 2006). A systematic review of infliximab and adalimumab showed that the risk of malignancy and serious infection was increased with odds ratios of 3.3 (95% confidence interval (CI) 1.2 to 9.1) and 2.0 (95% CI 1.3 to 3.1) respectively (Bongartz 2006). Five agents are currently licensed for use in RA in Europe and the US. These are adalimumab (Navarro Sarabia 2005), etanercept (Blumenauer 2003), golimumab (Singh 2010), infliximab (Blumenauer 2002) and now certolizumab. No controlled trials have compared one TNF inhibitor against another. An important limitation of their wide use is the high cost, between 10,000 and 25,000 USD per patient a year.

Certolizumab is a newly approved TNF inhibitor and consists of a humanised immunoglobulin fragment (Fab) conjugated to polyethylene glycol (PEG), also termed pegylation. Pegylation of this molecule yields a longer half-life and reduces the need for frequent dosing (Choy 2002). However lasting immunosuppression may be disadvantageous in the event of infections such as tuberculosis (Bongartz 2006).

OBJECTIVES

To determine the efficacy and safety of certolizumab pegol (CDP870) compared to placebo or any disease modifying anti-rheumatic drug (DMARD) in patients with rheumatoid arthritis (RA) who have not responded well to conventional DMARDs.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs)

Types of participants

Adults (18 years of age and older) with RA who have persistent disease activity despite current or previous use of conventional DMARDs.

Patients with RA were defined as those meeting the American College of Rheumatology (ACR) 1987 revised criteria (Arnett 1988) for RA. That is to say, they must have had an active form of the disease as demonstrated by at least two of the following symptoms:

1. three or more tender joint areas observed by a physician;
2. three or more swollen joint areas observed by a physician;
3. duration of early morning stiffness > 30 minutes;
4. acute phase reactants such as Westergren erythrocyte sedimentation rate (ESR) more than 30 mm/hour or C reactive protein (CRP) more than 10 mg/mL.

Types of interventions

The intervention was certolizumab pegol (CDP870) at any dose. The comparators were placebo or any disease modifying anti-rheumatic drug including other biologic agents used to treat RA.

Types of outcome measures

The major outcomes for this systematic review were:

- the proportion of patients achieving an ACR50;
- frequency of adverse events;
- health-related quality of life, such as the Health Assessment Questionnaire (HAQ) or Short Form Health Survey (SF-36).

ACR50 is defined as a 50% improvement in the number of tender and swollen joints and a 50% improvement in at least three of the following items: observer evaluation of overall disease activity, patient evaluation of overall disease activity, patient evaluation of pain, a score of physical disability, or improvements in blood acute-phase responses.

The following adverse events were sought: headache, fever, blood disorders, laboratory disorders, abdominal pain, nasopharyngitis, nausea, respiratory tract infections, urinary tract infections, neck pain, congestive heart failure, pruritus and anaphylaxis. Serious adverse effects were defined as malignancies; all infections, especially tuberculosis; and death. All causes of discontinuation of the medication were sought.

Minor outcomes were:

- ACR20 and ACR70 (a 20% or 70% improvement in the parameters described above);
- Disease Activity Score (DAS28, or other versions of DAS) and
- radiological changes (erosion score, modified total Sharp score, joint space narrowing).

Search methods for identification of studies

Electronic searches

The search strategy used the revision of the Cochrane Highly Sensitive Search Strategy (HSSS) for PubMed (Glanville 2006) and the best sensitivity filter developed by the Hedges Team (Wong (a) 2006; Wong (b) 2006) and followed the Cochrane Musculoskeletal Review Group recommendations. Searches included both MeSH headings and text terms for CDP870 and rheumatoid arthritis. We performed a search and, before the review was concluded, we updated the searches. The first and the second search strategies are shown in the appendices: MEDLINE (Appendix 1); EMBASE (Appendix 2); CINAHL (Appendix 3); Cochrane Database of Systematic Reviews (CDSR) and CENTRAL, HTA, DARE, NHS EED (*The Cochrane Library)* (Appendix 4); SCOPUS (Appendix 5); TOXLINE (TOXNET) (Appendix 6).

Safety data were obtained from clinical trials. The search strategy combined index and text terms for CDP870 and adverse effects reported in RCTs of certolizumab pegol and another anti-TNF alpha, with a strategy based on Golder (a) 2006. No language restrictions were applied. Search strategies to identify studies were carried out following the Cochrane Musculoskeletal Review Group recommendations.

The following databases were searched: Cochrane Central Register of Controlled Trials Register (CENTRAL) (*The Cochrane Library 2009*, Issue 3); MEDLINE (1966 to November 2009; EMBASE (1966 to November 2009); Web of Knowledge (until November 2009); Scopus (January 2004 to November 2009). The Food and Drug Administration (FDA) and the European Medicines Evaluation Agency (EMEA) websites were also searched (until November 2009). We performed a search, which we updated prior to finishing the review.

Searching other resources

1. Abstracts for the two key annual international rheumatology meetings, the American College of Rheumatology and the Congress of the European League Against Rheumatism (2006 to December 2008) were handsearched.
2. We consulted the information made available by the main researchers and sponsors.
3. We reviewed information on the clinical trial meta-register database (www.controlled-trials.com/mrct/).
4. We looked for Health Technology Assessment reports from the European, Canadian, North American and Australian national agencies to identify further trials.
5. The reference lists of all identified studies were inspected for more trials.
6. When published data were missing, incomplete, or inconsistent with the trial protocols, further information was sought from the authors and manufacturers (UCB) to request additional information.

Data collection and analysis

Selection of studies

Inclusion criteria

1. RCTs that compared certolizumab pegol with any other agent including placebo in adult RA patients with active RA despite current or prior treatment with DMARDs.
2. Trials that were fully published as a paper or available as a complete trial report. Where published only as abstracts the trial reports were requested from the manufacturers.
3. Studies having at least three months of follow-up to assess effectiveness.

To assess safety we also sought studies having a suboptimal length of follow-up, from eight weeks.

Exclusion criteria

1. Trials of certolizumab pegol in juvenile arthritis, Crohn's disease, psoriatic arthritis and other forms of spondyloarthritis.

2. Trials of certolizumab pegol comparing different doses or routes without another active or placebo control group (except for use for assessing safety outcomes).

3. Studies reporting solely on laboratory measures aimed at investigating disease or treatment mechanisms and which did not report relevant clinical outcomes.

4. Observational studies of certolizumab pegol.

5. Interim results of trials.

Data extraction and management

Two review authors independently reviewed titles and abstracts of studies identified in the search to assess which studies might potentially meet the inclusion criteria. Where there was doubt, the full article was acquired for further inspection. Potential studies identified by this process were then obtained and two authors independently screened them to see if they met the review criteria using a Web interface. A final table was produced in Excel. We did not need to resolve any disagreements through discussion.

Data were extracted, when possible for intention-to-treat populations, as raw numbers plus any summary measures with standard deviations, confidence intervals and P values of the outcomes reported. These were compiled into an Excel spreadsheet. Differences of opinion and data discrepancies were to be resolved by reference to a third review author (Encarnación Saiz) but that did not happen.

Assessment of risk of bias in included studies

According to the recommendations in the Cochrane Handbook (Higgins 2008), the risk of bias was assessed by creating a 'risk of bias' table for each study and a summary is presented below as a risk of bias graph.

The main criteria used to measure the risk of bias included: blinding of participants, allocation concealment, random sequence generation, incomplete outcome data, selective reporting of outcomes, and other biases (early stopping of trials or imbalance in the baseline characteristics of people in the different groups). The risk of bias in each study was explicitly judged on the basis of each criterion using the following standard: Yes (low risk of bias), No (high risk of bias), Unclear (either lack of information or uncertainty over the potential bias). These criteria were included in tables. Disagreements were resolved by discussion between the two review authors. If needed, a third review author was available for discussion, but we did not have any disagreements.

Measures of treatment effect

It has been shown that risk ratio (RR) is more intuitive (Boissel 1999) than odds ratios and that odds ratios tend to be interpreted as RR by clinicians (Higgins 2008). The risk difference was used to quantify the number needed to treat (NNT) (Laupacis 1988). For continuous data we used mean differences when the results were measured in the same way in the different studies. We used standardised mean differences when the results obtained were conceptually the same but used different measurement scales. The central estimate (mean) and standard deviation were recorded. Where these were not directly stated they were calculated from the standard error or the different means and their respective confidence intervals (CIs) or P values. When medians and interquartile ranges were the only data provided, the median was used as a proxy measure of the mean and the difference between the first and third interquartile as equivalent to 1.35 of the SD.

Unit of analysis issues

Most of the clinical trials had a simple parallel group design with participants individually randomised to one of two intervention groups, and unit of analysis was not an issue in this review.

Dealing with missing data

We carried out an intention-to-treat analysis. Everyone allocated to the intervention was counted whether they completed the follow-up or not. We have assumed that those who dropped out had no change in their outcome. This rule is conservative concerning response to treatment because it assumes that those discontinuing the studies would not have responded. It is not conservative concerning adverse effects but we felt that assuming that all those leaving early had developed side effects would overestimate risk.

When published data were missing, incomplete or inconsistent with the RCT protocols or meeting abstracts, we asked for further information from the authors and manufacturers. We only excluded abstracts of studies that were interim reports of studies that had not yet finished recruiting.

Assessment of heterogeneity

We have explored heterogeneity between the trials using the Chi ^{2} test for heterogeneity, using a 10% level of significance, and the I^2 statistic. We complied with the recommendations put forward in the Cochrane Handbook, which determine that a 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% considerable heterogeneity (Deeks 2008)

Assessment of reporting biases

We planned to explore reporting bias using funnel plots and heterogeneity when doing a meta-analysis for 10 or more studies. Since only five studies met the criteria, a funnel plot could not be made.

Data synthesis

The need to analyse the results according to a fixed-effect or random-effects analysis was explored (Laird 1990); or in the event of

significant heterogeneity a decision may be made to not present a combined result of the two (Schulz 1993). We have used fixed-effect models throughout, except where heterogeneity exists in which case a random-effects model was used as it introduces less bias than excluding trials altogether. The number needed to treat to benefit (NNT or NNTB) and the number needed treat to harm (NNTH) were calculated. The mean difference was used to calculate the benefit (absolute change expressed as both a percentage and in its original units) for continuous outcomes such as HAQ, SF-36 and radiological changes.

When studies were homogeneous we pooled them (for example, similarities between participants, interventions, outcome assessment). Forest plots (mean differences and risk ratios) were done. We chose the fixed-effect model to pool the data because statistical heterogeneity was not high and it was reasonable from a clinical point of view.

We have used the 'Grades of Recommendation, Assessment, Development and Evaluation' developed by the GRADE Working Group for grading the quality of evidence. The GRADE approach specifies four levels of quality. The highest quality rating is for randomised controlled trial evidence. Review authors can, however, downgrade randomised trial evidence to moderate, low, or even very low quality evidence depending on the presence of five specific factors (see Handbook Chapter XII (Higgins 2008)). We used the GRADE software to provide an overall grading of the quality of the evidence by outcome.

Subgroup analysis and investigation of heterogeneity

If heterogeneity was detected then a subgroup analysis would be carried out (Yusuf 1991), or a meta-regression, in order to explain it (Thompson 1999). Subgroup analyses were planned for the duration of the illness (approximately three years evolution), patients' sex, drug dose and administration and methodological quality.

Sensitivity analysis

The main criteria applied to measure the risk of bias included: blinding of participants, allocation concealment, random sequence generation, incomplete outcome data, selective outcome reporting and other sources of bias.

RESULTS

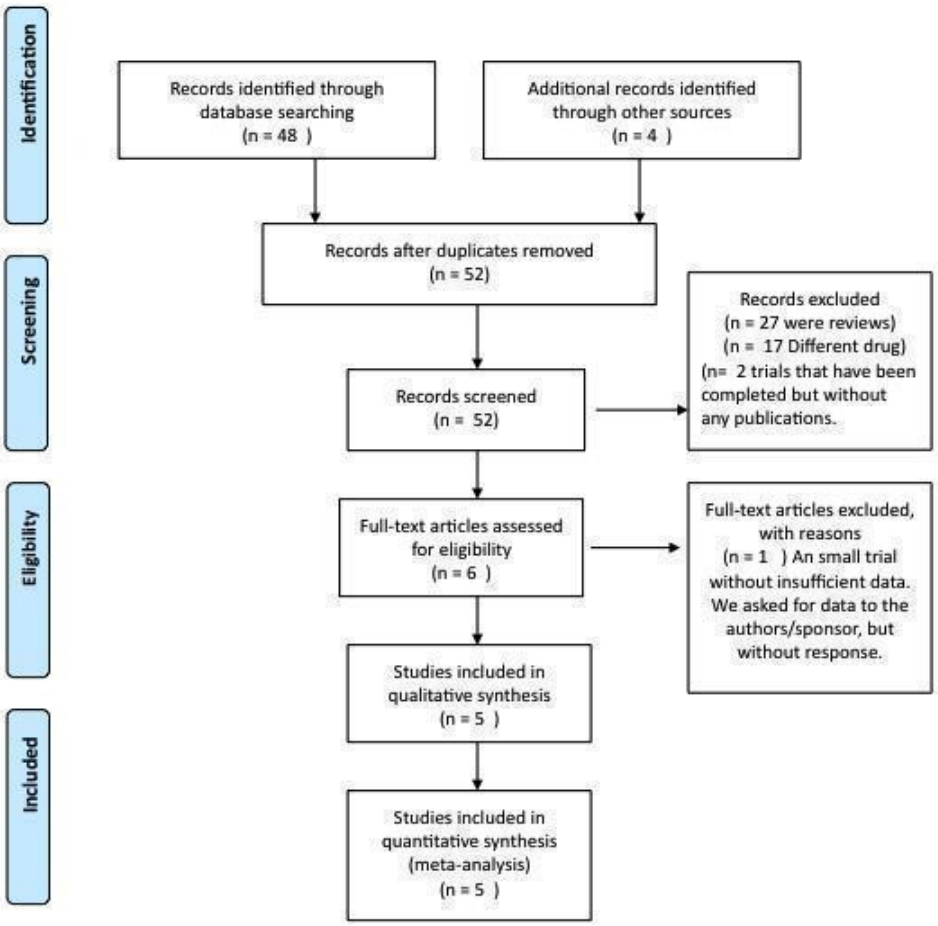
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

See flow chart (Figure 1)

Figure 1.



We screened 52 papers. We excluded 27 related to reviews; 17 that had a different drug of study; and two related to trials for which no informative papers were published. Six full text articles were assessed further.

Included studies

Finally five trials involving 2394 people for effectiveness studies and five trials with 2094 people for safety studies were included (see Characteristics of included studies table and Table 1). Of the trials identified (CDP870-004 2001; Choy 2002; FAST4WARD 2005; RAPID1 2005; RAPID2 2007; CDP870-014 2009), all trials were used to assess effectiveness and safety except two (CDP870-004 2001; Choy 2002). Due to the short follow-up to assess effectiveness in Choy's study, it was only included for safety data. The results of the other study (CDP870-004 2001) on effectiveness were considered in the present review and the study did not report any safety data. The data from these two studies could not be meta-analysed together with the rest of the studies due to the different follow-ups and doses used.

Phase II

Choy 2002

This was an 8-week, randomised, double-blind, placebo-controlled study. Thirty-six patients meeting the American College for Rheumatology (ACR) classification criteria for rheumatoid arthritis were included. Patients were required to have active disease, defined by having at least three of the following four criteria: tender joint count (TJC) > 6, swollen joint count (SJC) > 3 (based on 28 joint counts), morning stiffness of > 45 minutes, and ESR > 28 mm/h. Patients had to have failed treatment with at least one DMARD and have been off DMARD treatment for at least four weeks. Corticosteroids at a dose of prednisolone $\leq$ 7.5 mg per day were permitted.

The trial was a phase II ascending-dose group study in which 36 patients were divided into three groups. Each group of 12 patients was randomly assigned to a single intravenous infusion of placebo (four patients) or 1, 5 or 20 mg/kg of certolizumab (eight patients each). Thus a total of 12 patients were allocated placebo. The outcomes of the ACR20, ACR50, ACR70; pain score (0 to 10 cm); disease activity score (DAS); tender joint count (TJC); swollen joint count (SJC); Health Assessment Questionnaire (HAQ); and C-reactive protein (CRP) were examined after one, two, four, six and eight weeks of treatment. Following the blinded period of eight weeks, 32 patients received a single open-label infusion of either 1, 5 or 20 mg/kg of certolizumab, if the initial infusion was well tolerated. This study was only considered to assess safety because follow-up was less than eight weeks.

No funding sources were declared in the publication but Dr Choy confirmed that this study was funded by Celltech.

CDP870-004 2001

This was a double-blind, multiple dose, 12-week, placebo-controlled dose-ranging study to compare the efficacy and safety of certolizumab pegol and placebo in 326 participants with a history of inadequate response or intolerance to at least one DMARD and active RA at screening. DMARD therapy was discontinued at least one month prior to the start of the study; concomitant NSAID and $\leq$ 10 mg prednisone or equivalent/day were allowed. Patients in panel 1 received: 50, 100, 200, 400 mg subcutaneously (sc) every four weeks; and in panel 2: 600 and 800 mg sc every four weeks. The primary measure of efficacy was ACR20 responder rates at week 12. A number of secondary efficacy measures were also included, for example the ACR20 at all available visits except week 12, ACR50, ACR70, a subset of the ACR criteria, DAS. We only got data for ACR20, ACR50 and ACR70 in panel 1 (Keystone study) and panel 2 from the EMEA 2009. No data were described for adverse events that included mortality, tuberculosis, serious adverse events and serious infections.

Phase III

We retrieved four phase III trials (FAST4WARD 2005; RAPID1 2005; RAPID2 2007; CDP870-014 2009). All the studies used a lyophilised formulation but RAPID2 used a liquid formulation that was a proposed commercial form. All trials were funded by UCB. Data from CDP870-014 2009 were provided by UCB from the Clinical Study Summary www.clinicalstudyresults.org/documents/company-study˙4348˙0.pdf and the EMEA 2009 reports. This study was completed in 2004 but there are not any papers from this trial.

In Table 1 demographic and baseline characteristics in phase III trials are shown: age, gender, rheumatoid factor (RF) positive, MTX concomitant dose, number of previous DMARDs, basal HAQ, and basal DAS28 among others outcomes. We have also added the follow-up. Table 2 provides the flow chart of patients in phase III studies.

Excluded studies

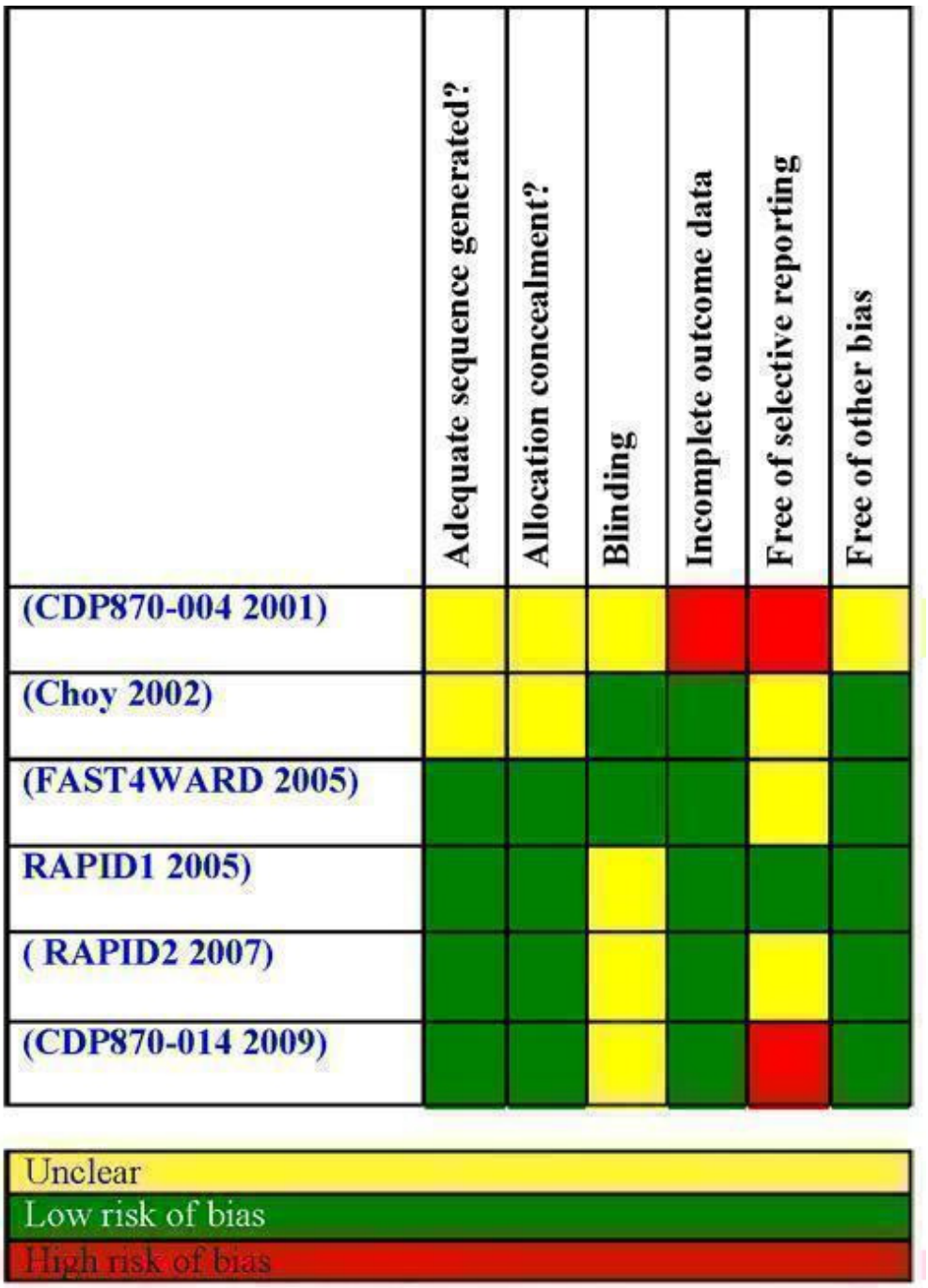
The main reasons for exclusion were: 1) reviews, 2) different drugs, 3) another outcome reported. See the table of Characteristics of excluded studies.

Risk of bias in included studies

All studies reported adequate methods of randomisation and allocation concealment. Blinding was unclear for some trials. The overall possibility of bias seemed to be low. Refer to Figure 2 and

'Risk of bias' tables for more information on all criteria for risk of bias.

Figure 2. Methodological quality summary: review authors's judgements about each methodological quality item for each included study.



Allocation

All six studies but the two phase II trials (CDP870-004 2001; Choy 2002) reported adequate methods of allocation concealment and randomisation. Neither the authors nor UCB provided any further detail. Four studies (FAST4WARD 2005; RAPID1 2005; RAPID2 2007; CDP870-014 2009) used the interactive voice response system (IVRS) method of allocation concealment. The risk of bias seemed low.

Blinding

RAPID1 2005 did not disclose the methods of blinding but explained: "Patients who withdrew at week 16 or who successfully completed the trial were offered enrolment in an open-label extension study of certolizumab pegol 400 mg every 2 weeks. Radiographs were read at a central location by 3 independent readers. Readers were blinded as to the patient's identity, clinical data, treatment, and time point (sequence) at which the radiograph was taken".

RAPID2 2007 did not disclose the methods of blinding, but explained: "Radiographs were read centrally and blinded (for treatment, visit and patient identification) and independently by two experienced readers".

FAST4WARD 2005 disclosed methods of blinding: "Solutions of active drug or placebo were prepared by the pharmacist or other unblinded, qualified site personnel, before distributing to blinded study personnel for administration".

CDP870-014 2009 did not disclose the methods of blinding ("Subjects who completed the current study or who withdrew on or after the Week 12 visit were eligible to participate in the open-label safety study (CDP870-015)". Neither the EMEA report nor the clinical study summary that UCB sent to us provided any further information on this issue.

CDP870-004 2001 did not disclose the methods of blinding.

Choy's study disclosed the methods of blinding: "Placebo (sodium acetate buffer) was given similarly as a single intravenous infusion of 100 ml over 60 min". Is unlikely that the blinding could have been broken.

In some studies we had some information about blinding (regarding the readers of radiographs) but not for the major outcomes (ACR50, HAQ, etc). So the risk of bias for outcomes such as ACR50 and HAQ could be different in each study, and the risk of bias was unclear.

Incomplete outcome data

All studies except the small phase II trial (CDP870-004 2001) reported adequate methods of handling missing outcome data.

In all the studies, as expected there were higher losses in the placebo groups compared with the active treatment groups, due to the lack of efficacy of the placebo. We have no data from CDP870-004 2001; and in the Choy 2002 study, 50% were missing data in the placebo group versus 9% in the different certolizumab groups. In phase III trials, missing data were: 1) 19% in the placebo group and 20% in the certolizumab group in FAST4WARD 2005; 2) 33% in the placebo group and 26% in the certolizumab group in CDP870-014 2009; 3) 79% in the placebo group, 31% in the certolizumab 200 mg group and 35 % in the certolizumab 200 mg group in RAPID1 2005; 4) 87% in the placebo group, 30% in the certolizumab 200 mg group and 27% in the certolizumab 200 mg group in RAPID2 2007.

The risk of bias seemed low.

Selective reporting

We could not discard the possibility of selective reporting in the trials, but not for the major outcomes. The risk of bias seemed high in 50% of studies.

FAST4WARD 2005 was poorly described: "ACR20, safety, health outcome measures and immunogenic profiles"; so it was difficult to know if some outcomes were not reported.

In CDP870-014 2009 ACR20, HAQ disability index and acute phase reactant (CRP) were described in the clinical study summary but the results only showed ACR20; no papers have been published.

All the outcomes reported in RAPID1 2005 on the Internet were shown in the paper.

We did not find details on the Internet of the protocol for RAPID2 2007 and Choy 2002.

In CDP870-004 2001 ACR20, ACR50, ACR70, a subset of the ACR criterion, DAS responder rates at week 12 were studied, but only ACR20 was reported.

Other potential sources of bias

All studies included in this review were sponsored by the manufacturer of certolizumab. We did not detect other potential threats to validity, such as early stopping or imbalance in the groups (relating to the baseline characteristics).

We searched for more trials as well as for more information regarding those trials that we had found as unpublished trials during the second search: NCT00160602 (see Characteristics of ongoing studies table). But no information was found, neither from the sponsors nor from any publication, so we cannot discard a serious bias.

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings certolizumab pegol 200 mg sc (with or without MTX) versus placebo (with or without MTX) for rheumatoid arthritis in adults

When we were about to finish this review, new data came out (from EMEA 2009; NICE 2009). As new trials were reported, we decided to perform less restrictive searches to be sure that we had not missed more trials. The strategies for these searches are presented in the appendices section (Appendix 1; Appendix 2; Appendix 3; Appendix 4; Appendix 6; Appendix 7).

The analysis was performed depending on the drug exposure time for doses of 200 mg and 400 mg sc, since these were the doses that appeared in the trials. As we had two periods of follow-up (six months and one year) in one study, we could not pool them, thus we pooled each outcome at each follow-up. Moreover, we had studies with more than one dose so we split the placebo arm to obtain a pooled value.

We used RR and the Peto odds ratio; we did not find any outcome using different measures for the same construct, therefore standardized mean difference was not used in this review.

Major outcomes

ACR50

Significant improvements were observed for all doses at any given time for the ACR50, ACR20 and ACR70. We calculated NNT from the risk ratio according to the formula NNT= 1/ACR*(1-RR), where ACR = assumed control risk and RR = risk ratio (see effectiveness tables, ACR Table 3, Data and analyses).

The main outcome ACR50 showed, for any dose at 24 weeks, a RR of 3.26 (95% CI 2.47 to 4.29) and at 52 weeks a RR of 2.58 (95% CI 1.83 to 3.62). The NNT was close to 5.

Adverse events (see Table 4)

We reported all adverse events in Data and analyses but not all of them were commented on in the present section, only those that we thought were the most interesting (see Table 4). We used Peto odds ratio (Peto OR) where the events rate was < 10%.

Any adverse event

We pooled data on any adverse event from four trials (CDP870-004 2001; FAST4WARD 2005; RAPID1 2005; RAPID2 2007): certolizumab 200 mg RR 1.21 (95% CI 1.08 to 1.35) and certolizumab 400 mg RR 1.20 (95% CI 1.10 to 1.30).

We excluded Choy's study because it showed more events than patients in the certolizumab group (62 events in 24 patients), as well as in the placebo group (19 events in 12 patients). Thus the RR could not be estimated.

Serious adverse events (SAE) as defined in the studies

Important adverse events were reported in all the studies. In FAST4WARD 2005 they were not defined and, furthermore, were calculated as the number of new cases per 100 patient-years (censored at the time of the first event by preferred term). In RAPID1, adverse events were defined according to the Medical Dictionary for Regulatory Activities (version 9.0). RAPID2 2007 described which severe infections were considered: erysipelas, disseminated tuberculosis, peritoneal tuberculosis, pulmonary tuberculosis, gastroenteritis, postoperative wound infection, tooth abscess and urosepsis, etc. The clinical study summary of CDP870-004 2001 did not define serious adverse events.

We reported adverse events depending on the doses: SAE for certolizumab 200 mg and any follow-up (Peto OR 2.02, 95% CI 1.24 to 3.30) and SAE for certolizumab 400 mg and any follow-up (Peto OR 1.92, 95% CI 1.30 to 2.83); 153 events were reported in the certolizumab groups versus 45 events in the control groups. See more details in Analysis 8.6; Analysis 9.7.

Adverse events: severe intensity as defined in the studies

There were no differences in the number of severe intensity adverse events between patients treated with 400 mg of certolizumab (Peto OR 1.24, 95% CI 0.79 to 1.95) and patients treated with 200 mg (RR 1.21, 95% CI 1 to 1.47). Moreover, treatment interruptions were similar with both doses: 68 events in the certolizumab groups were reported versus six events in the control groups. See more details in Analysis 8.4; Analysis 9.4.

Adverse events leading to death as defined in the studies

We did not find statistically significant differences in the number of adverse events leading to death between placebo and certolizumab-treated groups. Eight events in the certolizumab groups were reported versus two events in the control groups. Although the confidence interval was wide and non-significant for death, it has to be highlighted that it is due to the absence of mortality in the control groups. See more details in Analysis 8.8; Analysis 9.8.

Death

In RAPID1 2005, 2008, in the placebo treated group one patient died of myocardial infarction. In the certolizumab 200 mg treated group, one patient died of hepatic neoplasm, another died of peritonitis and cirrhosis and one more died during the post-treatment period (> 84 days after the last injection). In the certolizumab 400 mg treated group one died of cerebral stroke, one of myocardial necrosis, one of cardiac arrest and one of atrial fibrillation.

In RAPID2 2007, 2008, in the certolizumab 200 mg treated group one patient died of myocardial infarction; one patient died during the study in the certolizumab 400 mg treated group (fracture, shock), which was assessed as unlikely to be related to the study medication.

In Choy 2002, in the open phase, one patient in the certolizumab treated group (20 mg/kg CDP870) died from complications following rapid drainage of a large, chronic rheumatoid pericardial effusion. In the opinion of the investigator this event was unrelated to treatment with CDP870.

No deaths were reported in FAST4WARD 2005 and CDP870-

014 2009.

For certolizumab 200 mg the Peto OR was 1.85 (95% CI 0.29 to 11.86); and for certolizumab 400 mg the Peto OR was 2.16 (95% CI 0.40 to 11.79).

Serious adverse infections (SAI)

This composite outcome included any severe event of infections, infestations and tuberculous infections (disseminated tuberculosis, peritoneal tuberculosis, pulmonary tuberculosis, lymph node tuberculosis, tuberculosis), lower respiratory tract infection and obstructive chronic bronchitis with acute exacerbation. More serious adverse infections were reported in the certolizumab 200 mg treated group (Peto OR 3.30, 95% CI 1.45 to 7.51) and in the certolizumab 400 mg treated group (Peto OR 3.25, 95% CI 1.65 to 6.39); 58 events were reported in the certolizumab groups versus six events in the control groups. See more details in Analysis 8.7; Analysis 9.6.

Tuberculosis

A significant increase in the number of cases of tuberculosis was observed in both groups: five patients (0.8%) in the certolizumab 200 mg group and five patients (0.7%) in the certolizumab 400 mg group versus no cases in either placebo group: certolizumab 200 mg Peto OR 4.53 (95% CI 0.71 to 29.11); certolizumab 400 mg Peto OR 4.55 (95% CI 0.71 to 29.11). Both doses (200 and 400 mg) appeared to have a non-significant confidence interval because of the absence of events in the control group. Only one phase III trial (CDP870-014 2009) did not provide any data on tuberculosis incidence. In RAPID1 a total of five patients (one each from Estonia, Bulgaria, and Ukraine; two from Russia) developed tuberculosis after 1.5 to 9 months of treatment. In RAPID2, five patients in the certolizumab pegol arms developed tuberculosis (three from Russia, one each from Poland and Latvia).

Different infections

The types of different infections reported (pneumonitis, bacterial arthritis, mastitis, urinary tract infection, herpes viral, bacterial peritonitis and opportunistic infection) are presented in figures in 'Data and analyses'. Upper respiratory tract infection and nasopharyngitis were more frequent with certolizumab 200 mg than in the placebo group (Peto OR 2.21, 95% CI 1.15 to 4.25; Peto OR 2.71, 95% CI 1.30 to 5.66 respectively). Nasopharyngitis was more frequent with certolizumab 400 mg than in the placebo group (Peto OR 2.99, 95% CI 1.50 to 5.95).

Other adverse events

Hypertension was more frequent with both doses of certolizumab than in the placebo group: certolizumab 200 mg, Peto OR of 2.81 (95% CI 1.38 to 5.75); certolizumab 400 mg Peto OR of 3.23 (95% CI 1.71 to 6.08). The following secondary events: headache, fever, blood disorders, laboratory disorders, abdominal pain, nasopharyngitis, nausea, respiratory tract infections, urinary tract infections, neck pain, congestive heart failure, pruritus and anaphylaxis are described in detail in the 'Data and analyses' tables 8 and 9.

Health-related quality of life

The Health Assessment questionnaire (HAQ) scale ranged from 0 to 3, with a negative change indicating improvement.

The findings showed an improvement in quality of life measured as HAQ and SF-36 (in mental and physical components) at any time of follow-up (see 'Health-related quality of life' tables, Table 5).

HAQ disability index (Di), 24 weeks, any dose: MD -0.41 (95% CI -0.46 to -0.35); HAQ-Di 52 weeks, any doses: MD-0.43 (95% CI -0.52 to -0.35).

SF-36 physical component summary (PCS), 24 weeks, any dose: MD 5.47 (95% CI 4.47 to 6.48); SF-36 PCS, 52 weeks, any dose: MD 6.47 (95% CI 5.13 to 7.81).

SF-36 mental component summary (MCS), 24 weeks, any dose: MD 4.29 (95% CI 2.95 to 5.63); SF-36 MCS, 52 weeks, any dose: MD 4.30 (95% CI 2.57 to 6.03).

Minor outcomes

We have included in Summary of findings for the main comparison, DAS remission, some radiological changes and withdrawals.

ACR20 and ACR70

ACR20 for any dose at 24 weeks: RR 2.57 (95% CI 2.16 to 3.05); at 52 weeks: RR 2.06 (95% CI 1.61 to 2.62).

ACR70 for any dose at 24 weeks: RR 3.93 (95% CI 2.41 to 6.41); at 52 weeks: RR 3.14 (95% CI 1.86 to 5.29).

Pain

The appearance of pain at the injection site in the certolizumab 200 mg treated group was not statistically significant (Peto OR 4.60, 95% CI 1.05 to 20.10); certolizumab 400 mg treated group (Peto OR 1.74, 95% CI 0.41 to 7.42). These wide CIs were due to the fact that pain was not observed in any placebo group. Similar values were observed for local reactions at the injection site.

Patients' assessment of arthritis pain (visual analogue scale (VAS) score 0 to 100 mm) improved at any dose and at any time. At week 24, the overall mean difference (MD) was -21.63 (95% CI -24.23 to -19.02) and at week 52 the MD was -23.48 (95% CI -27.09 to -19.88).

DAS-28

Significant improvements were observed for all doses and at any given time. The proportion of patients achieving remission (< 2.6) was higher in the certolizumab 200 mg group than in the placebo group (Peto OR 3.88, 95% CI 2.33 to 6.45 at 24 weeks; Peto OR 10.36, 95% CI 3.29 to 32.58 at 52 weeks).

Despite the report from the EMEA, we could not extract more data on adverse events because those data were disclosed as combined

data, without the number of events in each trial; moreover, the adverse events were grouped by "primary system organ class".

Radiological changes

Radiological changes were expressed as modified total Sharp scores (mTSS), erosion score (ES) and joint space narrowing (JSN). All certolizumab groups showed improvements compared to placebo in the mean changes from baseline. There was a clear radiological improvement, regardless of the dose, that was associated with drug exposure time (see Radiological changes Table 6).
Erosion score (ES), any dose, 24 weeks: MD -0.70 (95% CI -0.98 to -0.42).
Erosion score (ES), any dose, 52 weeks: MD -1.45 (95% CI -2.11 to -0.79).
Joint space narrowing (JSN), any dose, 24 weeks: MD -0.50 (95% CI -0.79 to -0.21).
Joint space narrowing (JSN), any dose, 52 weeks: MD -1.10 (95% CI -1.88 to -0.33).
Modified total Sharp scores (mTSS), any dose, 24 weeks: MD -1.19 (95% CI -1.67 to -0.69).
Modified total Sharp scores (mTSS), any dose, 52 weeks: MD -2.50 (95% CI -3.70 to -1.30).

Withdrawals

There were more withdrawals because of lack of efficacy in the placebo group than in the certolizumab group. Adverse events leading to withdrawal did not seem to be dose dependent.
The placebo-treated patients withdrew because of lack of efficacy.
Withdrawn at any dose and at any follow-up: RR 0.39 (95% CI 0.36 to 0.43) (Analysis 45.1).
Withdrawn at any dose and at any follow-up due to lack of efficacy: RR 0.29 (95% CI 0.26 to 0.33) (Analysis 45.2).
Withdrawn at any dose and at any follow-up due to adverse events: RR 2.17 (95% CI 1.15 to 4.10) (Analysis 45.3).

Assessment of heterogeneity

When we analysed ACR50 response with 400 mg at week 24 for the four studies, we obtained a low probability of statistical heterogeneity, I^2 = 23%. Thus, heterogeneity did not seem to be important in the studies. When we analysed all studies but CDP870-014 2009, we obtained no statistical heterogeneity, I^2 = 0%. When we reviewed the demographics of phase III studies (Table 1): CDP870-014 2009 had a lower percentage of females (69%) than the other studies (83.6% in FAST4WARD 2005, 83.2% in RAPID1 2005 and 81.6% in RAPID2 2007) and higher MTX concomitant dose (mg/week) of 16.8 (versus 13.6 in RAPID1 2005 and 12.5 in RAPID2 2007). This could explain the heterogeneity results.
We did not find an important clinical or statistical heterogeneity that could hinder combining the data of the trials for the most important variables.
The funnel plot was not calculated to assess publication bias in view of the small number of studies for most of the results.

Subgroup analysis

We have not performed subgroup analysis. See the Differences between protocol and review.

Sensitivity analysis

We have done a sensitivity analysis with the major outcomes ACR50 and HAQ. The results remain unchanged when we re-analysed studies with adequate sequence generation (ACR50 RR 5.55, 95% CI 4.45 to 6.93), good allocation concealment (ACR50 RR 5.55, 95% CI 4.45 to 6.93), adequate blinding (ACR50 RR 6.14, 95% CI 2.21 to 17.05), lack of incomplete outcome data (ACR50 RR 5.74, 95% CI 4.56 to 7.23), free of selective reporting (ACR50 RR 5.74, 95% CI 4.56 to 7.23) and free of other bias (ACR50 RR 5.73, 95% CI 4.52 to 7.25). HAQ did not show changes in the same sensitivity analysis.

DISCUSSION

Summary of main results

The main results showed that when certolizumab pegol is used with or without MTX it produces a better efficacy than placebo for achieving ACR20, ACR50, ACR70, lower DAS 28 scores, and a higher remission of RA. The improvements in the physical and mental components measured by SF-36 and HAQ were significantly more impressive in the certolizumab pegol group than the placebo group. The improvements in radiological changes measured as modified total Sharp scores (mTSS), erosion scores (ES) and joint space narrowing (JSN) were also significantly more impressive in the certolizumab pegol groups than in the placebo group. Certolizumab pegol was associated with a higher risk of total adverse events than the placebo group. In addition, the risk of serious infections events was higher in the certolizumab groups than in the placebo group.
Withdrawals due to any reason and withdrawals due to an absence of efficacy were lower in the certolizumab pegol group than in the placebo group. This could indicate a better efficacy for certolizumab pegol compared to placebo.
The ACR50 at 24 weeks for any dose was RR 3.26 (95% CI 2.47 to 4.29), quite similar to that obtained when the study with the highest weight (RAPID1 2005) was removed (RR 4.70, 95% CI 2.93 to 7.54). The statistical heterogeneity was low (I^2 = 8%).

Moreover, when we analysed trials where MTX was added to the placebo group versus just placebo as comparator, the RR remained similar (RR 5.79, 95% CI 4.31 to 7.78).

This review has shown that certolizumab is effective when used with or without MTX in lowering RA disease activity (DAS-28), as well as improving RA disease activity (ACR20, ACR50, ACR70). The NNT for the ACR50 rates at any follow-up period and any dose was around 4, similar to that obtained in other reviews for the anti-rheumatic anti-TNF treatments: golimumab (Singh 2010), infliximab (Blumenauer 2002), etanercept (Blumenauer 2003; Chen 2006), abatacept (Maxwell L 2008), rituximab (Lopez-Olivo 2008) and adalimumab (Navarro Sarabia 2005).

The improvement in functional limitations has been shown to be important. HAQ scores in patients treated with certolizumab showed mean differences from placebo that ranged from 0.35 to 0.42 on a 0 to 3 scale.

Not all the variables that we analysed appeared in all the studies, and only one study provided information at 52 weeks. Therefore, conclusions on effectiveness with long-term treatment should be made with caution. The lack of information in studies like FAST4WARD 2005 concerning some variables, such as the physical component (SF-36 physical component summary, PCS) or the mental component (SF-36 mental component summary, PCS), has caused an underestimation of the statistical power of the present review when performing the meta-analysis.

A majority of patients in clinical trials of DMARDs over one to two years do not show radiographic progression. These data therefore reflect progression in fewer than half of the included patients and, indeed, if radiographic measurement error is taken into account an even smaller proportion of patients show radiographic progression. Laboratory and radiological changes are surrogate endpoints. They could be statistically but not clinically significant.

We do not have any information about the use of prospective or routine monitoring, spontaneous reporting, use of checklists, or systematic surveys of patients. Moreover, we do not have any definitions of reported adverse effects. No categories of adverse effects were reported by the investigators. The papers do not provide a definition for the terms serious adverse events, severe infections, adverse events of mild intensity and adverse events of severe intensity. None of the trials were designed with safety as the primary outcome. However, we have found more serious infections and more tuberculosis infections as adverse events. In addition, only one trial was designed with a long duration, so we cannot rule out that more adverse events, or more intense adverse events, could occur over time.

The review did not show a statistically significant increase in deaths (10 deaths in the certolizumab pegol group versus two in the placebo group), but in the open-label trials mentioned by EMEA 2009, 23 additional deaths were reported. So there could be a power problem with our meta-analysis, and an increase in deaths cannot be ruled out.

In the present review, a non-statistically significant increase in the number of tuberculosis infections was shown at 24 weeks and 52 weeks, even for patients with low probability (explored by thoracic x-rays, clinical history, tuberculin tests, etc.) of having the disease before starting the treatment. Our data (10 participants experienced tuberculosis) do not match the EMEA 2009 data that described "..30 subjects experienced 32 events of tuberculosis. Fifteen had pulmonary tuberculosis, 5 had tuberculosis, 5 disseminated tuberculosis, 1 peritoneal tuberculosis, 3 subjects had lymph node tuberculosis, and 2 subjects had tuberculous pleurisy". However, our data matches the data reported in the papers. These trials were performed in different countries with a different prevalence of tuberculosis. In the RAPID1 2005 and RAPID2 2007 papers, all the reported tuberculosis cases occurred in Eastern Europe (Russia, Latvia, Ukraine, Estonia, Bulgaria and Poland) and the authors assumed a high incidence of tuberculosis and a high prevalence of latent tuberculosis in all of these countries. However, a high incidence of tuberculosis is a rate of 40 per 100,000 population or higher. Only Russia, Ukraine and Latvia can be considered countries with a high incidence of tuberculosis, with 110, 102 and 53 per 100,000 population respectively (WHO 2009). In summary, it can be concluded that, as expected for other anti-TNF agents, certolizumab pegol is associated with an increased risk of tuberculosis, not only in countries with a high incidence of tuberculosis.

The risk of serious infections with certolizumab 200 mg and certolizumab 400 mg (Peto OR 3.30, 95% CI 1.45 to 7.51; Peto OR 3.25, 95% CI 1.65 to 6.39 respectively) is similar to other anti-TNFs; Bongartz 2006 reported a RR of 2 (95% CI 1.3 to 3.1). This adverse effect seems to be common to all anti-TNFs.

With regard to infections, in two studies (FAST4WARD 2005; RAPID1 2005) patients were non-eligible if they had a previous history of infections or a high risk of infections according to the researcher's criteria, thus the populations in the trials might not represent the real population.

The review of Bongartz 2006 and the FDA warnings issued on 04/06/2008 and 09/04/2009 indicate the possibility of developing lymphomas and other cancers in children and young adults. However, we were not able to detect these diseases. The studies were too short to detect an increase in cancer incidence. In addition, we did not detect an increase in histoplasmosis, other invasive fungal infections or leukaemia, as was mentioned in the FDA warning issued on 04/09/2008, again possibly because the studies were too short.

Overall completeness and applicability of evidence

We have included all RCTs available for patients with RA.

This evidence is relevant and applicable because it is the best data obtained from those RCTs. The present systematic review has a potential weakness regarding the meta-analysis, namely the lack of information from one RCT (NCT00160602). The fact that the results of that trial were not published could be that good results

for effectiveness were not obtained or the rates of adverse events were higher than expected. However, even in those instances the possibility that one trial could change the results of the major outcomes (ACR50, HAQ, etc) or increase the significance of some adverse events seems to be low.

At least in the most important studies (RAPID1 2005; RAPID2 2007), patients could not participate if they had previously participated in other anti-TNF trials and did not show a good response. Consequently, it should be considered that the studied population could possibly represent a population with a high response rate to anti-TNF agents.

Quality of the evidence

The quality of evidence found in the trials included in this review appears to be high because the studies reported adequate methods of allocation concealment and sequence generation. Methods of blinding for all outcomes were disclosed in one phase III trial; and it was only assured for the readers of radiographs in two more trials. Moreover, there are two more sources of concern for the quality of evidence: 1) we did not have access to information, such as complete study protocols, to make definitive judgments regarding the risk of selective reporting; and 2) we have found an unpublished trial. However, we doubt that more studies are likely to change the overall estimates. Using GRADE, the quality of evidence is variable, from low for some adverse events such as death (basically due to the low number of events in both groups) to high for ACR20, ACR50, ACR70 and for DAS remission.

Potential biases in the review process

This systematic review has some limitations. Initially, the present review was performed based on four trials (Choy 2002; FAST4WARD 2005; RAPID1 2005; RAPID2 2007), the only ones retrieved in the first search. However, when we were about to finish the review, other trials came to light that had to be included as well: one phase II and two phase III trials, namely CDP870-004 2001, and two phase III trials (CDP870-014 2009 without all the results, and NCT00544154 with no data at all). The finding of these trials at this late stage was surprising, because these trials were completed many years ago, but the data were either never disclosed or only partially disclosed. In fact, CDP870-004 2001 was cited in a conference proceeding, and the other two trials were finished in 2004 and 2005 but no data were published. Due to the limited scope of the data, we tried to obtain more information by contacting the sponsors. According to the sponsors the data were available at www.studyresults.org. We could not find any information on that website (accessed 10-12-2009) due to technical problems. After reporting this problem to the sponsors, they sent us the clinical study summary of CDP870-014 2009, and provided us with a new link to it, but no other information for NCT00544154 and CDP870-004 2001. Eventually, we decided to find out why the sponsors did not publish the information regarding the above clinical trials. Their justification was that making more data publicly available could jeopardize future publications. However, in a second search, we came across new data for all of the trials but NCT00544154 in two reports (EMEA 2009; NICE 2009). After reading these reports, again to our surprise the NICE report was made by the sponsors as a systematic review, but none of the two phase III trials were reported. In the EMEA report, the phase III trial NCT00544154 was also missing.

Our explanation for the absence of publications of some of the trials carried out with certolizumab pegol in RA could be, as the EMEA reported in CDP870-004 2001, that the difference in effectiveness between certolizumab pegol and control was lower than that observed with other anti-TNF agents in similar populations. This discrepancy led the sponsors to question the clinical relevance of their results, including secondary end-points.

The NICE 2009 (www.nice.org.uk/nicemedia/live/11903/45812/45812.pdf) and EMEA 2009 reports provided data to improve the information regarding the quality of the trials included in our review, such as randomisation, allocation concealment, withdrawals, demographics, etc. (see Table 1; Table 2). Despite the fact that these reports contained tables of adverse events, we could not use them in our review due to the way the data were presented. For example, the numbers of adverse events in all the trials were added together, both in NICE 2009 and EMEA 2009. Furthermore, the adverse effects were grouped in both reports according to the primary organ system affected, whereas in the papers corresponding to the trials the adverse effects were specified one by one and not grouped.

Agreements and disagreements with other studies or reviews

The NICE 2009 and EMEA 2009 reports, performed as systematic reviews, have shown results quite similar to those in our review. The effectiveness (ACR50) of another anti-TNF agent was also quite similar to certolizumab pegol.

AUTHORS' CONCLUSIONS

Implications for practice

Certolizumab pegol is the first pegylated anti-TNF agent approved by the FDA for the treatment of adult patients with moderate to severe, active RA. This review revealed an improvement in the clinical results (ACR20, ACR50, ACR70, and DAS-28 remission as well as HAQ scores) and SF-36 when patients were treated with certolizumab pegol. From week 16, it was associated with inhibition of the structural joint damage progression from baseline

in the modified total Sharp score (mTSS) at 24 and 54 weeks of treatment compared to MTX alone. Adverse events were more frequent in patients treated with certolizumab pegol than in those treated with placebo. An increase in the number of serious infections, especially tuberculosis, has been observed.

Implications for research

Limited data regarding the safety of certolizumab pegol, especially in the long term, are available. The preferred target for future research on treatments with certolizumab pegol should be the youngest population, since it is known that this population has developed lymphomas, tumours and leukaemia when treated with other anti-TNF agents and these adverse events have not been reported in the studies included in the present review. Clinical trials in this cohort population and follow-up studies will provide information in this regard.

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NCT00717236 *{published data only}*
Certolizumab Pegol for the Treatment of Patients With Active RA (Realistic). Ongoing study July 2008. Expected completion Nov 2010.

NCT00753454 *{published data only}*
Open Label Extension for Patients Coming From the Dosing Flexibility Study in Patients With Rheumatoid Arthritis (RA) (Dose Flex II). Ongoing study Sep 2008; expected completion date: Apr 2011.

NCT00791999 *{published data only}*
A Multicenter, Double-blind, Randomized, Placebo-controlled, Parallel-group Study to Assess the Efficacy, Pharmacokinetics and Safety of CDP870 as add-on Medication to Methotrexate (MTX) in Japanese Active Rheumatoid Arthritis (RA) Patients Who Have an Incomplete Response to MTX.. Ongoing study Nov 2008; expected completed date: Mar 2011.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

CDP870-004 2001

Methods	Double-blind, multiple dose, 12-week, placebo-controlled dose-ranging study
Participants	326 subjects with a history of inadequate response or intolerance to at least one DMARD and active RA at screening
Interventions	Patients received placebo, 50, 100, 200, 400, 600 and 800 mg sc q4w in two dose groups, panel 1 and panel 2
Outcomes	ACR20, ACR50, ACR70, subset of the ACR criterion, DASResponder Rates at week 12
Notes	We only have data from ACR20 at week 12

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	The EMEA report and UCB did not report any detail
Allocation concealment?	Unclear risk	The EMEA report and UCB did not report any detail
Incomplete outcome data addressed? Placebo	Low risk	Only data for ACR20
Incomplete outcome data addressed? certolizumab sc	Low risk	Only data for ACR20
Incomplete outcome data addressed? All outcomes	Low risk	Only data for ACR20

CDP870-014 2009

Methods	Randomised double-blind placebo controlled trial
Participants	Patients with rheumatoid arthritis (RA) who are partial responders to MTX. RA defined by the ACR classification criteria who had received MTX for $\geq$ 6 months (with at a stable dose of $\geq$ 15 mg/week) before baseline were included. At inclusion, patients had to have active disease as defined by: Active disease was defined as $\geq$ 9 tender and 9 swollen joints at screening and at baseline, with either an erythrocyte sedimentation rate (ESR; Westergen) $\geq$ 30 mm/hour or a C-reactive protein (CRP) level $\geq$ 15 mg/litre. Other DMARDs had to be discontinued at least 28 days before baseline or five half-

	lives,whatever longer, prior to first dose of study drug. We do not have more exclusion criteria in the files reported from UCB but probably were similar to another Phase III trial It was a 24 weeks, phase III, double-blind, randomised, multicenter, placebo-controlled study. 250 patients were randomised to one of two regimens of subcutaneous Certolizumab pegol 400 mg or placebo sc every 4 weeks for a total of 6 injections. Methotrexate treatment continue during the study taken prior to enrolment in the study. Subjects who completed the current study or who withdrew on or after the Week 12 visit were eligible to participate in the open-label safety study (CDP870-015) The primary objective of this study was to compare the efficacy of certolizumab pegol (CDP870 or CZP) in combination with methotrexate (MTX) to MTX alone in treating the signs and symptoms of subjects with rheumatoid arthritis (RA) who are partial responders to MTX. The study included 250 patients aged over 18 years with RA. Inclusion and exclusion criteria were identical to RAPID1, but were discontinued all DMARD at least 28 days or five half-lives, whatever longer, prior to first dose of study drug. The primary endpoint was ACR20 response at week 24 and safety. Secondary efficacy endpoints at week 24 included ACR50, ACR70
Interventions	Certolizumab pegol 400 mg plus MTX or placebo sc plus MTX every 4 weeks for a total of 6 injections
Outcomes	Primary: ACR20 and safety at 24 weeks. Secondary endpoints: Subject's Assessment of Pain (VAS), Subject's Global Assessment of Arthritis, Physician's Global Assessment of Arthritis, Subject's Assessment of Physical function by Health Assessment Questionnaire - disability index (HAQ-DI), acute phase reactant value (only CRP for this study)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	The randomisation code was generated by an independent group following instruction of the randomisation procedures, prepared by the Project statistician (EMEA report for the all Phase III)
Allocation concealment?	Low risk	Via Interactive voice recognition system (IVRS)
Incomplete outcome data addressed? Placebo	Low risk	We have data only for ACR20, ACR50 and ACR70and for safety
Incomplete outcome data addressed? certolizumab sc	Low risk	See above

Incomplete outcome data addressed? All outcomes	Low risk	See above

Choy 2002

Methods	Randomised double-blind placebo controlled trial
Participants	36 patients with rheumatoid arthritis defined by the American College for Rheumatology (ACR) classification criteria. Patients with active diseased defined as having 3 or the following 4 criteria: tender joint count (TJC) $\geq$ 6, swollen joint count (SJC) $\geq$ 3 (based on 28 joint counts), morning stiffness of $\geq$ 45 minutes, and ESR $\geq$ 28 mm/h. Patients had to have failed treatment with at least one DMARD and have been off treatment for at least 4 weeks
Interventions	Ascending-dose group study of a single intravenous infusion of placebo (n = 12) or 1, 5 or 20 mg/kg of certolizumab pegol (each n = 8) for 8 weeks
Outcomes	ACR20, ACR50, ACR70, Pain score (0-10 cm), Disease Activity score (DAS), TJC, SJC, Health assessment questionnaire (HAQ), C-reactive protein (CRP)
Notes	This study was only considered to assess safety because follow-up was less than 8 weeks Following the blinded dosing period of 8 weeks, 32 patients received a single open-label infusion of either 5 or 20 mg/kg of certolizumab In the open phase, one patient who received 20 mg/kg died from complications following rapid drainage of a large, chronic rheumatoid pericardial effusion. No infective agent was isolated from either the pericardial fluid or peripheral blood. In the opinion of the investigator, this event was unrelated to treatment

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Patients were divided into 4 groups. In each group of 12 patients 8 received active treatment and 4 received placebo. Methods for sequence generation: no information provided
Allocation concealment?	Unclear risk	Not described
Incomplete outcome data addressed? Placebo	Low risk	6 patients were withdrawn for deteriorating RA
Incomplete outcome data addressed? certolizumab sc	Low risk	2 patients were withdrawn for deteriorating RA or lost to follow-up

Choy 2002 (*Continued*)

Incomplete outcome data addressed? All outcomes	Low risk	Data for pain scores, TJC, SJC, HAQ, ESR, physicians global assessment of disease and CRP were reported in figures but numerical data were not available

FAST4WARD 2005

Methods	Randomised double-blind trial
Participants	220 patients aged between 18 and 75 years and with RA defined by the ACR classification criteria who had previously failed at least one disease modifying anti-rheumatic drug (DMARD) were included. Patients previously treated with a TNF inhibitor were excluded. Patients had to have a TJC of ≥ 9 (out of 68), SJC of ≥ 9 (out of 66) and one of the following: morning stiffness of ≥ 45 minutes; ESR ≥ 28 mm/h; or CRP > 10 mg/L. Patients with a previous history of a serious or life threatening infection were excluded. Patients with a history of tuberculosis (TB), or evidence of TB on a chest radiograph, or those with a positive reaction to purified protein derivative (PPD) reaction were also excluded. Patients on concurrent corticosteroids were allowed entry provided the dose was the equivalent of 10 mg or less of prednisolone. Parenteral corticosteroids were not permitted
Interventions	Certolizumab 400 mg sc every four weeks (n=111) or placebo (n=109) for 24 weeks
Outcomes	ACR20,50,70, HAQ-Di, Pain (VAS) and modified Brief pain Inventory (mBPI), DAS 28, Fatigue, and SF-36 at 24 weeks
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Code list prepared by independent group
Allocation concealment?	Low risk	Interactive voice recognition system (IVRS) used to allocate patient to treatment group (1:1 ratio)
Incomplete outcome data addressed? Placebo	Low risk	28 patients ended study
Incomplete outcome data addressed? certolizumab sc	Low risk	76 patients ended study
Incomplete outcome data addressed? All outcomes	High risk	All outcomes were shown

RAPID1 2005

Methods	Randomised double-blind trial
Participants	982 patients aged over 18 years and with RA defined by the ACR classification criteria who had received MTX for ≥ 6 months (with at a stable dose of ≥ 10 mg/week for at least 2 months) before baseline were included. Patients with a disease duration of >15 years were excluded. Patients previously treated with a TNF inhibitor were also excluded if they had previously failed to respond to treatment. Other DMARDs had to be discontinued at least 28 days before baseline. At inclusion, patients had to have active disease as defined by: Active disease was defined as ≥ 9 tender and 9 swollen joints at screening and at baseline, with either an erythrocyte sedimentation rate (ESR; Westergen) ≥ 30 mm/hour or a C-reactive protein (CRP) level ≥ 15 mg/L
Interventions	982 patients were randomised 2:2:1 to receive treatment with subcutaneous certolizumab pegol at an initial dosage of 400 mg given at weeks 0, 2, and 4, with a subsequent dosage of 200 mg or 400 mg given every 2 weeks, plus MTX, or placebo plus MTX
Outcomes	Co-primary end points were the ACR20 at week 24 and the mean change from baseline in the modified total Sharp score at week 52. Major secondary end points were: the change from baseline in modified total Sharp score at week 24, the change from baseline in the disability Index (DI) of the Health Assessment Questionnaire (HAQ) at weeks 24 and 52, the ACR20 responder rate at week 52, and the ACR50 and ACR70 responder rates at weeks 24 and 52
Notes	Patients with a history of tuberculosis or a chest radiograph showing active or latent tuberculosis or those with a positive reaction to purified protein derivative (PPD) reaction were also excluded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Code list prepared by independent group
Allocation concealment?	Low risk	Interactive voice recognition system (IVRS) used to allocate patient to treatment group (2:2:1 ratio)
Incomplete outcome data addressed? Placebo	Low risk	One patient in each group was lost to follow-up. For patients who withdrew before 52 weeks and who had radiographs taken at their withdrawal visit the modified total Sharp score was estimated by linear extrapolation of radiographic scores at the withdrawal visit or at week 24. Multiple sensitivity analyses were done on various assumptions regarding data imputation
Incomplete outcome data addressed? certolizumab sc	Low risk	See above
Incomplete outcome data addressed? All outcomes	Low risk	See above

RAPID2 2007

Methods	Randomised double-blind trial
Participants	619 patients (see note) aged over 18 years and with RA of at least 6 months and defined by the ACR classification criteria who had received MTX for ≥ 6 months with at a stable dose of ≥ 10 mg/week for at least 2 months before baseline were included. Patients with a disease duration of > 15 years were excluded. At inclusion, patients had to have active disease as defined by: TJC and SJC of ≥ 9, ESR ≥ 30 mm/h, and a CRP of ≥15 mg/L. Patients previously treated with a TNF inhibitor were also excluded if they had previously failed to respond to treatment
Interventions	Patients were randomised 2:2:1 to one of two regimens of subcutaneous liquid certolizumab pegol (400 mg at weeks 0, 2 and 4, followed by 200 or 400 mg every 2 weeks) plus MTX, or placebo (saline) plus MTX
Outcomes	The primary end point was ACR20 response at week 24, and physician's global assessment of disease activity, patient's assessment of pain, Health Assessment Questionnaire-Disability Index (HAQ-DI) and serum CRP or ESR Secondary efficacy end-points at week 24 included ACR50, ACR70, mean change from baseline in van der Heijde modified Total Sharp Scores (mTSS), Short Form-36 (SF-36) Health Survey,and individual ACR core set variables. Disease activity was assessed using the Disease Activity Score 28-joint assessment 4 (DAS28 (ESR)
Notes	Patients who did not show an ACR20 response at both weeks 12 and 14 were to be withdrawn from the study, designated ACR20 non-responders in the primary analysis and allowed to enter an open-label extension study at week 16 with certolizumab pegol 400 mg every 2 weeks Patients with history of, or positive chest x-ray findings for, tuberculosis, or a positive purified protein derivative (PPD) skin test (defined as positive indurations per local medical practice) were excluded. As per protocol, if a positive PPD skin test was assumed by the local investigators to be related to previous bacille Calmette-Guerin (BCG) vaccination and was not associated with clinical or radiographic suspicion of tuberculosis, patients could be enrolled at the discretion of the investigator. In total, 101 patients (16%) were enrolled with a PPD test > 5 mm at baseline

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Code list prepared by independent group
Allocation concealment?	Low risk	Interactive voice recognition system (IVRS) used to allocate patient to treatment group (2:2:1 ratio)
Incomplete outcome data addressed? Placebo	Low risk	More placebo-treated patients (79.5%; n=101) discontinued treatment owing to lack of ACR20 response at week 16
Incomplete outcome data addressed? certolizumab sc	Low risk	Discontinued treatment owing to lack of ACR20 response at week 16 versus certolizumab pegol 200 mg

		(19.9%; n=49) and 400 mg (18.7%; n=46)
Incomplete outcome data addressed? All outcomes	Low risk	All outcomes were reported

Choy's study didn't show number of patients in each arm, mean age (SD), percentage of female, of previous DMARD, on steroids, on NSAIDs and DAS was reported as mean change from baseline without SD.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Andreakos 2003	Different drug/agent studied
Anonymous 2003	Review; different drug/agent studied
Bain 2003	Different drug/agent studied
Bansback 2005	Different drug/agent studied
Barnes 2007	Review
Baugh 2001	Review
Bayes M 2006	Review
Chang 2006	Different drug/agent studied
Chikanza 2000a	Review in children
Chikanza 2000b	Review
Evans 2003	Different drug/agent studied
Fanet-Goguet 2004	Review
Fleischmann 2005	Review
Gabay 2002	Review
Garber 2005	Different drug/agent studied
Genovese 2005	Review

(*Continued*)

Goldblatt 2005	Review
Graninger 2002	Different drug/agent studied
Kathmann 2005	Review
Kaushik 2005	Review
Kavanaugh A	Assessed in RAPID1 and RAPID2 a work productivity survey (WPS-RA)
Kochbati 2004	Review
Mealy 2005	Different drug/agent studied
Mok 2004	Review
Mount 2005	Review
Osbourn 2003	Review
Paleolog 2003	Review
Pearce 2001	Review
Rose-John 2003	Review
Russo 2005	Different drug/agent studied
Sandborn 2003	Crohn's disease/ Review
Schreiber	Crohn's disease
Sorbera 2005	Review
Takeuchi 2005	Review
Taylor 2003	Different drug/agent studied
Taylor 2003a	Review
Toussirot 2004	Review
Toussirot 2007	Review
Zwerina 2005	Review

Characteristics of ongoing studies *[ordered by study ID]*

NCT00160602

Trial name or title	A Study of Liquid Certolizumab Pegol as Additional Medication to Methotrexate in the Treatment of Signs and Symptoms of Rheumatoid Arthritis and in Prevention of Joint Damage in Patients With Active Rheumatoid Arthritis
Methods	Treatment, randomised, double-blind, placebo control, parallel assignment, safety/efficacy study
Participants	Patients with active rheumatoid arthritis who have an incomplete response to methotrexate
Interventions	Compare efficacy of two dose regimens of certolizumab pegol in combination with MTX to MTX alone in patients with RA measured by the ACR20 at week 24
Outcomes	Not reported in clinical.trials.gov
Starting date	June 2005. Study completion date September 2006. No publications provided
Contact information	UCB Clinical Trial Call Center Tel: +1 877 822 9493
Notes	The link to the study summary on clinicalstudyresults.org does not work

NCT00160641

Trial name or title	A Phase III Multi-center, Open-label, Follow-up Study, to Assess the Efficacy and Safety of Liquid Certolizumab Pegol (CDP870) as Additional Medication to Methotrexate, in the Treatment of Signs and Symptoms and in the Prevention of Joint Damage in Patients With Active Rheumatoid Arthritis Who Participated in Study CDP870-050
Methods	Treatment, open-label, uncontrolled, single-group assignment, safety/efficacy study
Participants	Patients with active rheumatoid arthritis who participated in Study CDP870-050
Interventions	Follow-up
Outcomes	To assess the safety of certolizumab pegol, in patients with active rheumatoid arthritis (RA) by measuring ACR 20/50/70 responder rates every 12 weeks. Time Frame: 3 years. [Designated as safety issue: No]
Starting date	Dec 2005; expected completed data Mar 2011
Contact information	UCB Clinical Trial Call Center+1 877 822 9493 (UCB)
Notes	

NCT00160693

Trial name or title	Open Label Long-Term Safety Study of CDP870 (Certolizumab Pegol) for Patients With Rheumatoid Arthritis
Methods	Non-randomised, open-label, uncontrolled, single group assignment
Participants	Patients who have participated in CDP870 trial -014 for -011
Interventions	400 mg of certolizumab pegol subcutaneously every 4 weeks
Outcomes	To assess the long-term safety and tolerability of certolizumab pegol in subjects with rheumatoid arthritis [Time Frame: 8 years]
Starting date	Mar 2003; Expected completed data Mar 2011
Contact information	UCB Clinical Trial Call Center+1 877 822 9493 (UCB)
Notes	

NCT00175877

Trial name or title	A Study of the Safety and Effectiveness of Lyophilized Certolizumab Pegol in the Treatment of Signs and Symptoms of Rheumatoid Arthritis and in Prevention of Joint Damage in Patients With Active Rheumatoid Arthritis
Methods	A phase III multi-centre, open-label, follow-on study to CDP870-027
Participants	An open-ended study in which patients who completed the double-blind study (CDP870-027) are given certolizumab pegol and assessed for signs and symptoms of rheumatoid arthritis
Interventions	
Outcomes	To assess effectiveness of CDP870 in patients with active rheumatoid arthritis (RA) by measuring ACR 20/50/70 responder rates every 12 weeks [Time Frame: 3 years]
Starting date	June 2005; expected completion Mar 2011
Contact information	UCB Clinical Trial Call Center+1 877 822 9493 (UCB)
Notes	

NCT00580840

Trial name or title	Dosing Flexibility Study in Patients With Rheumatoid Arthritis (RA)
Methods	Treatment, randomised, double blind (subject, investigator), placebo control, parallel assignment, safety/efficacy study
Participants	Patients with active rheumatoid arthritis

NCT00580840 (*Continued*)

Interventions	The study design consists of an open-label run-in period (400mg CZP at week 0,2,4 and 200mg CZP plus placebo at week 6 through 16). At week 18 all patients will be grouped as responders or non-responders (based on ACR10 results at week 16). Non-responders will be withdrawn. Responders will be randomised at week 18 into one of three treatment arms (1:1:1): 400mg CZP q4w, 200mg CZP q2w, or placebo
Outcomes	Clinical response rate: ACR20, ACR50 and ACR70 week 16 (all patients) and week 34 (randomised patients) No reduction of disease activity: change from baseline in DAS28, SDAI and CDAI scores week 16 (all patients); week 34 (randomised patients) No achievement of clinical remission as measured by DAS28; SDAI and CDAI scores week 16 (all patients)
Starting date	December 2007 expected completion September 2010
Contact information	UCB Clinical Trial Call Center Tel: +1 877 822 9493
Notes	

NCT00674362

Trial name or title	Rheumatoid Arthritis (RA) Moderate to Low Disease Activity Study
Methods	A phase IIIB, multi-centre, double-blind, placebo-controlled, parallel group study to evaluate the safety and efficacy of certolizumab pegol, administered With DMARD
Participants	Patients with low to moderate disease activity rheumatoid arthritis on DMARDs therapy for at least six months
Interventions	Drug: certolizumab pegol 400 mg at W0, W2, W4 200 mg Q2W; placebo
Outcomes	Investigation of certolizumab pegol clinical efficacy in achieving clinical remission in patients with moderate to low disease activity rheumatoid arthritis both week 20 and week 24 No
Starting date	June 2008
Contact information	UCB Clinical Trial Call Center Tel: 1 877 822 9493
Notes	

NCT00717236

Trial name or title	Certolizumab Pegol for the Treatment of Patients With Active RA (Realistic)
Methods	Treatment, randomized, double blind (subject, outcomes assessor), parallel assignment, safety/efficacy study
Participants	Patients with established adult rheumatoid arthritis
Interventions	Not reported in clinical.trials.gov

NCT00717236 (*Continued*)

Outcomes	To assess the clinical responses rate as measured by ACR20 response rate Week 12 No. Another outcomes: responder rate, disease activity, fatigue, physical functioning. In the group remaining in the study after week 12: responder rate, disease activity, fatigue, physical functioning. [Time Frame: Week 12 and every 8 weeks thereafter, until study completion] [Designated as safety issue: No]
Starting date	July 2008. Expected completion Nov 2010
Contact information	UCB Clinical Trial Call Center Tel: 1 877 822 9493
Notes	

NCT00753454

Trial name or title	Open Label Extension for Patients Coming From the Dosing Flexibility Study in Patients With Rheumatoid Arthritis (RA) (Dose Flex II)
Methods	Open-label, single group assignment
Participants	Patients having completed the week 34 assessment in C87077 or having met the pre-defined criteria for flare, will be given the option to enrol in C87084 and receive: 400mg CZP at Entry, Week 2, and Week 4 followed by 200mg every two weeks in combination with MTX until the drug is commercially available for the indication of RA in the patient's country or region (or until further notice from UCB)
Interventions	Liquid certolizumab pegol administered every two weeks as a single injection (400 mg at entry, week 2, week 4, followed by 200 mg every 2 weeks)
Outcomes	Primary outcome measures: To continue to assess the safety of certolizumab pegol in combination with MTX as measured by adverse events frequency, severity and nature; PE and vitals; and laboratory values, blood parameters and urine parameters. [Time Frame: Time frame will vary - Treatment will continue until the drug is commercially available in the country or region] [Designated as safety issue: No] To assess the clinical response rate measured by ACR20, ACR50 and ACR70 responder rate. [Time Frame: Time frame will vary - Treatment will continue until the drug is commercially available in the country or region] [Designated as safety issue: No] To assess the reduction of disease activity measured by change from Baseline (in C87077) in DAS28, SDAI and CDAI scores. [Time Frame: Time frame will vary - Treatment will continue until the drug is commercially available in the country or region] [Designated as safety issue: No] To assess the achievement of clinical remission measured by DAS28 remission rate (< 2.6), SDAI remission rate (< 3.3) and CDAI remission rate (< 2.8.). [Time Frame: Time frame will vary - Treatment will continue until the drug is commercially available in the country or region] [Designated as safety issue: No] The improvement in physical function as measured by the Health Assessment Questionnaire Disability Index (HAQ-DI). [Time Frame: Time frame will vary - Treatment will continue until the drug is commercially available in the country or region] [Designated as safety issue: No] Reduction in fatigue as measured by the Fatigue Assessment Scale. [Time Frame: Time frame will vary - Treatment will continue until the drug is commercially available in the country or region] [Designated as safety issue: No] Improvement in patient's Health-Related Quality of Life (HRQOL) as measured by the 36-item Short Form

NCT00753454 (*Continued*)

	Health Survey (SF-36). [Time Frame: Time frame will vary - Treatment will continue until the drug is commercially available in the country or region] [Designated as safety issue: No] The relief in arthritis pain as measured by the Patient's Assessment of Arthritis Pain - Visual Analog Scale (VAS) [Time Frame: Time frame will vary - Treatment will continue until the drug is commercially available in the country or region] [Designated as safety issue: No] The reduction in disease activity as measured by the Patient's Global Assessment of Disease Activity - VAS. [Time Frame: Time frame will vary - Treatment will continue until the drug is commercially available in the country or region] [Designated as safety issue: No]
Starting date	Sep 2008; expected completion date: Apr 2011
Contact information	UCB Clinical Trial Call Center+1 877 822 9493 (UCB)
Notes	

NCT00791999

Trial name or title	A Multicenter, Double-blind, Randomized, Placebo-controlled, Parallel-group Study to Assess the Efficacy, Pharmacokinetics and Safety of CDP870 as add-on Medication to Methotrexate (MTX) in Japanese Active Rheumatoid Arthritis (RA) Patients Who Have an Incomplete Response to MTX
Methods	Treatment, randomised, double-blind (subject, caregiver, investigator, outcomes assessor), dose comparison, parallel assignment, safety/efficacy study
Participants	
Interventions	Drug: CDP870 400mg Drug: CDP870 200mg Drug: CDP870 100mg Drug: placebo of CDP870
Outcomes	Primary outcome measures: ACR20 responder rate [Time Frame: Week12, 24] [Designated as safety issue: Yes] Secondary outcome measures: ACR20/50/70 responder rate [Time Frame: Week 1, 2, 4, 6, 8, 12, 14, 16, 20, 24] [Designated as safety issue: Yes] DAS28 (ESR) [Time Frame: Week 1, 2, 4, 6, 8, 12, 14, 16, 20, 24] [Designated as safety issue: Yes] Modified Total Sharp Score [Time Frame: Week 24] [Designated as safety issue: Yes]
Starting date	Nov 2008; expected completed date: Mar 2011
Contact information	Drug Information Center opc_ctr@otsuka.jp
Notes	

NCT00843778

Trial name or title	Follow-up of Rheumatoid Arthritis (RA) Moderate to Low Disease Activity Study (CERTAIN 2)
Methods	Treatment, non-randomised, open-label, single group assignment, safety/efficacy study
Participants	Patients with active rheumatoid arthritis who were included in C87076 study
Interventions	Follow-up
Outcomes	Further assessment of the safety of Certolizumab pegol. [Time frame: every 8 weeks throughout the entire treatment period] Demonstration of clinical remission and improvement of physical function. [Time Frame: every 8 weeks throughout the entire treatment period]
Starting date	Jan 2009
Contact information	UCB Clinical Trial Call Center+1-877-822-9493 (UCB)
Notes	

NCT00850343

Trial name or title	Long-term Treatment Study of CDP870 Without Coadministration of MTX in Japanese Rheumatoid Arthritis (RA) Patients
Methods	Randomized, open-label, uncontrolled, parallel assignment
Participants	Japanese RA patients who are transferred from the study (Study 275-08-003), as well as to evaluate the effects of dosing regimens on safety and efficacy of CDP870 in the ACR20 responders who completed Study 275-08-003
Interventions	Drug: CDP870 200mg and CDP870 400mg
Outcomes	Primary outcome: adverse events [Time Frame: At any time] [Designated as safety issue: Yes]; Secondary outcome: ACR20/50/70 responder rate DAS28(ESR), Modified Total Sharp Score
Starting date	Mar 2009; expected completed date: Mar 2012
Contact information	Drug Information Centeropc_ctr@otsuka.jp
Notes	

NCT00851318

Trial name or title	Long-term Treatment Study of CDP870 as Add-on Medication to MTX in Japanese Rheumatoid Arthritis (RA) Patients
Methods	Randomised, open-label, uncontrolled, parallel assignment, safety/efficacy study
Participants	
Interventions	Two arms: CDP870 200 mg given every 2 weeks, SC; CP870 400mg given every 2 weeks, sc
Outcomes	ACR20/50/70 responder rate [Time Frame: Week 24, 52] [Designated as safety issue: Yes] DAS28(ESR) [Time Frame: Week 24, 52] [Designated as safety issue: Yes] Modified Total Sharp Score [Time Frame: Week 24] [Designated as safety issue: Yes]
Starting date	Mar 2009; expected completion Mar 2011
Contact information	Contact: Drug Information Centeropc_ctr@otsuka.jp
Notes	

NCT00993317

Trial name or title	A Phase III Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group, 24-week Study to Assess the Efficacy and Safety of Certolizumab Pegol as Additional Medication to MTX in Patients With Active Rheumatoid Arthritis Who Have an Incomplete Response to Methotrexate
Methods	Treatment, randomized, double-blind (subject, investigator, outcomes assessor), placebo control, parallel assignment, safety/efficacy study
Participants	Adult-onset RA of at least 6 months but not longer than 15 years in duration as defined by the 1987 ARA criteria, with active disease
Interventions	Drug: CDP870 200mg 400mg CDP870 given at Week 0, 2, 4 and thereafter 200mg CDP870 given every 2 weeks until week 22(sc)
Outcomes	ACR20 responder rate . Time Frame: week 24
Starting date	October 2009; expected completion June 2011
Contact information	Korea Otsuka Pharmaceutical Clinical Research Team82 2 3465 4351eunyoung1@otsuka.co.kr
Notes	

NCT00993668

Trial name or title	The Use of Certolizumab Pegol in Adult Subjects With Rheumatoid Arthritis to Assess the Antibody Response When Receiving Influenza Virus and Pneumococcal Vaccines
Methods	A phase 4, randomized, single-blind, placebo-controlled, multicentre study to evaluate the immunogenicity of pneumococcal and influenza vaccines in adult subjects with rheumatoid arthritis receiving certolizumab pegol or placebo
Participants	Patients with rheumatoid arthritis who had received influenza vaccine
Interventions	Biological: placebo Biological: certolizumab pegol
Outcomes	Percentage of subjects without baseline protective titers achieving a $\geq$ 2-fold titter increase in $\geq$ 3 of 6 pneumococcal antigens (6B, 9V, 14, 18C, 19F, and 23F) at week 6. Percentage of subjects without baseline protective titers achieving a $\geq$ 4-fold titre increase in $\geq$ 2 of 3 influenza antigens (2009/2010 composition) at week 6
Starting date	September 2009; expected completion September 2010
Contact information	UCB Clinical Trial Call Center+1-877-822-9493 (UCB)
Notes	

DATA AND ANALYSES

Comparison 1. Efficacy at 12 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR20	1	287	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.48, 0.68]
1.1 certolizumab 50 mg sc	1	47	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.13, 0.57]
1.2 certolizumab 100 mg sc	1	48	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.13, 0.56]
1.3 certolizumab 200 mg sc	1	49	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.25, 0.82]
1.4 certolizumab 400 mg sc	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.50, 1.27]
1.5 certolizumab 600 mg sc	1	47	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.51, 0.90]
1.6 certolizumab 800 mg sc	1	46	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.66, 1.04]
2 ACR50	1	194	Risk Ratio (M-H, Fixed, 95% CI)	3.31 [0.83, 13.26]
2.1 certolizumab 50 mg sc	1	47	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [0.09, 27.88]
2.2 certolizumab 100 mg sc	1	48	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.06, 20.96]
2.3 certolizumab 200 mg sc	1	49	Risk Ratio (M-H, Fixed, 95% CI)	3.21 [0.20, 51.33]
2.4 certolizumab 400 mg sc	1	50	Risk Ratio (M-H, Fixed, 95% CI)	7.33 [0.48, 110.96]
3 ACR70	1	194	Risk Ratio (M-H, Fixed, 95% CI)	2.14 [0.52, 8.76]
3.1 certolizumab 50 mg sc	1	47	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.06, 21.47]
3.2 certolizumab 100 mg sc	1	48	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.03, 14.89]
3.3 certolizumab 200 mg sc	1	49	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.08, 26.57]
3.4 certolizumab 400 mg sc	1	50	Risk Ratio (M-H, Fixed, 95% CI)	5.23 [0.34, 80.54]

Comparison 2. Efficacy at 24 weeks 200 mg certolizumab sc

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR 20	2	965	Risk Ratio (M-H, Fixed, 95% CI)	4.95 [3.65, 6.72]
2 ACR 50	2	965	Risk Ratio (M-H, Fixed, 95% CI)	6.01 [3.84, 9.40]
3 ACR 70	2	965	Risk Ratio (M-H, Fixed, 95% CI)	8.87 [4.20, 18.75]

Comparison 3. Efficacy at 24 weeks, 400 mg sc certolizumab

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR 20	4	1429	Risk Ratio (M-H, Fixed, 95% CI)	4.09 [3.27, 5.13]
2 ACR 50	4	1429	Risk Ratio (M-H, Fixed, 95% CI)	5.68 [3.93, 8.20]
3 ACR 70	4	1429	Risk Ratio (M-H, Fixed, 95% CI)	6.39 [3.32, 12.27]

Comparison 4. Efficacy at 24 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR20	4	2068	Risk Ratio (M-H, Fixed, 95% CI)	2.57 [2.16, 3.05]
1.1 certolizumab 200 mg sc	2	803	Risk Ratio (M-H, Fixed, 95% CI)	2.49 [1.87, 3.32]
1.2 certolizumab 400 mg sc	4	1265	Risk Ratio (M-H, Fixed, 95% CI)	2.62 [2.11, 3.25]
2 ACR50	4	2068	Risk Ratio (M-H, Fixed, 95% CI)	3.26 [2.47, 4.29]
2.1 certolizumab 200 mg sc	2	803	Risk Ratio (M-H, Fixed, 95% CI)	3.02 [1.96, 4.67]
2.2 certolizumab 400 mg sc	4	1265	Risk Ratio (M-H, Fixed, 95% CI)	3.43 [2.40, 4.90]
3 ACR70	4	2068	Risk Ratio (M-H, Fixed, 95% CI)	3.93 [2.41, 6.41]
3.1 certolizumab 200 mg sc	2	803	Risk Ratio (M-H, Fixed, 95% CI)	4.46 [2.13, 9.36]
3.2 certolizumab 400 mg sc	4	1265	Risk Ratio (M-H, Fixed, 95% CI)	3.51 [1.83, 6.75]

Comparison 5. Efficacy at 52 weeks, 200 mg sc certolizumab

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR 20	1	592	Risk Ratio (M-H, Fixed, 95% CI)	4.05 [2.80, 5.87]
2 ACR 50	1	592	Risk Ratio (M-H, Fixed, 95% CI)	5.03 [3.04, 8.32]
3 ACR 70	1	592	Risk Difference (M-H, Fixed, 95% CI)	0.18 [0.13, 0.22]

Comparison 6. Efficacy at 52 weeks, 400 mg sc certolizumab

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR 20	1	589	Risk Ratio (M-H, Fixed, 95% CI)	4.18 [2.89, 6.05]
2 ACR 50	1	589	Risk Ratio (M-H, Fixed, 95% CI)	5.27 [3.19, 8.71]
3 ACR 70	1	589	Risk Ratio (M-H, Fixed, 95% CI)	6.56 [3.10, 13.89]

Comparison 7. Efficacy at 52 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR20	1	982	Risk Ratio (M-H, Fixed, 95% CI)	2.06 [1.61, 2.62]
1.1 certolizumab 200 mg sc	1	493	Risk Ratio (M-H, Fixed, 95% CI)	2.04 [1.44, 2.87]
1.2 certolizumab 400 mg sc	1	489	Risk Ratio (M-H, Fixed, 95% CI)	2.08 [1.48, 2.93]
2 ACR50	1	982	Risk Ratio (M-H, Fixed, 95% CI)	2.58 [1.83, 3.62]
2.1 certolizumab 200 mg sc	1	493	Risk Ratio (M-H, Fixed, 95% CI)	2.53 [1.56, 4.10]
2.2 certolizumab 400 mg sc	1	489	Risk Ratio (M-H, Fixed, 95% CI)	2.62 [1.62, 4.25]

3 ACR70	1	982	Risk Ratio (M-H, Fixed, 95% CI)	3.14 [1.86, 5.29]
3.1 certolizumab 200 mg sc	1	493	Risk Ratio (M-H, Fixed, 95% CI)	3.02 [1.44, 6.32]
3.2 certolizumab 400 mg sc	1	489	Risk Ratio (M-H, Fixed, 95% CI)	3.26 [1.56, 6.82]

Comparison 8. Safety certolizumab 200 mg sc

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any adverse event	2	964	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [1.08, 1.35]
2 Adverse events Intensity mild	2	964	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [1.14, 1.53]
3 Adverse events Intensity moderate	2	964	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [1.00, 1.47]
4 Adverse events Intensity severe	2	964	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.38 [0.82, 2.34]
5 Adverse events related to study drug	2	964	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [1.26, 1.98]
6 Serious Adverse Events (SAE)	2	964	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.02 [1.24, 3.30]
7 Serious Infections	2	964	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.30 [1.45, 7.51]
8 Adverse events leading to death	2	964	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.47 [0.18, 11.76]
9 Adverse events leading to withdrawal	2	964	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.40 [1.16, 4.95]
10 Death	2	962	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.85 [0.29, 11.86]
11 Tuberculosis	2	964	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.53 [0.71, 29.11]
12 Malignancies included lymphoma	2	964	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.85 [0.50, 6.93]
13 Injection site pain	2	964	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.60 [1.05, 20.10]
14 Injection side reactions	2	964	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.59 [1.38, 15.32]
15 Neutralising Anti-certolizumab pegol antibodies	1	373	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.57 [0.71, 29.59]
16 Systemic lupus erythematosus	1	373	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.50 [0.07, 286.06]
17 Prolonged activated partial thromboplastin time (aPTT)	1	373	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.45 [0.79, 7.57]
18 Urinary tract infection	2	964	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.76 [0.43, 1.35]
19 Upper respiratory tract infection	2	964	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.21 [1.15, 4.25]
20 Lower respiratory tract infection/ lung infection	1	591	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.54 [0.41, 49.96]
21 Headache	2	964	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.31 [0.68, 2.50]
22 Bacteriuria	1	373	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [0.30, 3.40]
23 Nasopharyngitis	2	964	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.71 [1.30, 5.66]
24 Hypertension	2	964	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.81 [1.38, 5.75]
25 Hematuria	1	373	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.36 [0.09, 1.47]
26 Hepatic enzyme increased	1	373	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.34 [0.07, 1.66]
27 AST increased	1	373	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.18 [0.04, 0.86]
28 ALT increased	1	373	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.09 [0.02, 0.45]
29 Back pain	1	591	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.91 [1.11, 7.65]
30 Herpes viral infection	1	591	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.52 [0.07, 285.70]
31 Bacterial peritonitis	1	591	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.52 [0.07, 285.70]
32 Opportunistic infections	1	591	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable

33 Infections and infestations	2	947	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [1.10, 1.69]
34 Gastroenteritis	1	591	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
35 Hematologic abnormalities	1	591	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.53 [0.24, 85.22]
36 Decreased haemoglobin	1	591	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.02 [0.09, 11.18]
37 Increased platelet count	1	591	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable

Comparison 9. Safety certolizumab 400 mg sc

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any adverse events	4	1422	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [1.10, 1.30]
2 Adverse events Intensity mild	3	1179	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [1.19, 1.54]
3 Adverse events Intensity moderate	3	1179	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [1.05, 1.45]
4 Adverse events Intensity severe	3	1179	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.24 [0.79, 1.95]
5 Adverse events related to study drug	3	1179	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [1.19, 1.80]
6 Serious infections	4	1422	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.25 [1.65, 6.39]
7 Serious Adverse Events (SAE)	4	1422	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.92 [1.30, 2.83]
8 Adverse events leading to death	3	1179	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.16 [0.40, 11.79]
9 Adverse events leading to withdrawal	3	1179	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.41 [1.26, 4.63]
10 Death	4	1422	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.16 [0.40, 11.79]
11 Vomiting	1	220	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.00, 6.70]
12 Pneumonitis	1	220	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.00, 6.70]
13 Tuberculosis	3	1179	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.55 [0.71, 29.11]
14 Arthritis bacterial	1	220	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.26 [0.14, 365.79]
15 Mastitis	1	220	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.26 [0.14, 365.79]
16 Benign Tumour	1	220	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.32 [0.46, 117.84]
17 Ischaemeic stroke	1	220	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.26 [0.14, 365.79]
18 Dizziness postural	1	220	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.26 [0.14, 365.79]
19 Menorrhagia	1	220	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.26 [0.14, 365.79]
20 Malignancies included lymphoma	3	1179	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.26 [0.26, 6.08]
21 Injection site pain	3	1179	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.74 [0.41, 7.42]
22 Injection side reactions	3	1179	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.69 [0.31, 1.49]
23 Anti-certolizumab pegol antibodies	2	591	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.70 [2.18, 20.55]
24 Antinuclear antibodies (ANA)	1	220	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.65 [0.77, 3.53]
25 Prolonged activated partial thromboplastin time (aPTT)	1	371	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.46 [0.80, 7.60]
26 Urinary tract infection	2	959	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.87 [0.50, 1.52]
27 Back pain	1	588	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.15 [1.28, 7.74]
28 Upper respiratory tract infection	2	959	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.74 [0.83, 3.67]
29 Lower respiratory tract infection/ lung infection	1	588	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.57 [0.57, 36.44]
30 Headache	2	959	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.11 [0.56, 2.20]

31 Bacteriuria	1	371	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.75 [0.20, 2.82]
32 Hypertension	2	959	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.23 [1.71, 6.08]
33 Hematuria	1	371	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.37 [0.09, 1.49]
34 Hepatic enzyme increased	1	371	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.34 [0.07, 1.67]
35 AST increased	1	371	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.58 [0.16, 2.07]
36 ALT increased	1	373	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.67 [0.22, 2.05]
37 Herpes viral infection	1	588	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.53 [0.07, 285.35]
38 Bacterial peritonitis	1	588	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
39 Opportunistic infections	1	588	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
40 Infections and infestations	3	1202	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [1.31, 1.95]
41 Nasopharyngitis	2	959	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.99 [1.50, 5.95]
42 Gastrointestinal disorders	2	831	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.05 [0.54, 2.03]
43 Hematologic abnormalities	1	588	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.76 [0.12, 4.86]
44 Decreased Haemoglobin	1	588	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.49 [0.03, 9.10]
45 Increased platelet count	1	588	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.02 [0.09, 11.23]

Comparison 10. Mean HAQ-DI from baseline at week 24

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 certolizumab 200 mg sc	2	965	Mean Difference (IV, Fixed, 95% CI)	-0.39 [-0.45, -0.32]
2 certolizumab 400 mg sc	3	1182	Mean Difference (IV, Fixed, 95% CI)	-0.41 [-0.48, -0.35]

Comparison 11. HAQ-Di at 24 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	3	1821	Mean Difference (IV, Fixed, 95% CI)	-0.41 [-0.46, -0.35]
1.1 certolizumab 200 mg sc	2	803	Mean Difference (IV, Fixed, 95% CI)	-0.39 [-0.47, -0.30]
1.2 certolizumab 400 mg sc	3	1018	Mean Difference (IV, Fixed, 95% CI)	-0.42 [-0.50, -0.35]

Comparison 12. HAQ-Di at 52 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	1	982	Mean Difference (IV, Fixed, 95% CI)	-0.43 [-0.52, -0.35]
1.1 certolizumab 200 mg sc	1	493	Mean Difference (IV, Fixed, 95% CI)	-0.42 [-0.54, -0.30]
1.2 certolizumab 400 mg sc	1	489	Mean Difference (IV, Fixed, 95% CI)	-0.45 [-0.57, -0.33]

Comparison 13. SF-36 Physical Component Summary (PCS) week 24

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 certolizumab 200 mg sc	2	965	Mean Difference (IV, Fixed, 95% CI)	5.26 [4.17, 6.36]
2 certolizumab 400 mg sc	2	962	Mean Difference (IV, Fixed, 95% CI)	5.72 [4.62, 6.81]

Comparison 14. SF-36 Mental Component Summary (MCS) week 24

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 certolizumab 200 mg sc	2	965	Mean Difference (IV, Fixed, 95% CI)	4.18 [2.70, 5.66]
2 certolizumab 400 mg sc	2	962	Mean Difference (IV, Fixed, 95% CI)	4.39 [2.91, 5.88]

Comparison 15. SF-36 Mental Component Summary (MCS) week 52

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 certolizumab 200 mg sc	1	592	Mean Difference (IV, Fixed, 95% CI)	4.3 [2.40, 6.20]
2 certolizumab 400 mg sc	1	589	Mean Difference (IV, Fixed, 95% CI)	4.3 [2.40, 6.20]

Comparison 16. SF-36 Physical Component Summary (PCS) week 52

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 certolizumab 200 mg sc	1	592	Mean Difference (IV, Fixed, 95% CI)	6.06 [4.59, 7.53]
2 certolizumab 400 mg sc	1	589	Mean Difference (IV, Fixed, 95% CI)	6.88 [5.42, 8.34]

Comparison 17. SF-36 Physical Component Summary (PCS) week 24, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	2	1601	Mean Difference (IV, Fixed, 95% CI)	5.47 [4.47, 6.48]
1.1 certolizumab 200 mg sc	2	803	Mean Difference (IV, Fixed, 95% CI)	5.25 [3.84, 6.66]
1.2 certolizumab 400 mg sc	2	798	Mean Difference (IV, Fixed, 95% CI)	5.70 [4.28, 7.12]

Comparison 18. SF-36 Mental Component Summary (MCS) week 24, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	2	1601	Mean Difference (IV, Fixed, 95% CI)	4.29 [2.95, 5.63]
1.1 certolizumab 200 mg sc	2	803	Mean Difference (IV, Fixed, 95% CI)	4.18 [2.29, 6.07]
1.2 certolizumab 400 mg sc	2	798	Mean Difference (IV, Fixed, 95% CI)	4.39 [2.49, 6.29]

Comparison 19. SF-36 Physical Component Summary (PCS) week 52, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	1	982	Mean Difference (IV, Fixed, 95% CI)	6.47 [5.13, 7.81]
1.1 certolizumab 200 mg sc	1	493	Mean Difference (IV, Fixed, 95% CI)	6.06 [4.17, 7.95]
1.2 certolizumab 400 mg sc	1	489	Mean Difference (IV, Fixed, 95% CI)	6.88 [4.99, 8.77]

Comparison 20. SF-36 Mental Component Summary (MCS) week 52, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	1	982	Mean Difference (IV, Fixed, 95% CI)	4.3 [2.57, 6.03]
1.1 certolizumab 200 mg sc	1	493	Mean Difference (IV, Fixed, 95% CI)	4.3 [1.86, 6.74]
1.2 certolizumab 400 mg sc	1	489	Mean Difference (IV, Fixed, 95% CI)	4.3 [1.85, 6.75]

Comparison 21. Disease Activity Score (DAS28) (ESR) remission (< 2.6)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of patients achieving remission 24 weeks certolizumab 200 mg	2	957	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.88 [2.33, 6.45]
2 Proportion of patients achieving remission 24 weeks certolizumab 400 mg	2	954	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.97 [2.41, 6.54]
3 Proportion of patients achieving remission 52 weeks certolizumab 200 mg	1	587	Risk Ratio (M-H, Fixed, 95% CI)	10.36 [3.29, 32.58]
4 Proportion of patients achieving remission 52 weeks certolizumab 400 mg	1	583	Risk Ratio (M-H, Fixed, 95% CI)	12.49 [3.99, 39.12]

Comparison 22. Disease Activity Score (DAS28) (ESR) remission (< 2.6) any doses, 24 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of patients achieving remission 24 weeks	2	1595	Risk Ratio (M-H, Fixed, 95% CI)	4.46 [2.21, 9.00]
1.1 certolizumab 200 mg sc	2	800	Risk Ratio (M-H, Fixed, 95% CI)	4.38 [1.62, 11.82]
1.2 certolizumab 400 mg sc	2	795	Risk Ratio (M-H, Fixed, 95% CI)	4.54 [1.69, 12.24]

Comparison 23. Disease Activity Score (DAS28) (ESR) remission (< 2.6) any doses, 52 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of patients achieving remission 52 weeks	1	977	Risk Ratio (M-H, Fixed, 95% CI)	5.80 [2.60, 12.94]
1.1 certolizumab 200 mg sc	1	491	Risk Ratio (M-H, Fixed, 95% CI)	5.29 [1.69, 16.49]
1.2 certolizumab 400 mg sc	1	486	Risk Ratio (M-H, Fixed, 95% CI)	6.31 [2.03, 19.59]

Comparison 24. DAS-28 at 24 weeks 200 mg sc certolizumab

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 DAS 28 (ESR) change from baseline	1	373	Mean Difference (IV, Fixed, 95% CI)	-1.77 [-2.02, -1.52]

Comparison 25. DAS-28 at 24 weeks 400 mg sc certolizumab

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 DAS 28 (ESR) change from baseline	2	593	Mean Difference (IV, Fixed, 95% CI)	-1.77 [-1.99, -1.55]

Comparison 26. DAS-28 at week 52, certolizumab 200 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 DAS 28 (ESR) Change from baseline	1	592	Mean Difference (IV, Fixed, 95% CI)	-0.9 [-1.12, -0.68]

Comparison 27. DAS-28 at week 52, certolizumab 400 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 DAS 28 (ESR) Change from baseline	1	589	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-1.23, -0.77]

Comparison 28. DAS-28 at 24 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	2	839	Mean Difference (IV, Fixed, 95% CI)	-1.73 [-1.93, -1.52]
1.1 certolizumab 200 mg sc	1	310	Mean Difference (IV, Fixed, 95% CI)	-1.77 [-2.08, -1.46]
1.2 certolizumab 400 mg sc	2	529	Mean Difference (IV, Fixed, 95% CI)	-1.69 [-1.96, -1.43]

Comparison 29. DAS-28 at 52 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	1	982	Mean Difference (IV, Fixed, 95% CI)	-0.95 [-1.15, -0.75]
1.1 certolizumab 200 mg sc	1	493	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-1.19, -0.61]
1.2 certolizumab 400 mg sc	1	489	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-1.29, -0.71]

Comparison 30. Modified total Sharp scores (mTSS)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from the baseline mean mTSS 24 weeks 200 mg certolizumab.	2	859	Mean Difference (IV, Fixed, 95% CI)	-1.06 [-1.58, -0.55]
2 Change from the baseline mean mTSS 24 weeks 400 mg certolizumab.	2	869	Mean Difference (IV, Fixed, 95% CI)	-1.32 [-1.85, -0.78]
3 Change from the baseline mean mTSS 52 weeks 200 mg certolizumab sc	1	545	Mean Difference (IV, Fixed, 95% CI)	-2.4 [-3.68, -1.12]
4 Change from the baseline mean mTSS 52 weeks 400 mg certolizumab sc	1	544	Mean Difference (IV, Fixed, 95% CI)	-2.60 [-3.84, -1.36]

Comparison 31. Modified total Sharp scores (mTSS) at 24 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	2	1437	Mean Difference (IV, Fixed, 95% CI)	-1.18 [-1.67, -0.69]
1.1 certolizumab 200 mg sc	2	713	Mean Difference (IV, Fixed, 95% CI)	-1.06 [-1.75, -0.38]
1.2 certolizumab 400 mg sc	2	724	Mean Difference (IV, Fixed, 95% CI)	-1.30 [-1.99, -0.60]

Comparison 32. Modified total Sharp scores (mTSS) at 52 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	1	908	Mean Difference (IV, Fixed, 95% CI)	-2.50 [-3.70, -1.30]
1.1 certolizumab 200 mg sc	1	455	Mean Difference (IV, Fixed, 95% CI)	-2.4 [-4.11, -0.69]
1.2 certolizumab 400 mg sc	1	453	Mean Difference (IV, Fixed, 95% CI)	-2.60 [-4.29, -0.91]

Comparison 33. Erosion score (ES)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from the baseline mean ES at week 24, 200 mg certolizumab.	2	859	Mean Difference (IV, Fixed, 95% CI)	-0.67 [-0.96, -0.38]
2 Change from the baseline mean ES at week 24, 400 mg certolizumab.	2	869	Mean Difference (IV, Fixed, 95% CI)	-0.74 [-1.06, -0.42]
3 Change from the baseline mean ES at week 52, 200 mg certolizumab.	1	544	Mean Difference (IV, Fixed, 95% CI)	-1.4 [-2.08, -0.72]
4 Change from the baseline mean ES at week 52, 400 mg certolizumab.	1	543	Mean Difference (IV, Fixed, 95% CI)	-1.50 [-2.20, -0.80]

Comparison 34. Erosion score (ES) at 24 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	2	1437	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-0.98, -0.42]
1.1 certolizumab 200 mg sc	2	714	Mean Difference (IV, Fixed, 95% CI)	-0.67 [-1.06, -0.28]
1.2 certolizumab 400 mg sc	2	723	Mean Difference (IV, Fixed, 95% CI)	-0.73 [-1.14, -0.32]

Comparison 35. Erosion score (ES) at 52 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	1	908	Mean Difference (IV, Fixed, 95% CI)	-1.45 [-2.11, -0.79]
1.1 certolizumab 200 mg sc	1	455	Mean Difference (IV, Fixed, 95% CI)	-1.4 [-2.32, -0.48]
1.2 certolizumab 400 mg sc	1	453	Mean Difference (IV, Fixed, 95% CI)	-1.5 [-2.44, -0.56]

Comparison 36. Joint space narrowing (JSN)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from the baseline mean JSN 24 weeks 200 mg certolizumab.	2	861	Mean Difference (IV, Fixed, 95% CI)	-0.45 [-0.77, -0.13]
2 Change from the baseline mean JSN 24 weeks 400 mg certolizumab.	2	869	Mean Difference (IV, Fixed, 95% CI)	-0.55 [-0.86, -0.24]
3 Change from the baseline mean JSN 52 weeks 200 mg certolizumab.	1	548	Mean Difference (IV, Fixed, 95% CI)	1.00 [-1.85, -0.15]
4 Change from the baseline mean JSN 52 weeks 400 mg certolizumab	1	544	Mean Difference (IV, Fixed, 95% CI)	-1.2 [-1.98, -0.42]

Comparison 37. Joint space narrowing (JSN) at 24 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	2	1439	Mean Difference (IV, Fixed, 95% CI)	-0.50 [-0.79, -0.21]
1.1 certolizumab 200 mg sc	2	716	Mean Difference (IV, Fixed, 95% CI)	-0.46 [-0.87, -0.04]
1.2 certolizumab 400 mg sc	2	723	Mean Difference (IV, Fixed, 95% CI)	-0.54 [-0.96, -0.13]

Comparison 38. Joint space narrowing (JSN) at 52 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	1	911	Mean Difference (IV, Fixed, 95% CI)	-1.10 [-1.88, -0.33]
1.1 certolizumab 200 mg sc	1	458	Mean Difference (IV, Fixed, 95% CI)	1.00 [-2.11, 0.11]
1.2 certolizumab 400 mg sc	1	453	Mean Difference (IV, Fixed, 95% CI)	-1.2 [-2.27, -0.13]

Comparison 39. Patient's assessment of arthritis pain (VAS score 0 to 100 mm)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean change at 24 weeks certolizumab 200 mg	2	965	Mean Difference (IV, Fixed, 95% CI)	-20.49 [-23.43, -17.55]
2 Mean change at 24 weeks certolizumab 400 mg	3	1182	Mean Difference (IV, Fixed, 95% CI)	-22.69 [-25.53, -19.84]
3 Mean change at 52 weeks certolizumab 200 mg	1	592	Mean Difference (IV, Fixed, 95% CI)	-22.2 [-26.19, -18.21]
4 Mean change at 52 weeks certolizumab 400 mg	1	589	Mean Difference (IV, Fixed, 95% CI)	-24.7 [-28.62, -20.78]

Comparison 40. Patient's assessment of arthritis pain (VAS score 0 to 100 mm) at 24 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	3	1821	Mean Difference (IV, Fixed, 95% CI)	-21.63 [-24.23, -19.02]
1.1 certolizumab 200 mg sc	2	803	Mean Difference (IV, Fixed, 95% CI)	-20.48 [-24.26, -16.69]
1.2 certolizumab 400 mg sc	3	1018	Mean Difference (IV, Fixed, 95% CI)	-22.66 [-26.26, -19.06]

Comparison 41. Patient's assessment of arthritis pain (VAS score 0 to 100 mm) at 52 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	1	982	Mean Difference (IV, Fixed, 95% CI)	-23.48 [-27.09, -19.88]
1.1 certolizumab 200 mg sc	1	493	Mean Difference (IV, Fixed, 95% CI)	-22.2 [-27.37, -17.03]
1.2 certolizumab 400 mg sc	1	489	Mean Difference (IV, Fixed, 95% CI)	-24.7 [-29.73, -19.67]

Comparison 42. Certolizumab 1mg/kg/day sc

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Headache	1	20	Risk Ratio (M-H, Fixed, 95% CI)	4.5 [0.56, 35.98]
2 Lower respiratory tract infection	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.02, 10.54]
3 Adverse events Intensity severe	1	20	Risk Ratio (M-H, Fixed, 95% CI)	4.33 [0.20, 94.83]
4 Antinuclear antibodies (ANA)	1	20	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.32, 27.83]
5 Urinary tract infection	1	20	Risk Ratio (M-H, Fixed, 95% CI)	4.33 [0.20, 94.83]

Comparison 43. Certolizumab 5 mg/kg/day sc

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lower respiratory tract infection	1	20	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.11, 20.68]
2 Urinary tract infection	1	20	Risk Ratio (M-H, Fixed, 95% CI)	4.33 [0.20, 94.83]

Comparison 44. Certolizumab 20 mg/kg/day sc

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Headache	1	20	Risk Ratio (M-H, Fixed, 95% CI)	4.5 [0.56, 35.98]
2 Lower respiratory tract infection	1	20	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.32, 27.83]
3 Death	1	20	Risk Ratio (M-H, Fixed, 95% CI)	4.33 [0.20, 94.83]
4 Antinuclear antibodies (ANA)	1	20	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.11, 20.68]
5 Urinary tract infection	1	20	Risk Ratio (M-H, Fixed, 95% CI)	4.33 [0.20, 94.83]

Comparison 45. Withdrawals

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All Withdrawn: any doses any follow up	5	2107	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.36, 0.43]
2 Withdrawn due to lack of efficacy: any doses any follow up	4	2071	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.26, 0.33]
3 Withdrawn due to adverse events: any doses any follow up	4	2071	Risk Ratio (M-H, Fixed, 95% CI)	2.17 [1.15, 4.10]

Comparison 46. Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR 50 200 mg certolizumab 24 weeks	2	965	Risk Ratio (M-H, Fixed, 95% CI)	6.01 [3.84, 9.40]
2 HAQ change from baseline 200 mg certolizumab 24 weeks	2	965	Mean Difference (IV, Fixed, 95% CI)	-0.39 [-0.45, -0.32]
3 Serious adverse events certolizumab 200 mg sc	2	964	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.02 [1.24, 3.30]
3.1 certolizumab 200 mg	2	964	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.02 [1.24, 3.30]
4 Proportion of patients achieving DAS <2.6 (Remission) 200 mg certolizumab 24 weeks	2	957	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.88 [2.33, 6.45]
4.1 certolizumab 200 mg sc 24 weeks	2	957	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.88 [2.33, 6.45]
5 Radiological changes: Erosion Scores (ES) 200 mg certolizumab 200 mg sc	2	859	Mean Difference (IV, Fixed, 95% CI)	-0.67 [-0.96, -0.38]
5.1 certolizumab 200 mg sc 24 weeks	2	859	Mean Difference (IV, Fixed, 95% CI)	-0.67 [-0.96, -0.38]
6 All Withdrawals:	5	2107	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.36, 0.43]
7 Withdrawals due to adverse events	4	2071	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.93 [1.15, 3.23]

Analysis 1.1. Comparison 1 Efficacy at 12 weeks, any dose, Outcome 1 ACR20.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 1 Efficacy at 12 weeks, any dose

Outcome: 1 ACR20

Study or subgroup	Certolizumab n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 certolizumab 50 mg sc					
CDP870-004 2001	8/39	6/8		14.7 %	0.27 [0.13, 0.57]
Subtotal (95% CI)	**39**	**8**		**14.7 %**	**0.27 [0.13, 0.57]**
Total events: 8 (Certolizumab), 6 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.45 (P = 0.00056)					
2 certolizumab 100 mg sc					
CDP870-004 2001	8/40	6/8		14.8 %	0.27 [0.13, 0.56]
Subtotal (95% CI)	**40**	**8**		**14.8 %**	**0.27 [0.13, 0.56]**
Total events: 8 (Certolizumab), 6 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.51 (P = 0.00045)					
3 certolizumab 200 mg sc					
CDP870-004 2001	14/41	6/8		14.8 %	0.46 [0.25, 0.82]
Subtotal (95% CI)	**41**	**8**		**14.8 %**	**0.46 [0.25, 0.82]**
Total events: 14 (Certolizumab), 6 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.64 (P = 0.0082)					
4 certolizumab 400 mg sc					
CDP870-004 2001	25/42	6/8		14.9 %	0.79 [0.50, 1.27]
Subtotal (95% CI)	**42**	**8**		**14.9 %**	**0.79 [0.50, 1.27]**
Total events: 25 (Certolizumab), 6 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.96 (P = 0.34)					
5 certolizumab 600 mg sc					
CDP870-004 2001 (1)	25/39	8/8		20.5 %	0.68 [0.51, 0.90]
Subtotal (95% CI)	**39**	**8**		**20.5 %**	**0.68 [0.51, 0.90]**
Total events: 25 (Certolizumab), 8 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.73 (P = 0.0064)					
6 certolizumab 800 mg sc					
CDP870-004 2001 (2)	30/38	8/8		20.4 %	0.83 [0.66, 1.04]
Subtotal (95% CI)	**38**	**8**		**20.4 %**	**0.83 [0.66, 1.04]**
Total events: 30 (Certolizumab), 8 (Control)					

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Study or subgroup	Certolizumab n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heterogeneity: not applicable					
Test for overall effect: Z = 1.61 (P = 0.11)					
Total (95% CI)	**239**	**48**	◆	**100.0 %**	**0.57 [0.48, 0.68]**
Total events: 110 (Certolizumab), 40 (Control)					
Heterogeneity: Chi² = 21.73, df = 5 (P = 0.00059); I² =77%					
Test for overall effect: Z = 6.22 (P < 0.00001)					

(1) From EMEA report, only data for ACR20

(2) From EMEA report, only data for ACR20

Analysis 1.2. Comparison 1 Efficacy at 12 weeks, any dose, Outcome 2 ACR50.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 1 Efficacy at 12 weeks, any dose

Outcome: 2 ACR50

Study or subgroup	Certolizumab n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 certolizumab 50 mg sc					
CDP870-004 2001	3/39	0/8		24.8 %	1.58 [0.09, 27.88]
Subtotal (95% CI)	**39**	**8**		**24.8 %**	**1.58 [0.09, 27.88]**
Total events: 3 (Certolizumab), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.31 (P = 0.76)					
2 certolizumab 100 mg sc					
CDP870-004 2001	2/40	0/8		24.9 %	1.10 [0.06, 20.96]
Subtotal (95% CI)	**40**	**8**		**24.9 %**	**1.10 [0.06, 20.96]**
Total events: 2 (Certolizumab), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.06 (P = 0.95)					
3 certolizumab 200 mg sc					
CDP870-004 2001	7/41	0/8		25.1 %	3.21 [0.20, 51.33]

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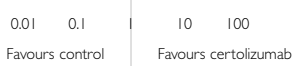
Study or subgroup	Certolizumab n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**41**	**8**		**25.1 %**	**3.21 [0.20, 51.33]**
Total events: 7 (Certolizumab), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.83 (P = 0.41)					
4 certolizumab 400 mg sc					
CDP870-004 2001	17/42	0/8		25.2 %	7.33 [0.48, 110.96]
Subtotal (95% CI)	**42**	**8**		**25.2 %**	**7.33 [0.48, 110.96]**
Total events: 17 (Certolizumab), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.44 (P = 0.15)					
Total (95% CI)	**162**	**32**		**100.0 %**	**3.31 [0.83, 13.26]**
Total events: 29 (Certolizumab), 0 (Control)					
Heterogeneity: Chi^2 = 1.12, df = 3 (P = 0.77); I^2 =0.0%					
Test for overall effect: Z = 1.69 (P = 0.090)					

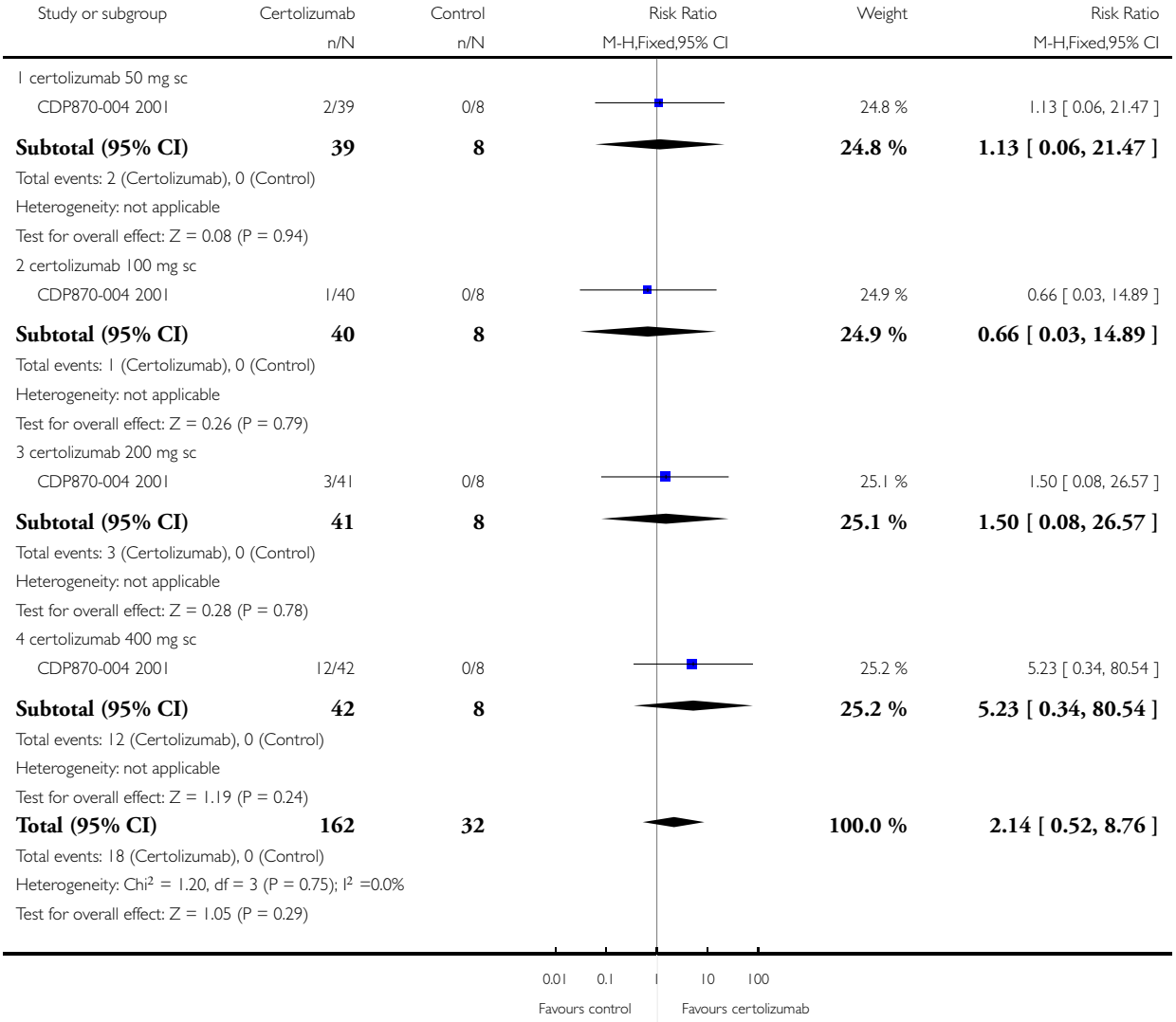


Analysis 1.3. Comparison 1 Efficacy at 12 weeks, any dose, Outcome 3 ACR70.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 1 Efficacy at 12 weeks, any dose

Outcome: 3 ACR70



Analysis 2.1. Comparison 2 Efficacy at 24 weeks 200 mg certolizumab sc, Outcome 1 ACR 20.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 2 Efficacy at 24 weeks 200 mg certolizumab sc

Outcome: 1 ACR 20

Study or subgroup	Certolizumab 200 mg sc n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
RAPID1 2005	228/393	27/199		71.2 %	4.28 [2.98, 6.13]
RAPID2 2007	141/246	11/127		28.8 %	6.62 [3.72, 11.76]
Total (95% CI)	**639**	**326**		**100.0 %**	**4.95 [3.65, 6.72]**

Total events: 369 (Certolizumab 200 mg sc), 38 (Placebo)

Heterogeneity: Chi^2 = 1.61, df = 1 (P = 0.20); I^2 =38%

Test for overall effect: Z = 10.25 (P < 0.00001)

Analysis 2.2. Comparison 2 Efficacy at 24 weeks 200 mg certolizumab sc, Outcome 2 ACR 50.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 2 Efficacy at 24 weeks 200 mg certolizumab sc

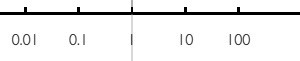
Outcome: 2 ACR 50

Study or subgroup	Certolizumab 200 mg sc n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
RAPID1 2005	144/393	15/199		79.1 %	4.86 [2.94, 8.04]
RAPID2 2007	80/246	4/127		20.9 %	10.33 [3.87, 27.54]
Total (95% CI)	**639**	**326**		**100.0 %**	**6.01 [3.84, 9.40]**

Total events: 224 (Certolizumab 200 mg sc), 19 (Placebo)

Heterogeneity: Chi^2 = 1.85, df = 1 (P = 0.17); I^2 =46%

Test for overall effect: Z = 7.84 (P < 0.00001)



Analysis 2.3. Comparison 2 Efficacy at 24 weeks 200 mg certolizumab sc, Outcome 3 ACR 70.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 2 Efficacy at 24 weeks 200 mg certolizumab sc

Outcome: 3 ACR 70

Study or subgroup	Certolizumab 200 mg sc n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
RAPID1 2005	83/393	6/199		85.8 %	7.00 [3.11, 15.76]
RAPID2 2007	39/246	1/127		14.2 %	20.13 [2.80, 144.86]
Total (95% CI)	**639**	**326**		**100.0 %**	**8.87 [4.20, 18.75]**

Total events: 122 (Certolizumab 200 mg sc), 7 (Placebo)

Heterogeneity: $Chi^2 = 0.99$, df = 1 (P = 0.32); $I^2 = 0.0\%$

Test for overall effect: Z = 5.71 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 3.1. Comparison 3 Efficacy at 24 weeks, 400 mg sc certolizumab, Outcome 1 ACR 20.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 3 Efficacy at 24 weeks, 400 mg sc certolizumab

Outcome: 1 ACR 20

Study or subgroup	Certolizumab n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
CDP870-014 2009	56/126	27/121		31.3 %	1.99 [1.35, 2.93]
FAST4WARD 2005	50/111	10/109		11.5 %	4.91 [2.63, 9.18]
RAPID1 2005	236/390	27/199		40.7 %	4.46 [3.11, 6.39]
RAPID2 2007	141/246	11/127		16.5 %	6.62 [3.72, 11.76]
Total (95% CI)	**873**	**556**		**100.0 %**	**4.09 [3.27, 5.13]**

Total events: 483 (Certolizumab), 75 (Control)

Heterogeneity: $Chi^2 = 16.64$, df = 3 (P = 0.00084); $I^2 = 82\%$

Test for overall effect: Z = 12.21 (P < 0.00001)

Analysis 3.2. Comparison 3 Efficacy at 24 weeks, 400 mg sc certolizumab, Outcome 2 ACR 50.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 3 Efficacy at 24 weeks, 400 mg sc certolizumab

Outcome: 2 ACR 50

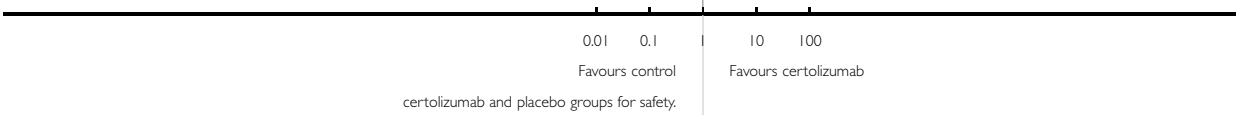
Study or subgroup	Certolizumab n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
CDP870-014 2009 (1)	22/126	7/121		19.7 %	3.02 [1.34, 6.81]
FAST4WARD 2005	25/111	4/109		11.1 %	6.14 [2.21, 17.05]
RAPID1 2005	155/390	15/199		54.7 %	5.27 [3.19, 8.71]
RAPID2 2007	81/246	4/127		14.5 %	10.45 [3.92, 27.88]
Total (95% CI)	**873**	**556**		**100.0 %**	**5.68 [3.93, 8.20]**

Total events: 283 (Certolizumab), 30 (Control)

Heterogeneity: $Chi^2 = 3.91$, df = 3 (P = 0.27); $I^2 = 23\%$

Test for overall effect: Z = 9.27 (P < 0.00001)

Test for subgroup differences: Not applicable



certolizumab and placebo groups for safety.

(1) EMEA report quotes 126 and 121 patients in certoluzimab and placebo group. Clinical Study Summary (CSS) from UCB quotes n=125 for both groups for effectiveness and 119 and 124 for

Analysis 3.3. Comparison 3 Efficacy at 24 weeks, 400 mg sc certolizumab, Outcome 3 ACR 70.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 3 Efficacy at 24 weeks, 400 mg sc certolizumab

Outcome: 3 ACR 70

Study or subgroup	Certolizumab n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
CDP870-014 2009 (1)	0/126	2/121		20.7 %	0.19 [0.01, 3.96]
FAST4WARD 2005	6/111	0/109		4.1 %	12.77 [0.73, 223.93]
RAPID1 2005	80/390	6/199		64.5 %	6.80 [3.02, 15.32]
RAPID2 2007	26/246	1/127		10.7 %	13.42 [1.84, 97.78]
Total (95% CI)	**873**	**556**		**100.0 %**	**6.39 [3.32, 12.27]**
Total events: 112 (Certolizumab), 9 (Control)					
Heterogeneity: Chi^2 = 5.94, df = 3 (P = 0.11); I^2 =49%					
Test for overall effect: Z = 5.57 (P < 0.00001)					
Test for subgroup differences: Not applicable					

(1) From EMEA report

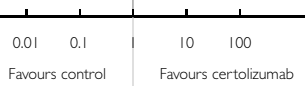
Analysis 4.1. Comparison 4 Efficacy at 24 weeks, any dose, Outcome 1 ACR20.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 4 Efficacy at 24 weeks, any dose

Outcome: 1 ACR20

Study or subgroup	Certolizumab n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 certolizumab 200 mg sc					
RAPID1 2005	228/393	27/100		27.1 %	2.15 [1.54, 3.00]
RAPID2 2007	141/246	11/64		11.0 %	3.33 [1.93, 5.77]
Subtotal (95% CI)	**639**	**164**		**38.1 %**	**2.49 [1.87, 3.32]**
Total events: 369 (Certolizumab), 38 (Control)					
Heterogeneity: Chi^2 = 1.84, df = 1 (P = 0.17); I^2 =46%					
Test for overall effect: Z = 6.25 (P < 0.00001)					
2 certolizumab 400 mg sc					
CDP870-014 2009	56/126	27/121		17.4 %	1.99 [1.35, 2.93]
FAST4WARD 2005	50/111	10/109		6.4 %	4.91 [2.63, 9.18]
RAPID1 2005	236/390	27/99		27.1 %	2.22 [1.59, 3.09]
RAPID2 2007	141/246	11/63		11.0 %	3.28 [1.90, 5.68]
Subtotal (95% CI)	**873**	**392**		**61.9 %**	**2.62 [2.11, 3.25]**
Total events: 483 (Certolizumab), 75 (Control)					
Heterogeneity: Chi^2 = 7.44, df = 3 (P = 0.06); I^2 =60%					
Test for overall effect: Z = 8.76 (P < 0.00001)					
Total (95% CI)	**1512**	**556**		**100.0 %**	**2.57 [2.16, 3.05]**
Total events: 852 (Certolizumab), 113 (Control)					
Heterogeneity: Chi^2 = 9.30, df = 5 (P = 0.10); I^2 =46%					
Test for overall effect: Z = 10.75 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.0, df = 1 (P = 0.0), I^2 =0.0%					



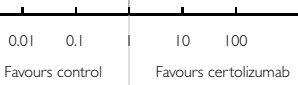
Analysis 4.2. Comparison 4 Efficacy at 24 weeks, any dose, Outcome 2 ACR50.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 4 Efficacy at 24 weeks, any dose

Outcome: 2 ACR50

Study or subgroup	Certolizumab n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 certolizumab 200 mg sc					
RAPID1 2005	144/393	15/100		33.3 %	2.44 [1.50, 3.96]
RAPID2 2007	80/246	4/64		8.8 %	5.20 [1.98, 13.67]
Subtotal (95% CI)	**639**	**164**		**42.2 %**	**3.02 [1.96, 4.67]**
Total events: 224 (Certolizumab), 19 (Control)					
Heterogeneity: Chi^2 = 1.96, df = 1 (P = 0.16); I^2 =49%					
Test for overall effect: Z = 4.98 (P < 0.00001)					
2 certolizumab 400 mg sc					
CDP870-014 2009	22/126	7/121		10.0 %	3.02 [1.34, 6.81]
FAST4WARD 2005	25/111	4/109		5.6 %	6.14 [2.21, 17.05]
RAPID1 2005	155/390	15/99		33.4 %	2.62 [1.62, 4.25]
RAPID2 2007	81/246	4/63		8.9 %	5.19 [1.98, 13.61]
Subtotal (95% CI)	**873**	**392**		**57.8 %**	**3.43 [2.40, 4.90]**
Total events: 283 (Certolizumab), 30 (Control)					
Heterogeneity: Chi^2 = 3.23, df = 3 (P = 0.36); I^2 =7%					
Test for overall effect: Z = 6.76 (P < 0.00001)					
Total (95% CI)	**1512**	**556**		**100.0 %**	**3.26 [2.47, 4.29]**
Total events: 507 (Certolizumab), 49 (Control)					
Heterogeneity: Chi^2 = 5.44, df = 5 (P = 0.37); I^2 =8%					
Test for overall effect: Z = 8.39 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.0, df = 1 (P = 0.0), I^2 =0.0%					

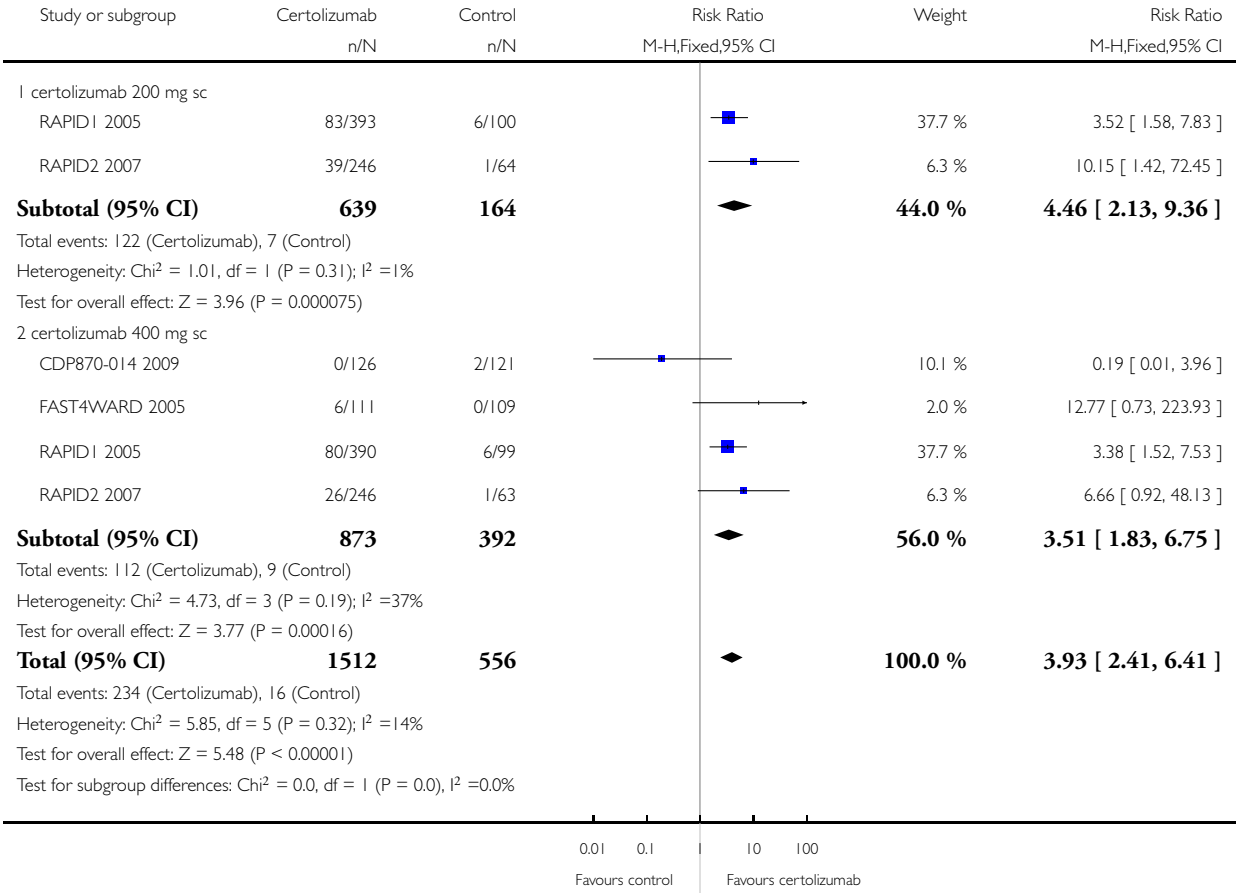


Analysis 4.3. Comparison 4 Efficacy at 24 weeks, any dose, Outcome 3 ACR70.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 4 Efficacy at 24 weeks, any dose

Outcome: 3 ACR70



Analysis 5.1. Comparison 5 Efficacy at 52 weeks, 200 mg sc certolizumab, Outcome 1 ACR 20.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 5 Efficacy at 52 weeks, 200 mg sc certolizumab

Outcome: 1 ACR 20

Study or subgroup	Certolizumab n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
RAPID1 2005	208/393	26/199		100.0 %	4.05 [2.80, 5.87]
Total (95% CI)	**393**	**199**		**100.0 %**	**4.05 [2.80, 5.87]**
Total events: 208 (Certolizumab), 26 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 7.40 (P < 0.00001)					
Test for subgroup differences: Not applicable					

Analysis 5.2. Comparison 5 Efficacy at 52 weeks, 200 mg sc certolizumab, Outcome 2 ACR 50.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 5 Efficacy at 52 weeks, 200 mg sc certolizumab

Outcome: 2 ACR 50

Study or subgroup	Certolizumab n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
RAPID1 2005	149/393	15/199		100.0 %	5.03 [3.04, 8.32]
Total (95% CI)	**393**	**199**		**100.0 %**	**5.03 [3.04, 8.32]**
Total events: 149 (Certolizumab), 15 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 6.30 (P < 0.00001)					
Test for subgroup differences: Not applicable					

Analysis 5.3. Comparison 5 Efficacy at 52 weeks, 200 mg sc certolizumab, Outcome 3 ACR 70.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 5 Efficacy at 52 weeks, 200 mg sc certolizumab

Outcome: 3 ACR 70

Study or subgroup	Certolizumab n/N	Control n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
RAPID1 2005	83/393	7/199		100.0 %	0.18 [0.13, 0.22]
Total (95% CI)	**393**	**199**		**100.0 %**	**0.18 [0.13, 0.22]**
Total events: 83 (Certolizumab), 7 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 7.22 (P < 0.00001)					
Test for subgroup differences: Not applicable					

Analysis 6.1. Comparison 6 Efficacy at 52 weeks, 400 mg sc certolizumab, Outcome 1 ACR 20.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 6 Efficacy at 52 weeks, 400 mg sc certolizumab

Outcome: 1 ACR 20

Study or subgroup	Certolizumab n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
RAPID1 2005	213/390	26/199		100.0 %	4.18 [2.89, 6.05]
Total (95% CI)	**390**	**199**		**100.0 %**	**4.18 [2.89, 6.05]**
Total events: 213 (Certolizumab), 26 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 7.58 (P < 0.00001)					
Test for subgroup differences: Not applicable					

Analysis 6.2. Comparison 6 Efficacy at 52 weeks, 400 mg sc certolizumab, Outcome 2 ACR 50.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 6 Efficacy at 52 weeks, 400 mg sc certolizumab

Outcome: 2 ACR 50

Study or subgroup	Certolizumab n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
RAPID1 2005	155/390	15/199		100.0 %	5.27 [3.19, 8.71]
Total (95% CI)	**390**	**199**		**100.0 %**	**5.27 [3.19, 8.71]**
Total events: 155 (Certolizumab), 15 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 6.49 (P < 0.00001)					
Test for subgroup differences: Not applicable					

Analysis 6.3. Comparison 6 Efficacy at 52 weeks, 400 mg sc certolizumab, Outcome 3 ACR 70.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 6 Efficacy at 52 weeks, 400 mg sc certolizumab

Outcome: 3 ACR 70

Study or subgroup	Certolizumab n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
RAPID1 2005	90/390	7/199		100.0 %	6.56 [3.10, 13.89]
Total (95% CI)	**390**	**199**		**100.0 %**	**6.56 [3.10, 13.89]**
Total events: 90 (Certolizumab), 7 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.92 (P < 0.00001)					
Test for subgroup differences: Not applicable					

Analysis 7.1. Comparison 7 Efficacy at 52 weeks, any dose, Outcome 1 ACR20.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 7 Efficacy at 52 weeks, any dose

Outcome: 1 ACR20

Study or subgroup	Certolizumab n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 certolizumab 200 mg sc					
RAPID1 2005	208/393	26/100		50.0 %	2.04 [1.44, 2.87]
Subtotal (95% CI)	**393**	**100**		**50.0 %**	**2.04 [1.44, 2.87]**
Total events: 208 (Certolizumab), 26 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.06 (P = 0.000050)					
2 certolizumab 400 mg sc					
RAPID1 2005	213/390	26/99		50.0 %	2.08 [1.48, 2.93]
Subtotal (95% CI)	**390**	**99**		**50.0 %**	**2.08 [1.48, 2.93]**
Total events: 213 (Certolizumab), 26 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.19 (P = 0.000028)					
Total (95% CI)	**783**	**199**		**100.0 %**	**2.06 [1.61, 2.62]**
Total events: 421 (Certolizumab), 52 (Control)					
Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.93); I^2 =0.0%					
Test for overall effect: Z = 5.83 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.0, df = 1 (P = 0.0), I^2 =0.0%					

Analysis 7.2. Comparison 7 Efficacy at 52 weeks, any dose, Outcome 2 ACR50.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 7 Efficacy at 52 weeks, any dose

Outcome: 2 ACR50

Study or subgroup	Certolizumab n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 certolizumab 200 mg sc					
RAPID1 2005	149/393	15/100		50.0 %	2.53 [1.56, 4.10]
Subtotal (95% CI)	**393**	**100**		**50.0 %**	**2.53 [1.56, 4.10]**
Total events: 149 (Certolizumab), 15 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.76 (P = 0.00017)					
2 certolizumab 400 mg sc					
RAPID1 2005	155/390	15/99		50.0 %	2.62 [1.62, 4.25]
Subtotal (95% CI)	**390**	**99**		**50.0 %**	**2.62 [1.62, 4.25]**
Total events: 155 (Certolizumab), 15 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.92 (P = 0.000088)					
Total (95% CI)	**783**	**199**		**100.0 %**	**2.58 [1.83, 3.62]**
Total events: 304 (Certolizumab), 30 (Control)					
Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.92); I^2 =0.0%					
Test for overall effect: Z = 5.43 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.0, df = 1 (P = 0.0), I^2 =0.0%					

Analysis 7.3. Comparison 7 Efficacy at 52 weeks, any dose, Outcome 3 ACR70.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 7 Efficacy at 52 weeks, any dose

Outcome: 3 ACR70

Study or subgroup	Certolizumab n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 certolizumab 200 mg sc					
RAPID1 2005	83/393	7/100		50.0 %	3.02 [1.44, 6.32]
Subtotal (95% CI)	**393**	**100**		**50.0 %**	**3.02 [1.44, 6.32]**
Total events: 83 (Certolizumab), 7 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.93 (P = 0.0034)					
2 certolizumab 400 mg sc					
RAPID1 2005	90/390	7/99		50.0 %	3.26 [1.56, 6.82]
Subtotal (95% CI)	**390**	**99**		**50.0 %**	**3.26 [1.56, 6.82]**
Total events: 90 (Certolizumab), 7 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.15 (P = 0.0017)					
Total (95% CI)	**783**	**199**		**100.0 %**	**3.14 [1.86, 5.29]**
Total events: 173 (Certolizumab), 14 (Control)					
Heterogeneity: Chi^2 = 0.02, df = 1 (P = 0.88); I^2 =0.0%					
Test for overall effect: Z = 4.30 (P = 0.000017)					
Test for subgroup differences: Chi^2 = 0.0, df = 1 (P = 0.0), I^2 =0.0%					

Analysis 8.1. Comparison 8 Safety certolizumab 200 mg sc, Outcome 1 Any adverse event.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety certolizumab 200 mg sc

Outcome: 1 Any adverse event

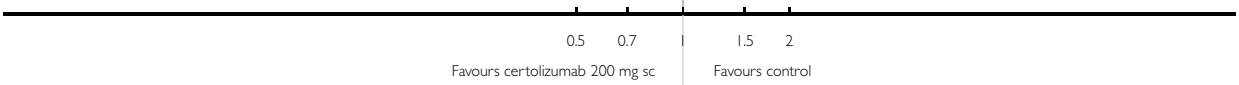
Study or subgroup	Certolizumab 200 mg sc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
RAPID1 2005	293/392	115/199		63.5 %	1.29 [1.13, 1.48]
RAPID2 2007	139/248	66/125		36.5 %	1.06 [0.87, 1.30]
Total (95% CI)	**640**	**324**		**100.0 %**	**1.21 [1.08, 1.35]**

Total events: 432 (Certolizumab 200 mg sc), 181 (Control)

Heterogeneity: Chi^2 = 2.65, df = 1 (P = 0.10); I^2 =62%

Test for overall effect: Z = 3.37 (P = 0.00075)

Test for subgroup differences: Not applicable



Analysis 8.2. Comparison 8 Safety certolizumab 200 mg sc, Outcome 2 Adverse events Intensity mild.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety certolizumab 200 mg sc

Outcome: 2 Adverse events Intensity mild

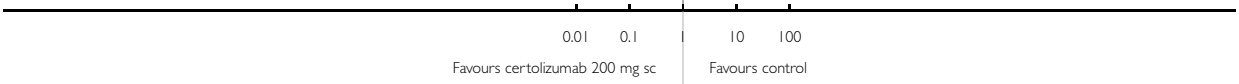
Study or subgroup	Certolizumab 200 mg sc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
RAPID1 2005	244/392	90/199		66.6 %	1.38 [1.16, 1.63]
RAPID2 2007	108/248	45/125		33.4 %	1.21 [0.92, 1.59]
Total (95% CI)	**640**	**324**		**100.0 %**	**1.32 [1.14, 1.53]**

Total events: 352 (Certolizumab 200 mg sc), 135 (Control)

Heterogeneity: Chi^2 = 0.62, df = 1 (P = 0.43); I^2 =0.0%

Test for overall effect: Z = 3.75 (P = 0.00018)

Test for subgroup differences: Not applicable



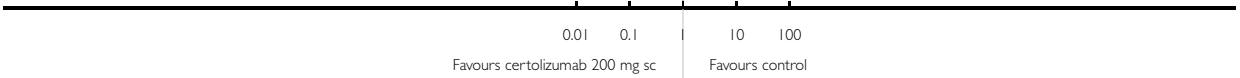
Analysis 8.3. Comparison 8 Safety certolizumab 200 mg sc, Outcome 3 Adverse events Intensity moderate.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety certolizumab 200 mg sc

Outcome: 3 Adverse events Intensity moderate

Study or subgroup	Certolizumab 200 mg sc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
RAPID1 2005	174/392	66/199		67.3 %	1.34 [1.07, 1.68]
RAPID2 2007	61/248	32/125		32.7 %	0.96 [0.66, 1.39]
Total (95% CI)	**640**	**324**		**100.0 %**	**1.21 [1.00, 1.47]**
Total events: 235 (Certolizumab 200 mg sc), 98 (Control)					
Heterogeneity: Chi^2 = 2.25, df = 1 (P = 0.13); I^2 =56%					
Test for overall effect: Z = 1.98 (P = 0.048)					



Analysis 8.4. Comparison 8 Safety certolizumab 200 mg sc, Outcome 4 Adverse events Intensity severe.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety certolizumab 200 mg sc

Outcome: 4 Adverse events Intensity severe

Study or subgroup	Certolizumab 200 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
RAPID1 2005	32/392	13/199		66.8 %	1.26 [0.66, 2.40]
RAPID2 2007	17/248	5/125		33.2 %	1.67 [0.67, 4.16]
Total (95% CI)	**640**	**324**		**100.0 %**	**1.38 [0.82, 2.34]**

Total events: 49 (Certolizumab 200 mg sc), 18 (Control)

Heterogeneity: $Chi^2 = 0.24$, df = 1 (P = 0.62); $I^2 = 0.0\%$

Test for overall effect: Z = 1.21 (P = 0.23)

Test for subgroup differences: Not applicable

Analysis 8.5. Comparison 8 Safety certolizumab 200 mg sc, Outcome 5 Adverse events related to study drug.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety certolizumab 200 mg sc

Outcome: 5 Adverse events related to study drug

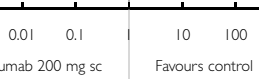
Study or subgroup	Certolizumab 200 mg sc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
RAPID1 2005	167/392	50/199		68.4 %	1.70 [1.30, 2.21]
RAPID2 2007	61/248	23/125		31.6 %	1.34 [0.87, 2.05]
Total (95% CI)	**640**	**324**		**100.0 %**	**1.58 [1.26, 1.98]**

Total events: 228 (Certolizumab 200 mg sc), 73 (Control)

Heterogeneity: $Chi^2 = 0.85$, df = 1 (P = 0.36); $I^2 = 0.0\%$

Test for overall effect: Z = 3.98 (P = 0.000068)

Test for subgroup differences: Not applicable



Analysis 8.6. Comparison 8 Safety certolizumab 200 mg sc, Outcome 6 Serious Adverse Events (SAE).

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety certolizumab 200 mg sc

Outcome: 6 Serious Adverse Events (SAE)

Study or subgroup	Certolizumab 200 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
RAPID1 2005	45/392	11/199		71.0 %	2.00 [1.12, 3.58]
RAPID2 2007	18/248	4/125		29.0 %	2.07 [0.83, 5.16]
Total (95% CI)	**640**	**324**		**100.0 %**	**2.02 [1.24, 3.30]**

Total events: 63 (Certolizumab 200 mg sc), 15 (Control)

Heterogeneity: $Chi^2 = 0.00$, df = 1 (P = 0.95); $I^2 = 0.0\%$

Test for overall effect: Z = 2.81 (P = 0.0050)

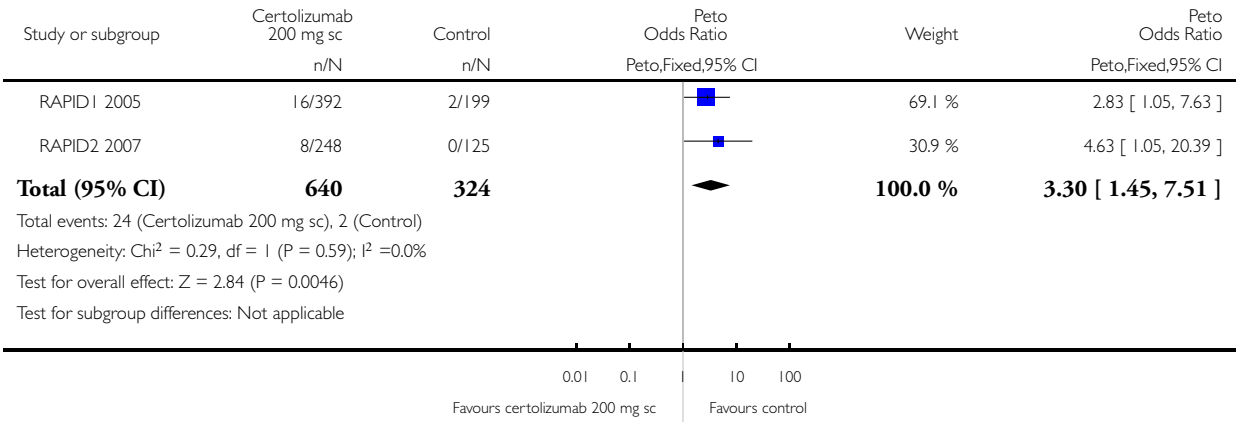
Test for subgroup differences: Not applicable

Analysis 8.7. Comparison 8 Safety certolizumab 200 mg sc, Outcome 7 Serious Infections.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety certolizumab 200 mg sc

Outcome: 7 Serious Infections

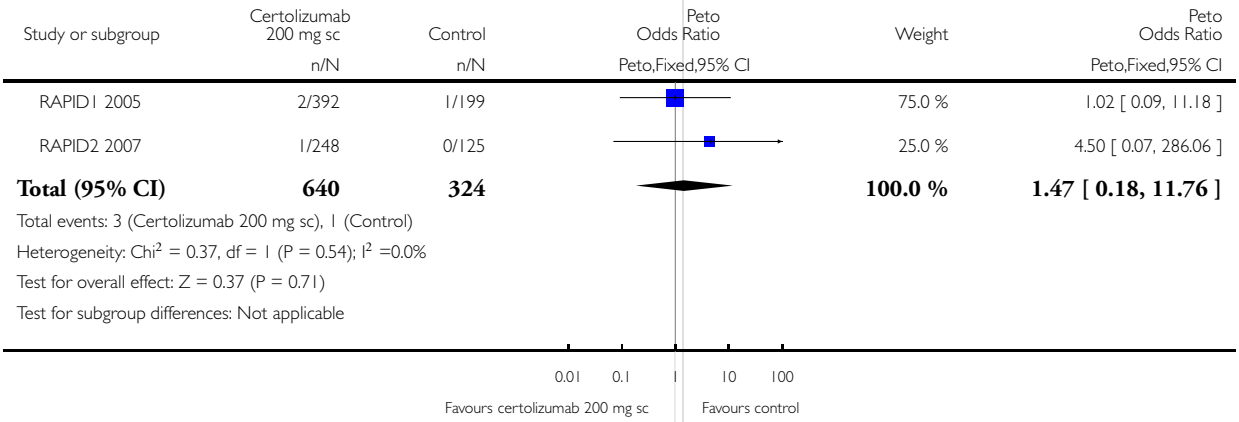


Analysis 8.8. Comparison 8 Safety certolizumab 200 mg sc, Outcome 8 Adverse events leading to death.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety certolizumab 200 mg sc

Outcome: 8 Adverse events leading to death



Analysis 8.9. Comparison 8 Safety certolizumab 200 mg sc, Outcome 9 Adverse events leading to withdrawal.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety certolizumab 200 mg sc

Outcome: 9 Adverse events leading to withdrawal

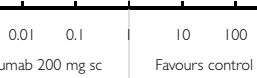
Study or subgroup	Certolizumab 200 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
RAPID1 2005	17/392	3/199		58.9 %	2.37 [0.92, 6.09]
RAPID2 2007	12/248	2/125		41.1 %	2.45 [0.79, 7.57]
Total (95% CI)	**640**	**324**		**100.0 %**	**2.40 [1.16, 4.95]**

Total events: 29 (Certolizumab 200 mg sc), 5 (Control)

Heterogeneity: $Chi^2 = 0.00$, df = 1 (P = 0.97); $I^2 = 0.0\%$

Test for overall effect: Z = 2.37 (P = 0.018)

Test for subgroup differences: Not applicable

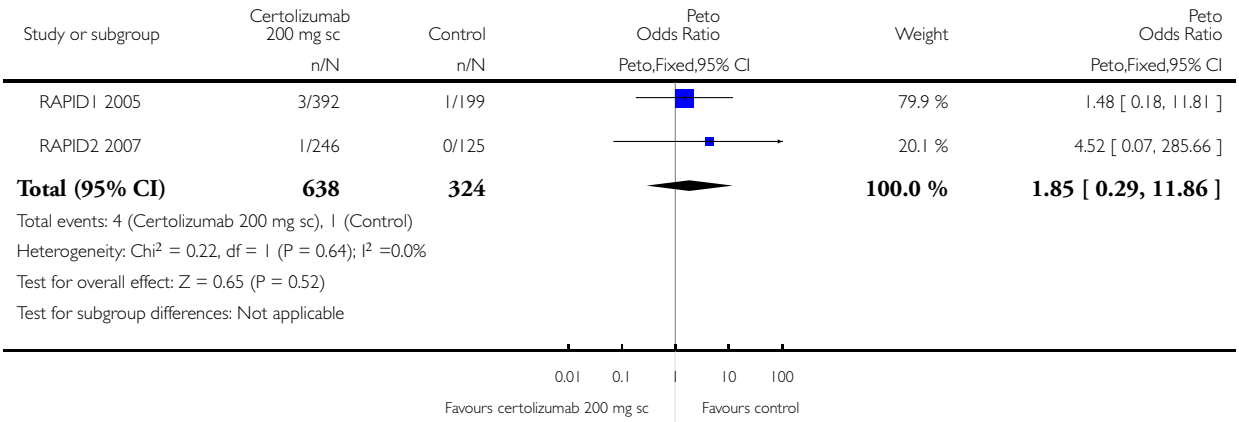


Analysis 8.10. Comparison 8 Safety certolizumab 200 mg sc, Outcome 10 Death.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety certolizumab 200 mg sc

Outcome: 10 Death

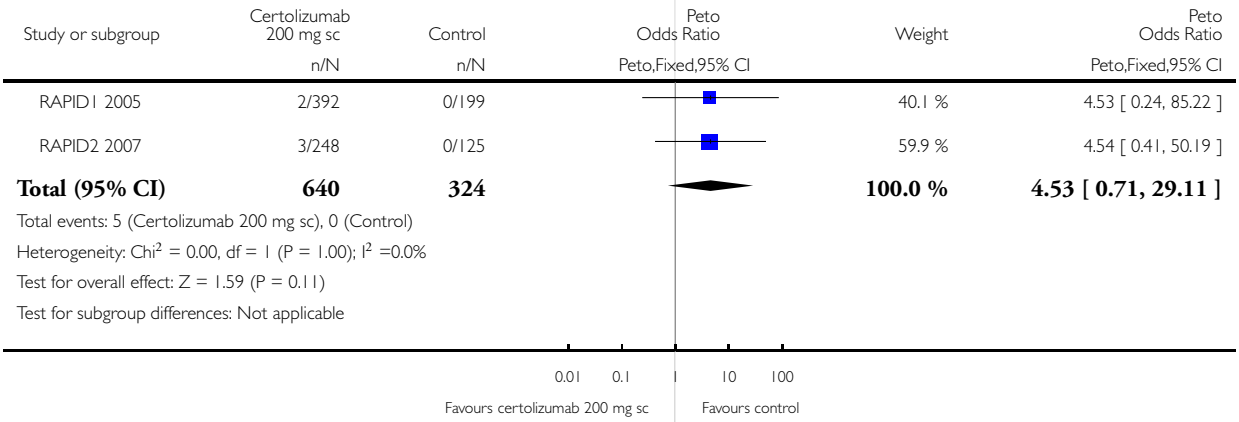


Analysis 8.11. Comparison 8 Safety certolizumab 200 mg sc, Outcome 11 Tuberculosis.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety certolizumab 200 mg sc

Outcome: 11 Tuberculosis



Analysis 8.12. Comparison 8 Safety certolizumab 200 mg sc, Outcome 12 Malignancies included lymphoma.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety certolizumab 200 mg sc

Outcome: 12 Malignancies included lymphoma

Study or subgroup	Certolizumab 200 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
RAPID1 2005 (1)	7/392	1/199		79.9 %	2.61 [0.60, 11.41]
RAPID2 2007	1/248	1/125		20.1 %	0.48 [0.03, 9.01]
Total (95% CI)	**640**	**324**		**100.0 %**	**1.85 [0.50, 6.93]**

Total events: 8 (Certolizumab 200 mg sc), 2 (Control)

Heterogeneity: Chi^2 = 1.03, df = 1 (P = 0.31); I^2 =3%

Test for overall effect: Z = 0.92 (P = 0.36)

Test for subgroup differences: Not applicable

(1) One patient in the arm of placebo suffered a thyroid neoplasm and 7 in the arm of certolizumab 200 mg sc suffered: three basal cell carcinomas [one with metastasis to the central nervous system], one adrenal adenoma, one hepatic neoplasm one esophageal carcinoma, and uterine cancer

Analysis 8.13. Comparison 8 Safety certolizumab 200 mg sc, Outcome 13 Injection site pain.

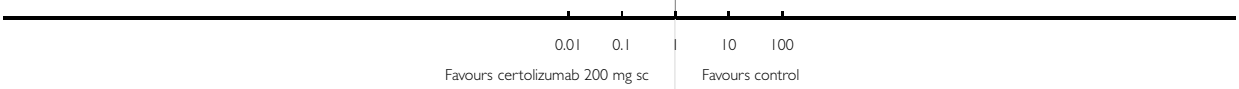
Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety certolizumab 200 mg sc

Outcome: 13 Injection site pain

Study or subgroup	Certolizumab 200 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
RAPID1 2005	8/392	0/199		100.0 %	4.60 [1.05, 20.10]
RAPID2 2007	0/248	0/125			Not estimable
Total (95% CI)	**640**	**324**		**100.0 %**	**4.60 [1.05, 20.10]**

Total events: 8 (Certolizumab 200 mg sc), 0 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 2.03 (P = 0.043)
Test for subgroup differences: Not applicable



Analysis 8.14. Comparison 8 Safety certolizumab 200 mg sc, Outcome 14 Injection side reactions.

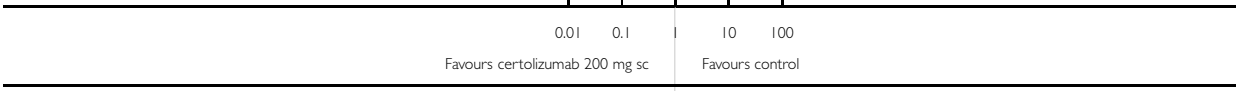
Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety certolizumab 200 mg sc

Outcome: 14 Injection side reactions

Study or subgroup	Certolizumab 200 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
RAPID1 2005	9/392	0/199		74.9 %	4.61 [1.15, 18.55]
RAPID2 2007	3/248	0/125		25.1 %	4.54 [0.41, 50.19]
Total (95% CI)	**640**	**324**		**100.0 %**	**4.59 [1.38, 15.32]**

Total events: 12 (Certolizumab 200 mg sc), 0 (Control)
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.99); I^2 =0.0%
Test for overall effect: Z = 2.48 (P = 0.013)
Test for subgroup differences: Not applicable



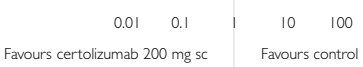
Analysis 8.15. Comparison 8 Safety certolizumab 200 mg sc, Outcome 15 Neutralising Anti-certolizumab pegol antibodies.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety certolizumab 200 mg sc

Outcome: 15 Neutralising Anti-certolizumab pegol antibodies

Study or subgroup	Certolizumab 200 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
RAPID2 2007	5/248	0/125		100.0 %	4.57 [0.71, 29.59]
Total (95% CI)	**248**	**125**		**100.0 %**	**4.57 [0.71, 29.59]**
Total events: 5 (Certolizumab 200 mg sc), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.60 (P = 0.11)					
Test for subgroup differences: Not applicable					

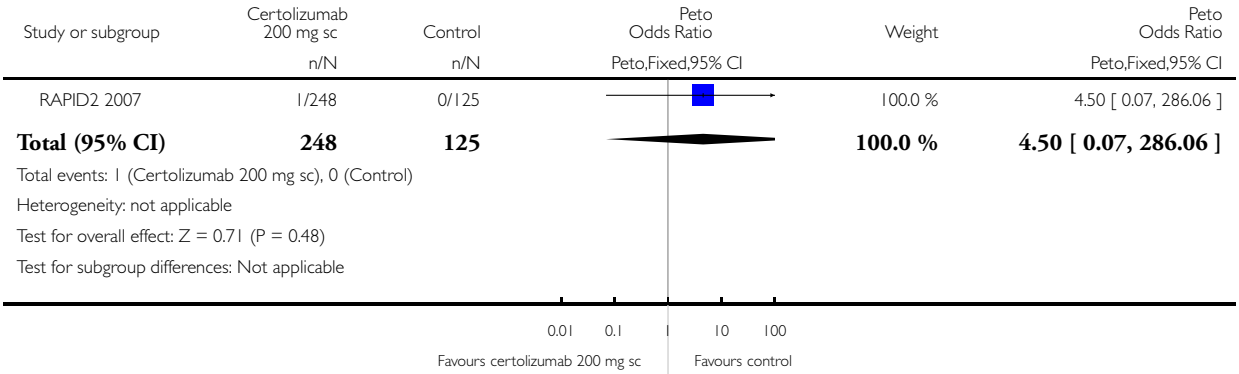


Analysis 8.16. Comparison 8 Safety certolizumab 200 mg sc, Outcome 16 Systemic lupus erythematosus.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety certolizumab 200 mg sc

Outcome: 16 Systemic lupus erythematosus

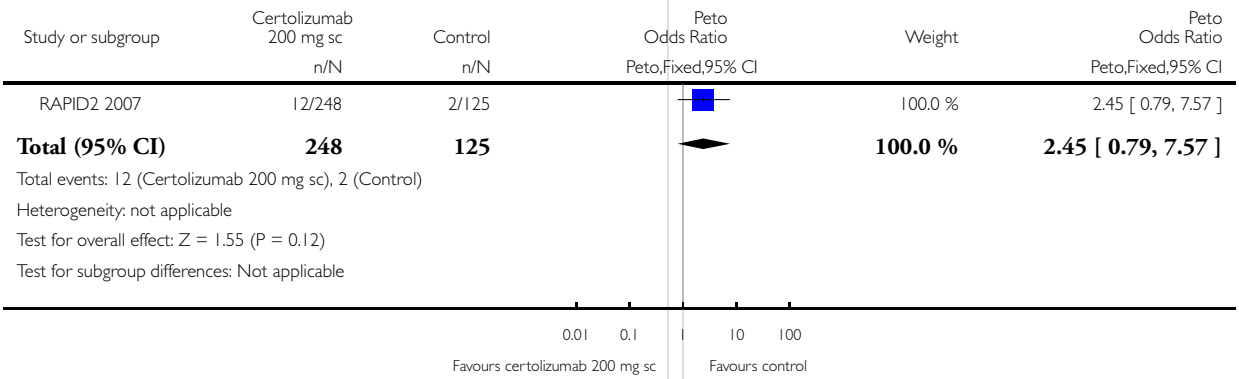


Analysis 8.17. Comparison 8 Safety certolizumab 200 mg sc, Outcome 17 Prolonged activated partial thromboplastin time (aPTT).

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety certolizumab 200 mg sc

Outcome: 17 Prolonged activated partial thromboplastin time (aPTT)

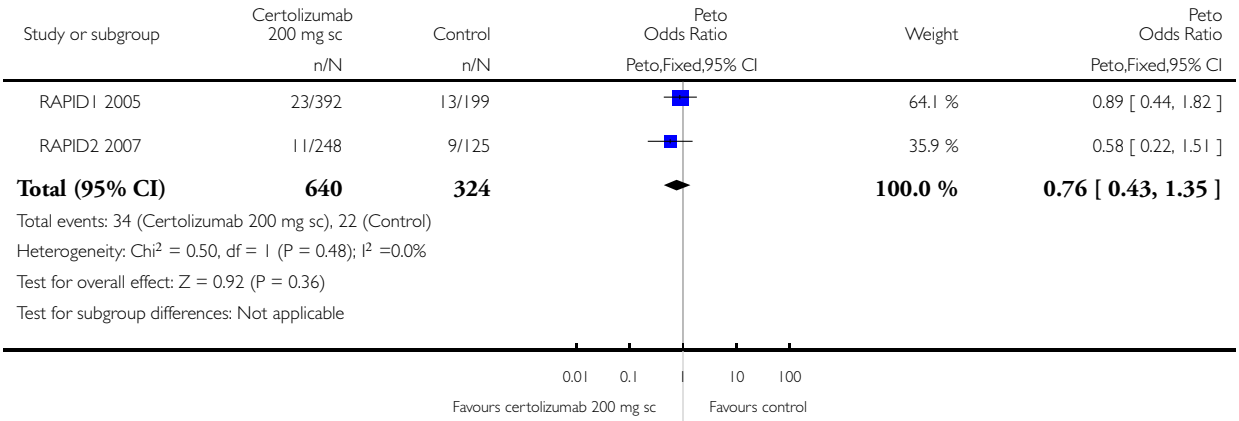


Analysis 8.18. Comparison 8 Safety certolizumab 200 mg sc, Outcome 18 Urinary tract infection.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety certolizumab 200 mg sc

Outcome: 18 Urinary tract infection

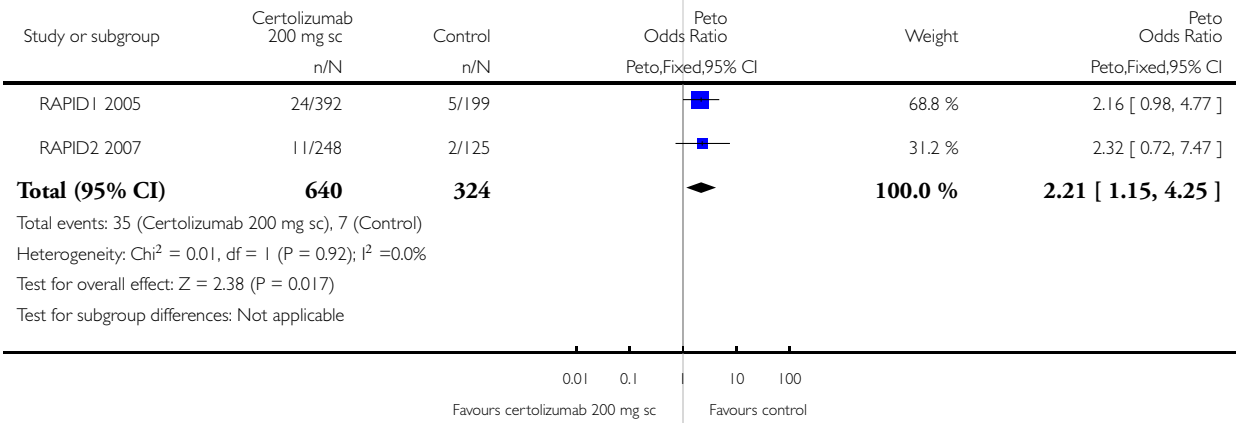


Analysis 8.19. Comparison 8 Safety certolizumab 200 mg sc, Outcome 19 Upper respiratory tract infection.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety certolizumab 200 mg sc

Outcome: 19 Upper respiratory tract infection



Analysis 8.20. Comparison 8 Safety certolizumab 200 mg sc, Outcome 20 Lower respiratory tract infection/ lung infection.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety certolizumab 200 mg sc

Outcome: 20 Lower respiratory tract infection/ lung infection

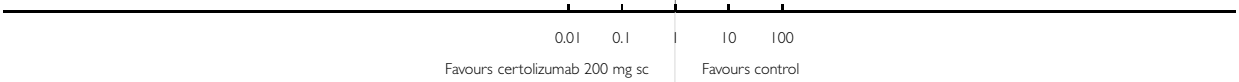
Study or subgroup	Certolizumab 200 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
RAPID1 2005	3/392	0/199		100.0 %	4.54 [0.41, 49.96]
Total (95% CI)	**392**	**199**		**100.0 %**	**4.54 [0.41, 49.96]**

Total events: 3 (Certolizumab 200 mg sc), 0 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 1.24 (P = 0.22)

Test for subgroup differences: Not applicable



Analysis 8.21. Comparison 8 Safety certolizumab 200 mg sc, Outcome 21 Headache.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety certolizumab 200 mg sc

Outcome: 21 Headache

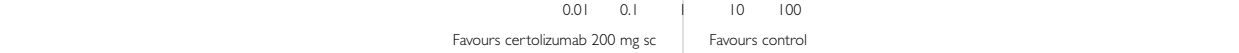
Study or subgroup	Certolizumab 200 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
RAPID1 2005	22/392	11/199		76.2 %	1.02 [0.48, 2.13]
RAPID2 2007	9/248	1/125		23.8 %	2.95 [0.78, 11.14]
Total (95% CI)	**640**	**324**		**100.0 %**	**1.31 [0.68, 2.50]**

Total events: 31 (Certolizumab 200 mg sc), 12 (Control)

Heterogeneity: Chi^2 = 1.88, df = 1 (P = 0.17); I^2 =47%

Test for overall effect: Z = 0.81 (P = 0.42)

Test for subgroup differences: Not applicable



Analysis 8.22. Comparison 8 Safety certolizumab 200 mg sc, Outcome 22 Bacteriuria.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety certolizumab 200 mg sc

Outcome: 22 Bacteriuria

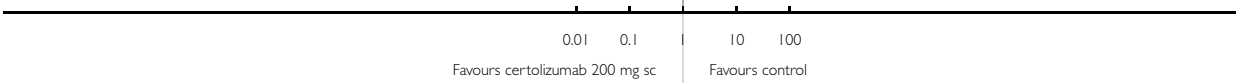
Study or subgroup	Certolizumab 200 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
RAPID2 2007	8/248	4/125		100.0 %	1.01 [0.30, 3.40]
Total (95% CI)	**248**	**125**		**100.0 %**	**1.01 [0.30, 3.40]**

Total events: 8 (Certolizumab 200 mg sc), 4 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 0.01 (P = 0.99)

Test for subgroup differences: Not applicable



Analysis 8.23. Comparison 8 Safety certolizumab 200 mg sc, Outcome 23 Nasopharyngitis.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety certolizumab 200 mg sc

Outcome: 23 Nasopharyngitis

Study or subgroup	Certolizumab 200 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
RAPID1 2005	21/392	3/199		72.4 %	2.68 [1.13, 6.36]
RAPID2 2007	8/248	1/125		27.6 %	2.79 [0.69, 11.32]
Total (95% CI)	**640**	**324**		**100.0 %**	**2.71 [1.30, 5.66]**

Total events: 29 (Certolizumab 200 mg sc), 4 (Control)

Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.96); I^2 =0.0%

Test for overall effect: Z = 2.66 (P = 0.0078)

Test for subgroup differences: Not applicable

Analysis 8.24. Comparison 8 Safety certolizumab 200 mg sc, Outcome 24 Hypertension.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety certolizumab 200 mg sc

Outcome: 24 Hypertension

Study or subgroup	Certolizumab 200 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
RAPID1 2005	25/392	2/199		76.7 %	3.42 [1.51, 7.74]
RAPID2 2007	6/248	2/125		23.3 %	1.48 [0.34, 6.50]
Total (95% CI)	**640**	**324**		**100.0 %**	**2.81 [1.38, 5.75]**

Total events: 31 (Certolizumab 200 mg sc), 4 (Control)

Heterogeneity: Chi^2 = 0.95, df = 1 (P = 0.33); I^2 =0.0%

Test for overall effect: Z = 2.84 (P = 0.0046)

Test for subgroup differences: Not applicable

Analysis 8.25. Comparison 8 Safety certolizumab 200 mg sc, Outcome 25 Hematuria.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety certolizumab 200 mg sc

Outcome: 25 Hematuria

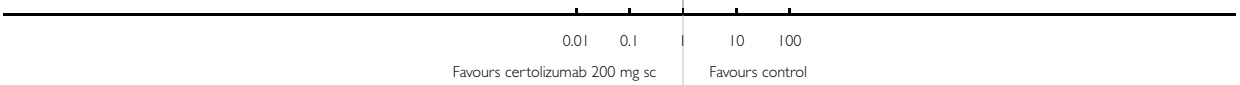
Study or subgroup	Certolizumab 200 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
RAPID2 2007	4/248	5/125		100.0 %	0.36 [0.09, 1.47]
Total (95% CI)	**248**	**125**		**100.0 %**	**0.36 [0.09, 1.47]**

Total events: 4 (Certolizumab 200 mg sc), 5 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 1.42 (P = 0.16)

Test for subgroup differences: Not applicable



Analysis 8.26. Comparison 8 Safety certolizumab 200 mg sc, Outcome 26 Hepatic enzyme increased.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety certolizumab 200 mg sc

Outcome: 26 Hepatic enzyme increased

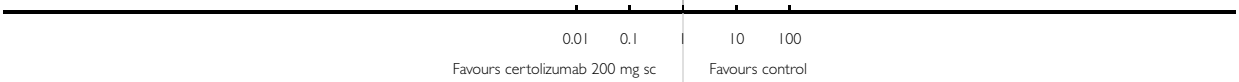
Study or subgroup	Certolizumab 200 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
RAPID2 2007	3/248	4/125		100.0 %	0.34 [0.07, 1.66]
Total (95% CI)	**248**	**125**		**100.0 %**	**0.34 [0.07, 1.66]**

Total events: 3 (Certolizumab 200 mg sc), 4 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 1.34 (P = 0.18)

Test for subgroup differences: Not applicable



Analysis 8.27. Comparison 8 Safety certolizumab 200 mg sc, Outcome 27 AST increased.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety certolizumab 200 mg sc

Outcome: 27 AST increased

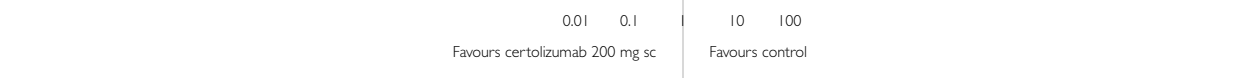
Study or subgroup	Certolizumab 200 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
RAPID2 2007	2/248	5/125		100.0 %	0.18 [0.04, 0.86]
Total (95% CI)	**248**	**125**		**100.0 %**	**0.18 [0.04, 0.86]**

Total events: 2 (Certolizumab 200 mg sc), 5 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 2.14 (P = 0.032)

Test for subgroup differences: Not applicable



Analysis 8.28. Comparison 8 Safety certolizumab 200 mg sc, Outcome 28 ALT increased.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety certolizumab 200 mg sc

Outcome: 28 ALT increased

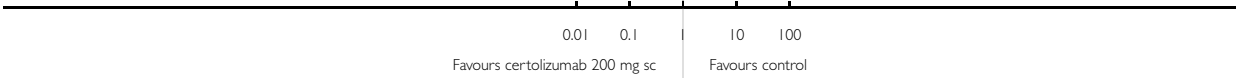
Study or subgroup	Certolizumab 200 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
RAPID2 2007	1/248	6/125		100.0 %	0.09 [0.02, 0.45]
Total (95% CI)	**248**	**125**		**100.0 %**	**0.09 [0.02, 0.45]**

Total events: 1 (Certolizumab 200 mg sc), 6 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 2.95 (P = 0.0032)

Test for subgroup differences: Not applicable



Analysis 8.29. Comparison 8 Safety certolizumab 200 mg sc, Outcome 29 Back pain.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety certolizumab 200 mg sc

Outcome: 29 Back pain

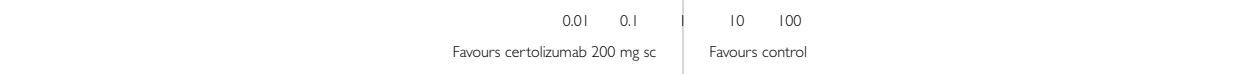
Study or subgroup	Certolizumab 200 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
RAPID1 2005	17/392	2/199		100.0 %	2.91 [1.11, 7.65]
Total (95% CI)	**392**	**199**		**100.0 %**	**2.91 [1.11, 7.65]**

Total events: 17 (Certolizumab 200 mg sc), 2 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 2.17 (P = 0.030)

Test for subgroup differences: Not applicable

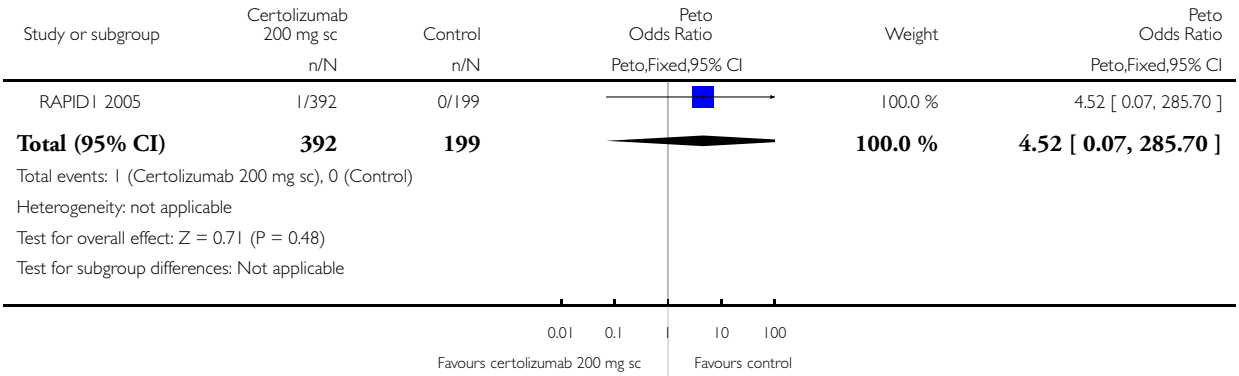


Analysis 8.30. Comparison 8 Safety certolizumab 200 mg sc, Outcome 30 Herpes viral infection.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety certolizumab 200 mg sc

Outcome: 30 Herpes viral infection

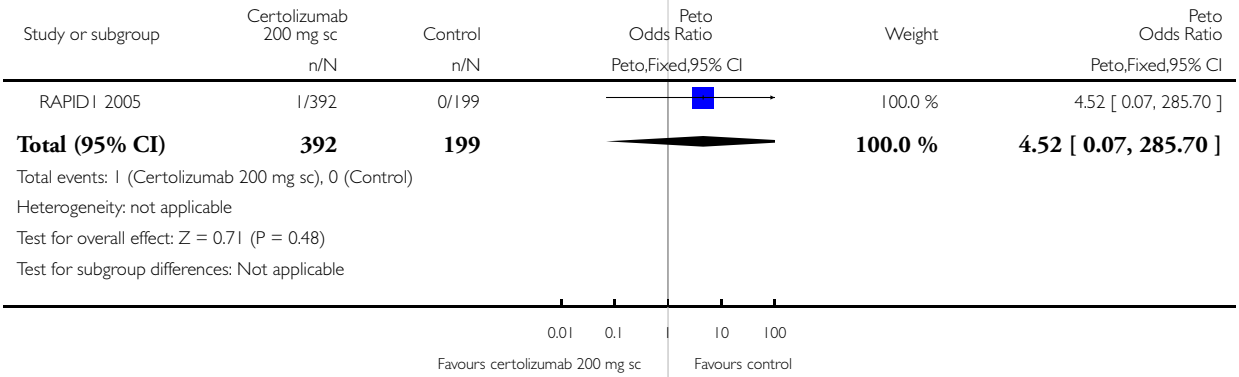


Analysis 8.31. Comparison 8 Safety certolizumab 200 mg sc, Outcome 31 Bacterial peritonitis.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety certolizumab 200 mg sc

Outcome: 31 Bacterial peritonitis



Analysis 8.32. Comparison 8 Safety certolizumab 200 mg sc, Outcome 32 Opportunistic infections.

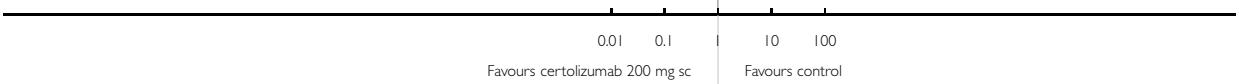
Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety certolizumab 200 mg sc

Outcome: 32 Opportunistic infections

Study or subgroup	Certolizumab 200 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
RAPID1 2005	0/392	0/199			Not estimable
Total (95% CI)	**392**	**199**			**Not estimable**

Total events: 0 (Certolizumab 200 mg sc), 0 (Control)
Heterogeneity: not applicable
Test for overall effect: not applicable
Test for subgroup differences: Not applicable



Analysis 8.33. Comparison 8 Safety certolizumab 200 mg sc, Outcome 33 Infections and infestations.

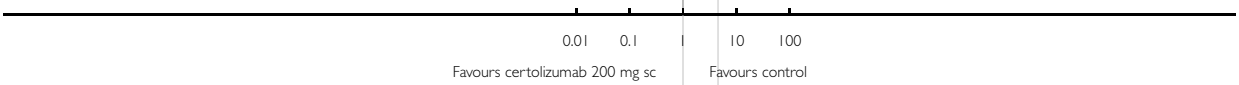
Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety certolizumab 200 mg sc

Outcome: 33 Infections and infestations

Study or subgroup	Certolizumab 200 mg sc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
RAPID1 2005	171/392	52/199		62.2 %	1.67 [1.29, 2.16]
RAPID2 2007	26/108	69/248		37.8 %	0.87 [0.59, 1.28]
Total (95% CI)	**500**	**447**		**100.0 %**	**1.37 [1.10, 1.69]**

Total events: 197 (Certolizumab 200 mg sc), 121 (Control)
Heterogeneity: $Chi^2 = 7.55$, df = 1 (P = 0.01); $I^2 = 87\%$
Test for overall effect: Z = 2.86 (P = 0.0042)

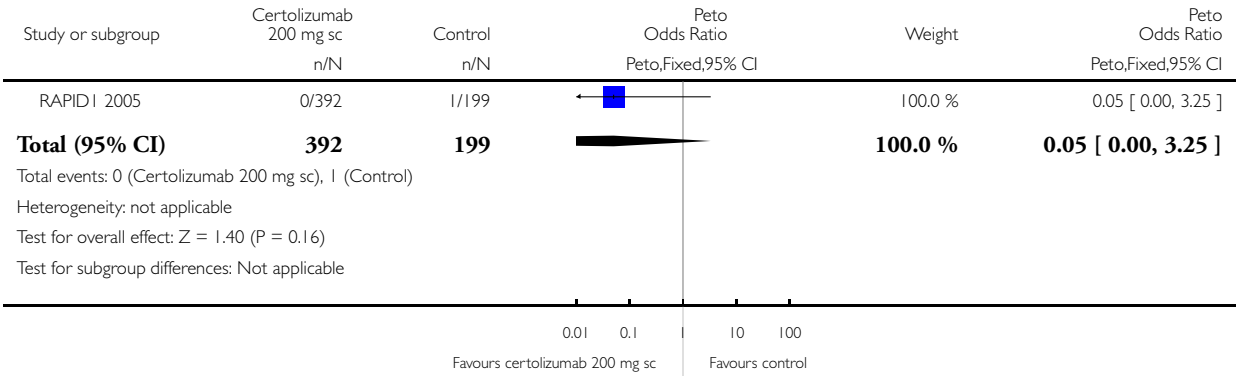


Analysis 8.34. Comparison 8 Safety certolizumab 200 mg sc, Outcome 34 Gastroenteritis.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety certolizumab 200 mg sc

Outcome: 34 Gastroenteritis

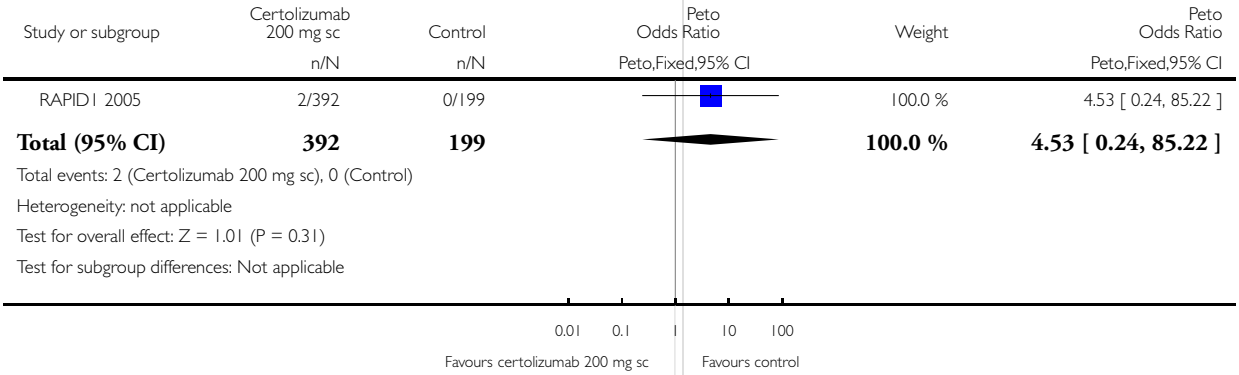


Analysis 8.35. Comparison 8 Safety certolizumab 200 mg sc, Outcome 35 Hematologic abnormalities.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety certolizumab 200 mg sc

Outcome: 35 Hematologic abnormalities

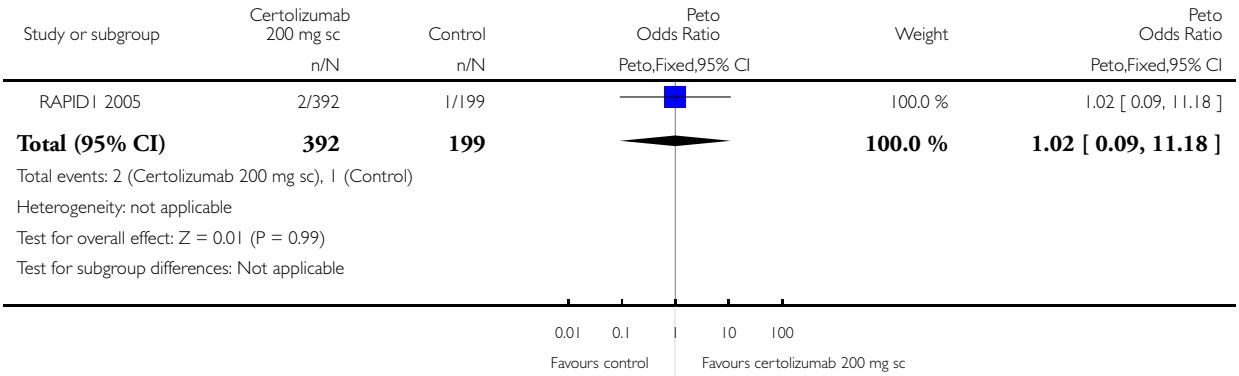


Analysis 8.36. Comparison 8 Safety certolizumab 200 mg sc, Outcome 36 Decreased haemoglobin.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety certolizumab 200 mg sc

Outcome: 36 Decreased haemoglobin

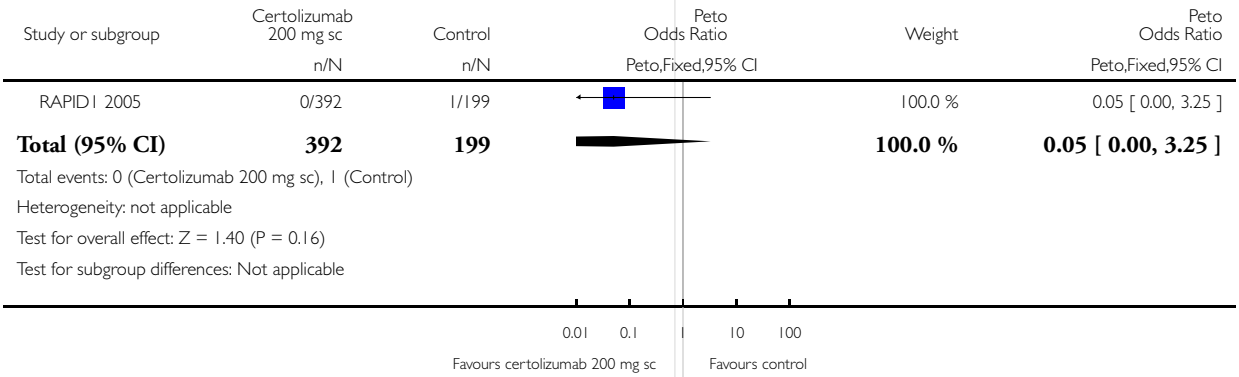


Analysis 8.37. Comparison 8 Safety certolizumab 200 mg sc, Outcome 37 Increased platelet count.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 8 Safety certolizumab 200 mg sc

Outcome: 37 Increased platelet count



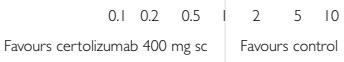
Analysis 9.1. Comparison 9 Safety certolizumab 400 mg sc, Outcome 1 Any adverse events.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 1 Any adverse events

Study or subgroup	Certolizumab 400 mg sc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
CDP870-014 2009	97/124	83/119		21.8 %	1.12 [0.96, 1.30]
FAST4WARD 2005	84/111	63/109		16.4 %	1.31 [1.08, 1.59]
RAPID1 2005	298/389	115/199		39.2 %	1.33 [1.16, 1.51]
RAPID2 2007	125/246	66/125		22.6 %	0.96 [0.78, 1.18]
Total (95% CI)	**870**	**552**		**100.0 %**	**1.20 [1.10, 1.30]**
Total events: 604 (Certolizumab 400 mg sc), 327 (Control)					
Heterogeneity: Chi^2 = 8.19, df = 3 (P = 0.04); I^2 =63%					
Test for overall effect: Z = 4.28 (P = 0.000019)					
Test for subgroup differences: Not applicable					



Analysis 9.2. Comparison 9 Safety certolizumab 400 mg sc, Outcome 2 Adverse events Intensity mild.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 2 Adverse events Intensity mild

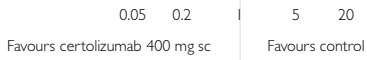
Study or subgroup	Certolizumab 400 mg sc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
FAST4WARD 2005	62/111	43/109		19.5 %	1.42 [1.06, 1.88]
RAPID1 2005	254/389	90/199		53.6 %	1.44 [1.22, 1.71]
RAPID2 2007	101/246	45/125		26.9 %	1.14 [0.86, 1.51]
Total (95% CI)	**746**	**433**		**100.0 %**	**1.36 [1.19, 1.54]**

Total events: 417 (Certolizumab 400 mg sc), 178 (Control)

Heterogeneity: $Chi^2 = 2.11$, df = 2 (P = 0.35); $I^2 = 5\%$

Test for overall effect: Z = 4.63 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 9.3. Comparison 9 Safety certolizumab 400 mg sc, Outcome 3 Adverse events Intensity moderate.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 3 Adverse events Intensity moderate

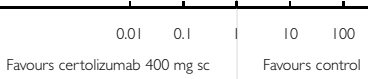
Study or subgroup	Certolizumab 400 mg sc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
FAST4WARD 2005	52/111	40/109		23.7 %	1.28 [0.93, 1.75]
RAPID1 2005	177/389	66/199		51.3 %	1.37 [1.10, 1.72]
RAPID2 2007	57/246	32/125		24.9 %	0.91 [0.62, 1.32]
Total (95% CI)	**746**	**433**		**100.0 %**	**1.23 [1.05, 1.45]**

Total events: 286 (Certolizumab 400 mg sc), 138 (Control)

Heterogeneity: $Chi^2 = 3.51$, df = 2 (P = 0.17); $I^2 = 43\%$

Test for overall effect: Z = 2.49 (P = 0.013)

Test for subgroup differences: Not applicable



Analysis 9.4. Comparison 9 Safety certolizumab 400 mg sc, Outcome 4 Adverse events Intensity severe.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 4 Adverse events Intensity severe

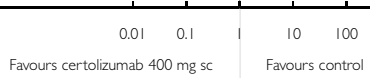
Study or subgroup	Certolizumab 400 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
FAST4WARD 2005	8/111	11/109		23.1 %	0.69 [0.27, 1.78]
RAPID1 2005	38/389	13/199		55.4 %	1.50 [0.82, 2.76]
RAPID2 2007	14/246	5/125		21.4 %	1.41 [0.53, 3.75]
Total (95% CI)	**746**	**433**		**100.0 %**	**1.24 [0.79, 1.95]**

Total events: 60 (Certolizumab 400 mg sc), 29 (Control)

Heterogeneity: Chi^2 = 1.92, df = 2 (P = 0.38); I^2 =0.0%

Test for overall effect: Z = 0.94 (P = 0.35)

Test for subgroup differences: Not applicable



Analysis 9.5. Comparison 9 Safety certolizumab 400 mg sc, Outcome 5 Adverse events related to study drug.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

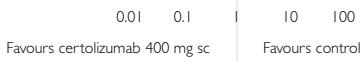
Outcome: 5 Adverse events related to study drug

Study or subgroup	Certolizumab 400 mg sc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
FAST4WARD 2005	27/111	24/109		20.0 %	1.10 [0.68, 1.79]
RAPID1 2005	166/389	50/199		54.7 %	1.70 [1.30, 2.22]
RAPID2 2007	56/246	23/125		25.2 %	1.24 [0.80, 1.91]
Total (95% CI)	**746**	**433**		**100.0 %**	**1.46 [1.19, 1.80]**

Total events: 249 (Certolizumab 400 mg sc), 97 (Control)

Heterogeneity: Chi^2 = 3.08, df = 2 (P = 0.21); I^2 =35%

Test for overall effect: Z = 3.65 (P = 0.00027)



Analysis 9.6. Comparison 9 Safety certolizumab 400 mg sc, Outcome 6 Serious infections.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 6 Serious infections

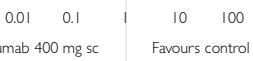
Study or subgroup	Certolizumab 400 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
CDP870-014 2009	3/124	2/119		14.6 %	1.44 [0.25, 8.44]
FAST4WARD 2005	2/111	0/109		5.9 %	7.32 [0.46, 117.84]
RAPID1 2005	23/389	2/199		63.8 %	3.33 [1.43, 7.76]
RAPID2 2007	6/246	0/125		15.7 %	4.61 [0.84, 25.36]
Total (95% CI)	**870**	**552**		**100.0 %**	**3.25 [1.65, 6.39]**

Total events: 34 (Certolizumab 400 mg sc), 4 (Control)

Heterogeneity: Chi^2 = 1.31, df = 3 (P = 0.73); I^2 =0.0%

Test for overall effect: Z = 3.42 (P = 0.00063)

Test for subgroup differences: Not applicable



Analysis 9.7. Comparison 9 Safety certolizumab 400 mg sc, Outcome 7 Serious Adverse Events (SAE).

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 7 Serious Adverse Events (SAE)

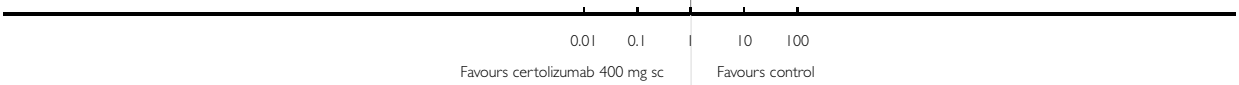
Study or subgroup	Certolizumab 400 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
CDP870-014 2009	16/124	12/119		24.5 %	1.32 [0.60, 2.89]
FAST4WARD 2005	8/111	3/109		10.3 %	2.54 [0.76, 8.53]
RAPID1 2005	48/389	11/199		46.9 %	2.12 [1.20, 3.75]
RAPID2 2007	18/246	4/125		18.3 %	2.09 [0.84, 5.19]
Total (95% CI)	**870**	**552**		**100.0 %**	**1.92 [1.30, 2.83]**

Total events: 90 (Certolizumab 400 mg sc), 30 (Control)

Heterogeneity: Chi^2 = 1.24, df = 3 (P = 0.74); I^2 =0.0%

Test for overall effect: Z = 3.28 (P = 0.0010)

Test for subgroup differences: Not applicable



Analysis 9.8. Comparison 9 Safety certolizumab 400 mg sc, Outcome 8 Adverse events leading to death.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 8 Adverse events leading to death

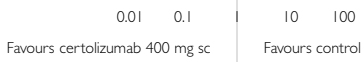
Study or subgroup	Certolizumab 400 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
FAST4WARD 2005	0/111	0/109			Not estimable
RAPID1 2005	4/389	1/199		83.3 %	1.86 [0.29, 11.96]
RAPID2 2007	1/246	0/125		16.7 %	4.52 [0.07, 285.66]
Total (95% CI)	**746**	**433**		**100.0 %**	**2.16 [0.40, 11.79]**

Total events: 5 (Certolizumab 400 mg sc), 1 (Control)

Heterogeneity: $Chi^2 = 0.15$, df = 1 (P = 0.70); $I^2 = 0.0\%$

Test for overall effect: Z = 0.89 (P = 0.37)

Test for subgroup differences: Not applicable



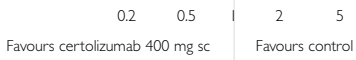
Analysis 9.9. Comparison 9 Safety certolizumab 400 mg sc, Outcome 9 Adverse events leading to withdrawal.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 9 Adverse events leading to withdrawal

Study or subgroup	Certolizumab 400 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
FAST4WARD 2005	5/111	2/109		18.8 %	2.37 [0.53, 10.64]
RAPID1 2005	22/389	3/199		59.4 %	2.77 [1.19, 6.44]
RAPID2 2007	7/246	2/125		21.8 %	1.69 [0.42, 6.84]
Total (95% CI)	**746**	**433**		**100.0 %**	**2.41 [1.26, 4.63]**
Total events: 34 (Certolizumab 400 mg sc), 7 (Control)					
Heterogeneity: $Chi^2 = 0.35$, df = 2 (P = 0.84); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.65 (P = 0.0081)					
Test for subgroup differences: Not applicable					



Analysis 9.10. Comparison 9 Safety certolizumab 400 mg sc, Outcome 10 Death.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 10 Death

Study or subgroup	Certolizumab 400 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
CDP870-014 2009	0/124	0/119			Not estimable
FAST4WARD 2005	0/111	0/109			Not estimable
RAPID1 2005	4/389	1/199		83.3 %	1.86 [0.29, 11.96]
RAPID2 2007	1/246	0/125		16.7 %	4.52 [0.07, 285.66]
Total (95% CI)	**870**	**552**		**100.0 %**	**2.16 [0.40, 11.79]**

Total events: 5 (Certolizumab 400 mg sc), 1 (Control)

Heterogeneity: $Chi^2 = 0.15$, df = 1 (P = 0.70); $I^2 = 0.0\%$

Test for overall effect: Z = 0.89 (P = 0.37)

Test for subgroup differences: Not applicable

Analysis 9.11. Comparison 9 Safety certolizumab 400 mg sc, Outcome 11 Vomiting.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 11 Vomiting

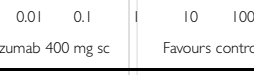
Study or subgroup	Certolizumab 400 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
FAST4WARD 2005	0/111	1/109		100.0 %	0.13 [0.00, 6.70]
Total (95% CI)	**111**	**109**		**100.0 %**	**0.13 [0.00, 6.70]**

Total events: 0 (Certolizumab 400 mg sc), 1 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 1.01 (P = 0.31)

Test for subgroup differences: Not applicable



Analysis 9.12. Comparison 9 Safety certolizumab 400 mg sc, Outcome 12 Pneumonitis.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 12 Pneumonitis

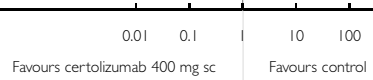
Study or subgroup	Certolizumab 400 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
FAST4WARD 2005	0/111	1/109		100.0 %	0.13 [0.00, 6.70]
Total (95% CI)	**111**	**109**		**100.0 %**	**0.13 [0.00, 6.70]**

Total events: 0 (Certolizumab 400 mg sc), 1 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 1.01 (P = 0.31)

Test for subgroup differences: Not applicable



Analysis 9.13. Comparison 9 Safety certolizumab 400 mg sc, Outcome 13 Tuberculosis.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 13 Tuberculosis

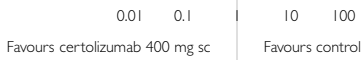
Study or subgroup	Certolizumab 400 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
FAST4WARD 2005	0/111	0/109			Not estimable
RAPID1 2005	3/389	0/199		60.0 %	4.56 [0.42, 50.01]
RAPID2 2007	2/246	0/125		40.0 %	4.54 [0.24, 85.48]
Total (95% CI)	**746**	**433**		**100.0 %**	**4.55 [0.71, 29.11]**

Total events: 5 (Certolizumab 400 mg sc), 0 (Control)

Heterogeneity: $Chi^2 = 0.00$, df = 1 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 1.60 (P = 0.11)

Test for subgroup differences: Not applicable



Analysis 9.14. Comparison 9 Safety certolizumab 400 mg sc, Outcome 14 Arthritis bacterial.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 14 Arthritis bacterial

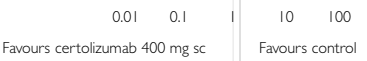
Study or subgroup	Certolizumab 400 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
FAST4WARD 2005	1/111	0/109		100.0 %	7.26 [0.14, 365.79]
Total (95% CI)	**111**	**109**		**100.0 %**	**7.26 [0.14, 365.79]**

Total events: 1 (Certolizumab 400 mg sc), 0 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 0.99 (P = 0.32)

Test for subgroup differences: Not applicable



Analysis 9.15. Comparison 9 Safety certolizumab 400 mg sc, Outcome 15 Mastitis.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 15 Mastitis

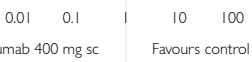
Study or subgroup	Certolizumab 400 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
FAST4WARD 2005	1/111	0/109		100.0 %	7.26 [0.14, 365.79]
Total (95% CI)	**111**	**109**		**100.0 %**	**7.26 [0.14, 365.79]**

Total events: 1 (Certolizumab 400 mg sc), 0 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 0.99 (P = 0.32)

Test for subgroup differences: Not applicable



Analysis 9.16. Comparison 9 Safety certolizumab 400 mg sc, Outcome 16 Benign Tumour.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 16 Benign Tumour

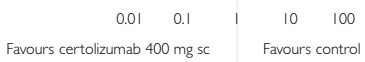
Study or subgroup	Certolizumab 400 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
FAST4WARD 2005	2/111	0/109		100.0 %	7.32 [0.46, 117.84]
Total (95% CI)	**111**	**109**		**100.0 %**	**7.32 [0.46, 117.84]**

Total events: 2 (Certolizumab 400 mg sc), 0 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 1.40 (P = 0.16)

Test for subgroup differences: Not applicable



Analysis 9.17. Comparison 9 Safety certolizumab 400 mg sc, Outcome 17 Ischaemeic stroke.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 17 Ischaemeic stroke

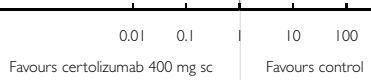
Study or subgroup	Certolizumab 400 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
FAST4WARD 2005	1/111	0/109		100.0 %	7.26 [0.14, 365.79]
Total (95% CI)	**111**	**109**		**100.0 %**	**7.26 [0.14, 365.79]**

Total events: 1 (Certolizumab 400 mg sc), 0 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 0.99 (P = 0.32)

Test for subgroup differences: Not applicable

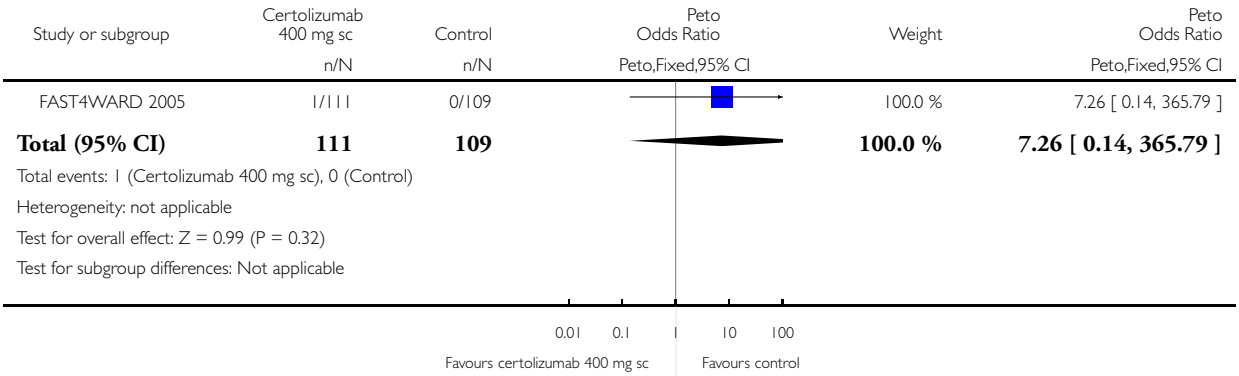


Analysis 9.18. Comparison 9 Safety certolizumab 400 mg sc, Outcome 18 Dizziness postural.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 18 Dizziness postural

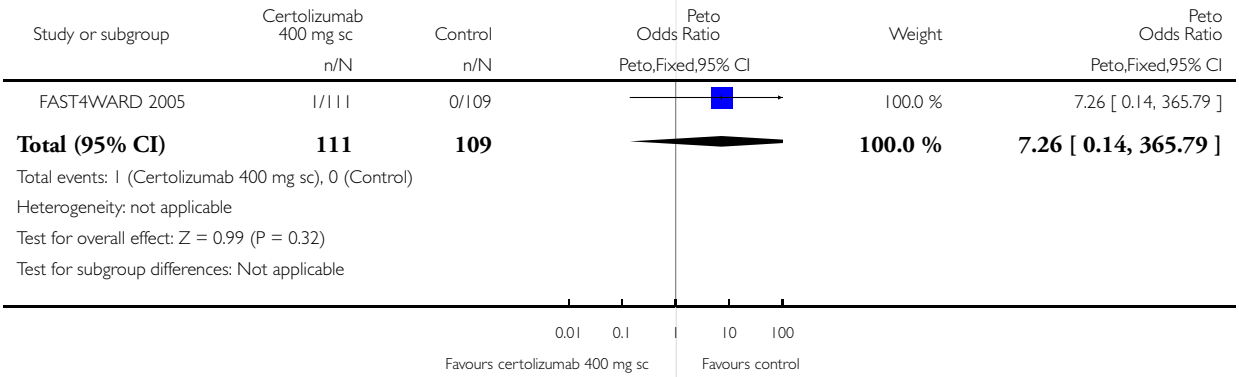


Analysis 9.19. Comparison 9 Safety certolizumab 400 mg sc, Outcome 19 Menorrhagia.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 19 Menorrhagia



Analysis 9.20. Comparison 9 Safety certolizumab 400 mg sc, Outcome 20 Malignancies included lymphoma.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 20 Malignancies included lymphoma

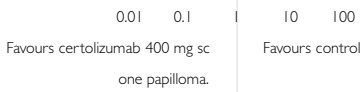
Study or subgroup	Certolizumab 400 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
FAST4WARD 2005	0/111	0/109			Not estimable
RAPID1 2005 (1)	4/389	1/199		71.4 %	1.86 [0.29, 11.96]
RAPID2 2007 (2)	1/246	1/125		28.6 %	0.48 [0.03, 9.06]
Total (95% CI)	**746**	**433**		**100.0 %**	**1.26 [0.26, 6.08]**

Total events: 5 (Certolizumab 400 mg sc), 2 (Control)

Heterogeneity: $Chi^2 = 0.58$, df = 1 (P = 0.44); $I^2 = 0.0\%$

Test for overall effect: Z = 0.29 (P = 0.77)

Test for subgroup differences: Not applicable



one papilloma.

(1) In the placebo arm one patient suffered a thyroid neoplasm and 4 in the certolizumab 400 mg sc suffered two tongue neoplasm, 1 extranodal marginal zone B cell limphoma and

(2) One case of malignant neoplasm was reported in each arm, namely bladder cancer in the placebo group and colon cancer in certolizumab pegol 400 mg group

Analysis 9.21. Comparison 9 Safety certolizumab 400 mg sc, Outcome 21 Injection site pain.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 21 Injection site pain

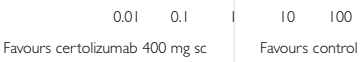
Study or subgroup	Certolizumab 400 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
FAST4WARD 2005	0/111	2/109		27.2 %	0.13 [0.01, 2.12]
RAPID1 2005	5/389	0/199		60.7 %	4.58 [0.71, 29.39]
RAPID2 2007	1/246	0/125		12.2 %	4.52 [0.07, 285.66]
Total (95% CI)	**746**	**433**		**100.0 %**	**1.74 [0.41, 7.42]**

Total events: 6 (Certolizumab 400 mg sc), 2 (Control)

Heterogeneity: $Chi^2 = 4.56$, df = 2 (P = 0.10); $I^2 = 56\%$

Test for overall effect: Z = 0.75 (P = 0.45)

Test for subgroup differences: Not applicable



Analysis 9.22. Comparison 9 Safety certolizumab 400 mg sc, Outcome 22 Injection side reactions.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 22 Injection side reactions

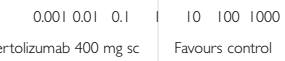
Study or subgroup	Certolizumab 400 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
FAST4WARD 2005	5/111	15/109		72.0 %	0.33 [0.13, 0.82]
RAPID1 2005	3/389	0/199		10.6 %	4.56 [0.42, 50.01]
RAPID2 2007	5/246	0/125		17.4 %	4.59 [0.71, 29.64]
Total (95% CI)	**746**	**433**		**100.0 %**	**0.69 [0.31, 1.49]**

Total events: 13 (Certolizumab 400 mg sc), 15 (Control)

Heterogeneity: $Chi^2 = 8.88$, df = 2 (P = 0.01); $I^2 = 77\%$

Test for overall effect: Z = 0.95 (P = 0.34)

Test for subgroup differences: Not applicable



Analysis 9.23. Comparison 9 Safety certolizumab 400 mg sc, Outcome 23 Anti-certolizumab pegol antibodies.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 23 Anti-certolizumab pegol antibodies

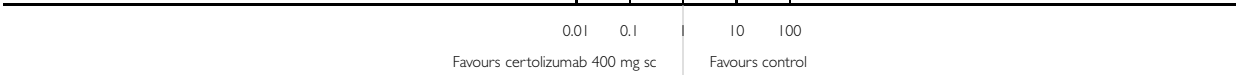
Study or subgroup	Certolizumab 400 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
FAST4WARD 2005	9/111	0/109		71.0 %	7.82 [2.07, 29.62]
RAPID2 2007	4/246	0/125		29.0 %	4.57 [0.57, 36.68]
Total (95% CI)	**357**	**234**		**100.0 %**	**6.70 [2.18, 20.55]**

Total events: 13 (Certolizumab 400 mg sc), 0 (Control)

Heterogeneity: $Chi^2 = 0.18$, df = 1 (P = 0.67); $I^2 = 0.0\%$

Test for overall effect: Z = 3.32 (P = 0.00089)

Test for subgroup differences: Not applicable



Analysis 9.24. Comparison 9 Safety certolizumab 400 mg sc, Outcome 24 Antinuclear antibodies (ANA).

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 24 Antinuclear antibodies (ANA)

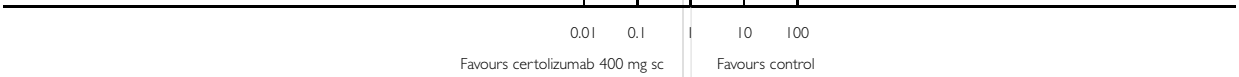
Study or subgroup	Certolizumab 400 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
FAST4WARD 2005	19/111	12/109		100.0 %	1.65 [0.77, 3.53]
Total (95% CI)	**111**	**109**		**100.0 %**	**1.65 [0.77, 3.53]**

Total events: 19 (Certolizumab 400 mg sc), 12 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 1.30 (P = 0.19)

Test for subgroup differences: Not applicable



Analysis 9.25. Comparison 9 Safety certolizumab 400 mg sc, Outcome 25 Prolonged activated partial thromboplastin time (aPTT).

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 25 Prolonged activated partial thromboplastin time (aPTT)

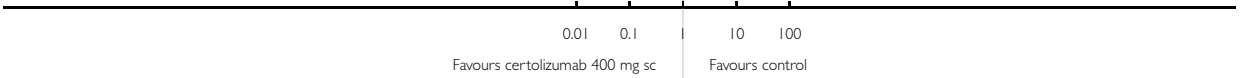
Study or subgroup	Certolizumab 400 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
RAPID2 2007	12/246	2/125		100.0 %	2.46 [0.80, 7.60]
Total (95% CI)	**246**	**125**		**100.0 %**	**2.46 [0.80, 7.60]**

Total events: 12 (Certolizumab 400 mg sc), 2 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 1.56 (P = 0.12)

Test for subgroup differences: Not applicable

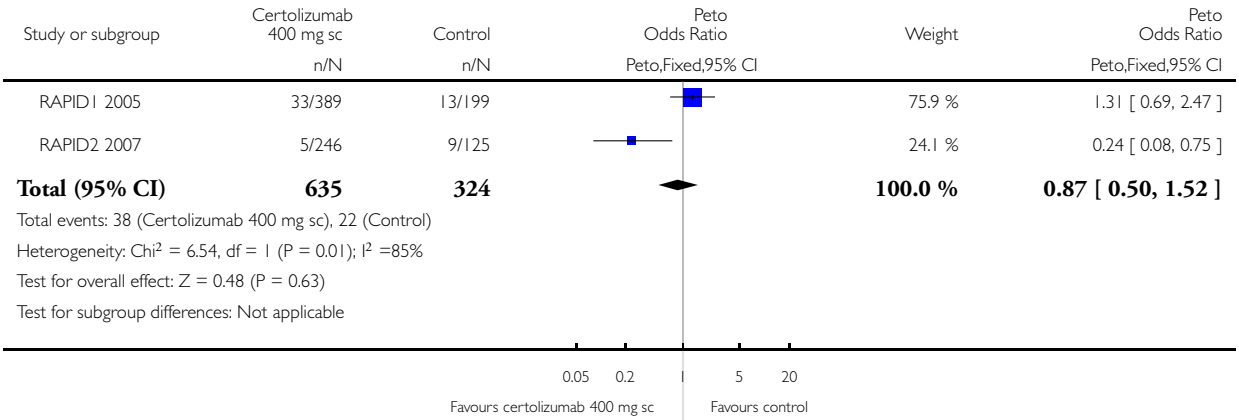


Analysis 9.26. Comparison 9 Safety certolizumab 400 mg sc, Outcome 26 Urinary tract infection.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 26 Urinary tract infection

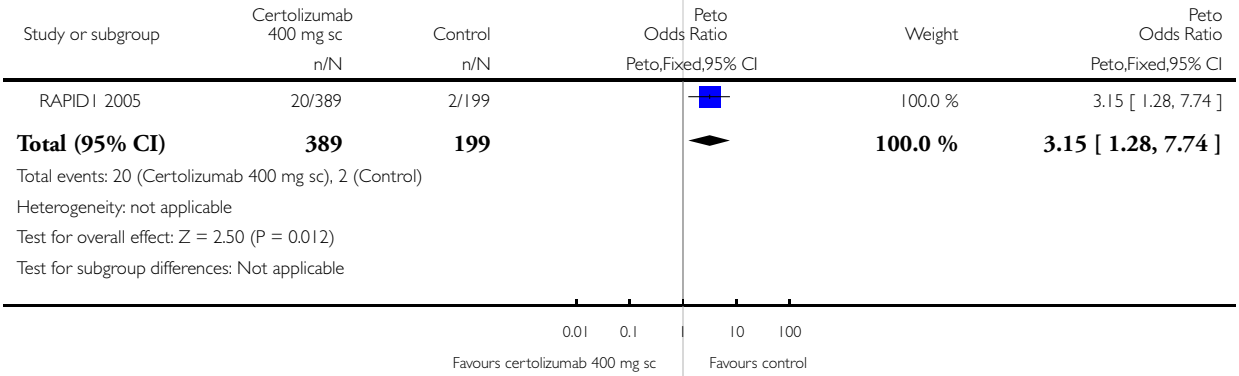


Analysis 9.27. Comparison 9 Safety certolizumab 400 mg sc, Outcome 27 Back pain.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 27 Back pain



Analysis 9.28. Comparison 9 Safety certolizumab 400 mg sc, Outcome 28 Upper respiratory tract infection.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 28 Upper respiratory tract infection

Study or subgroup	Certolizumab 400 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
RAPID1 2005	21/389	5/199		80.8 %	1.98 [0.86, 4.54]
RAPID2 2007	4/246	2/125		19.2 %	1.02 [0.18, 5.59]
Total (95% CI)	**635**	**324**		**100.0 %**	**1.74 [0.83, 3.67]**

Total events: 25 (Certolizumab 400 mg sc), 7 (Control)

Heterogeneity: $Chi^2 = 0.47$, df = 1 (P = 0.49); $I^2 = 0.0\%$

Test for overall effect: Z = 1.46 (P = 0.15)

Test for subgroup differences: Not applicable

Analysis 9.29. Comparison 9 Safety certolizumab 400 mg sc, Outcome 29 Lower respiratory tract infection/ lung infection.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 29 Lower respiratory tract infection/ lung infection

Study or subgroup	Certolizumab 400 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
RAPID1 2005	4/389	0/199		100.0 %	4.57 [0.57, 36.44]
Total (95% CI)	**389**	**199**		**100.0 %**	**4.57 [0.57, 36.44]**

Total events: 4 (Certolizumab 400 mg sc), 0 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 1.43 (P = 0.15)

Test for subgroup differences: Not applicable

Analysis 9.30. Comparison 9 Safety certolizumab 400 mg sc, Outcome 30 Headache.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 30 Headache

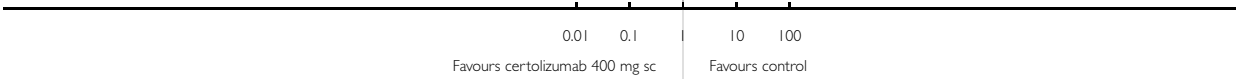
Study or subgroup	Certolizumab 400 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
RAPID1 2005	18/389	11/199		75.9 %	0.83 [0.38, 1.82]
RAPID2 2007	8/246	1/125		24.1 %	2.81 [0.69, 11.36]
Total (95% CI)	**635**	**324**		**100.0 %**	**1.11 [0.56, 2.20]**

Total events: 26 (Certolizumab 400 mg sc), 12 (Control)

Heterogeneity: $Chi^2 = 2.24$, df = 1 (P = 0.13); $I^2 = 55\%$

Test for overall effect: Z = 0.30 (P = 0.77)

Test for subgroup differences: Not applicable

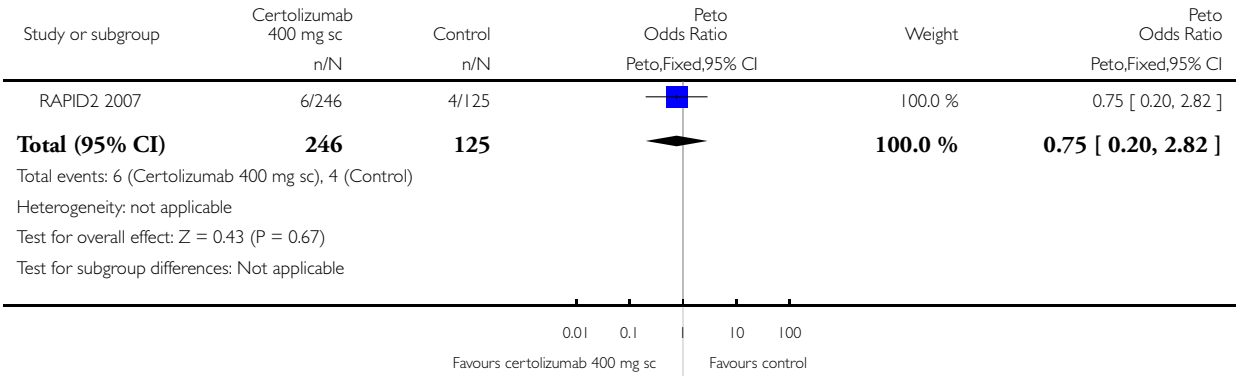


Analysis 9.31. Comparison 9 Safety certolizumab 400 mg sc, Outcome 31 Bacteriuria.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 31 Bacteriuria

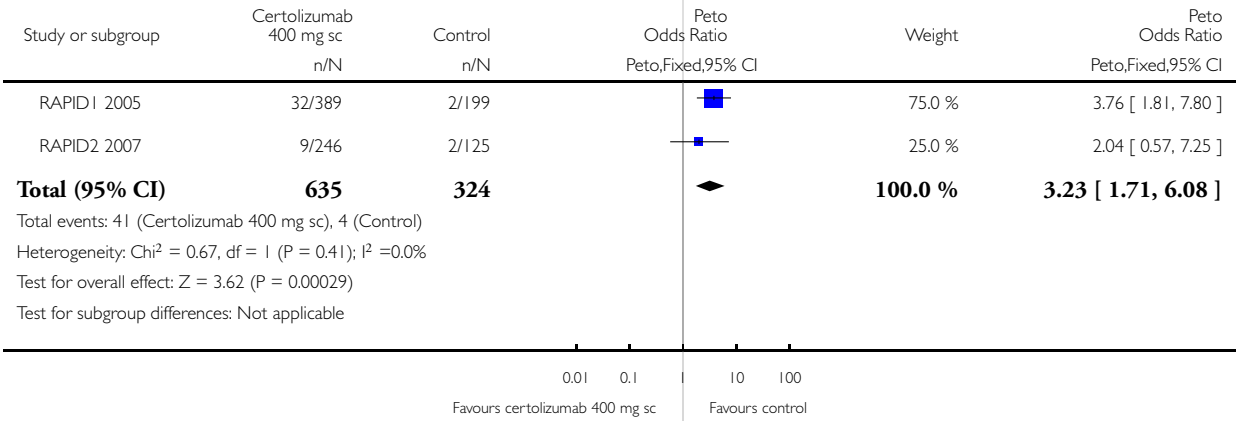


Analysis 9.32. Comparison 9 Safety certolizumab 400 mg sc, Outcome 32 Hypertension.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 32 Hypertension

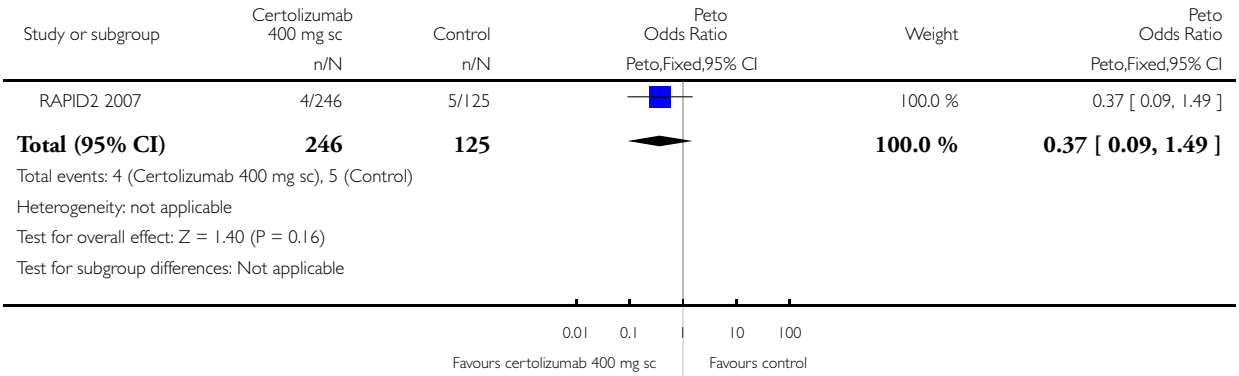


Analysis 9.33. Comparison 9 Safety certolizumab 400 mg sc, Outcome 33 Hematuria.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 33 Hematuria

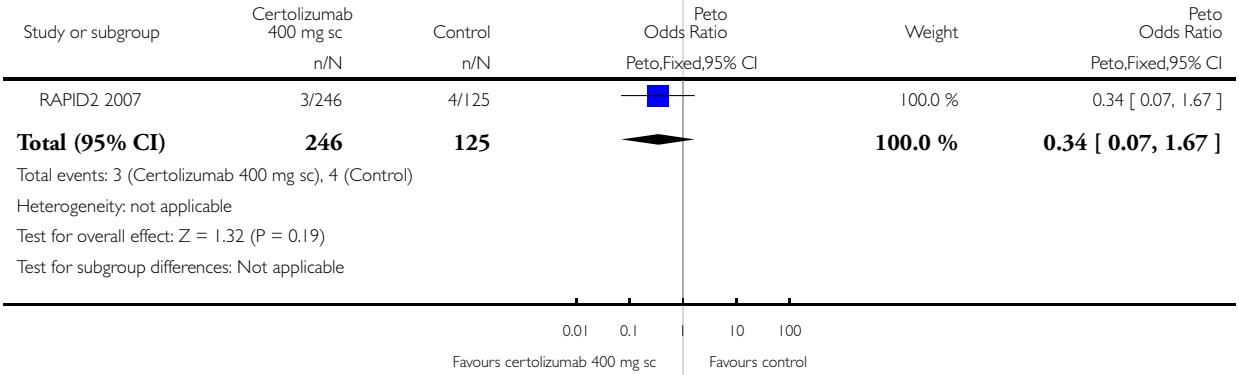


Analysis 9.34. Comparison 9 Safety certolizumab 400 mg sc, Outcome 34 Hepatic enzyme increased.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 34 Hepatic enzyme increased

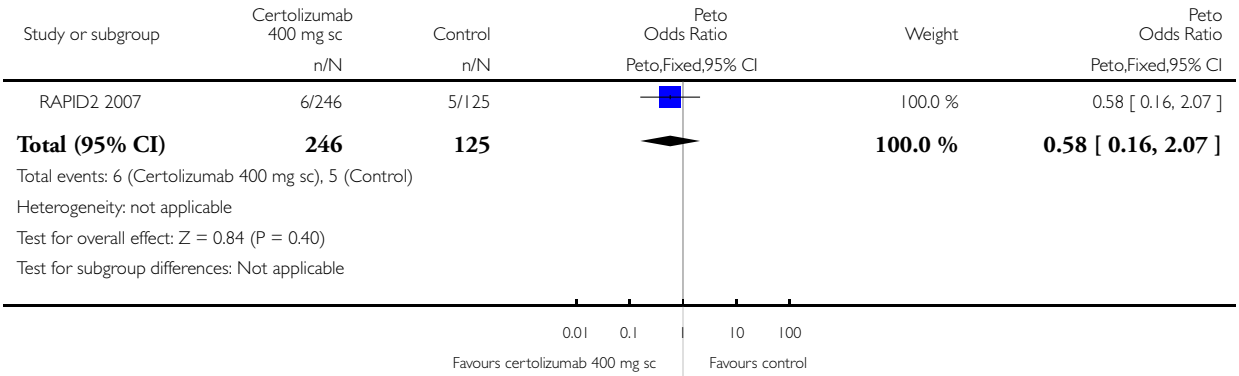


Analysis 9.35. Comparison 9 Safety certolizumab 400 mg sc, Outcome 35 AST increased.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 35 AST increased

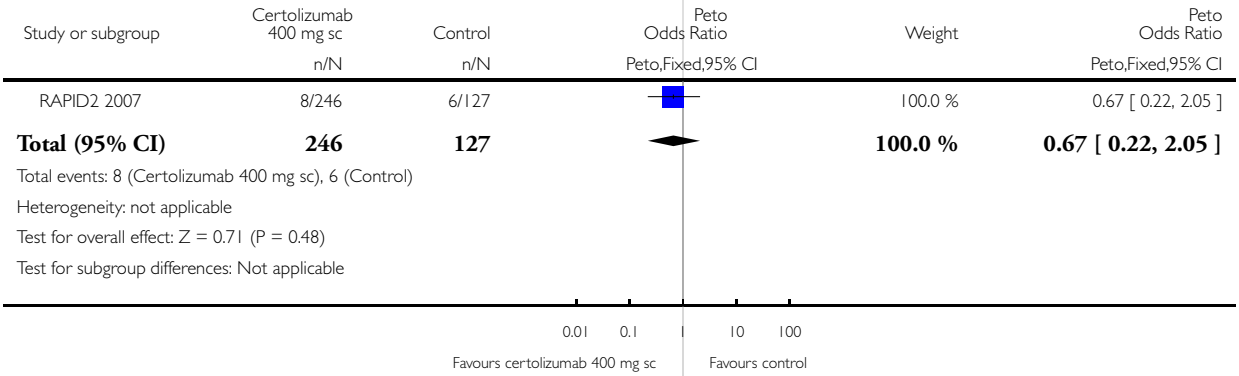


Analysis 9.36. Comparison 9 Safety certolizumab 400 mg sc, Outcome 36 ALT increased.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 36 ALT increased

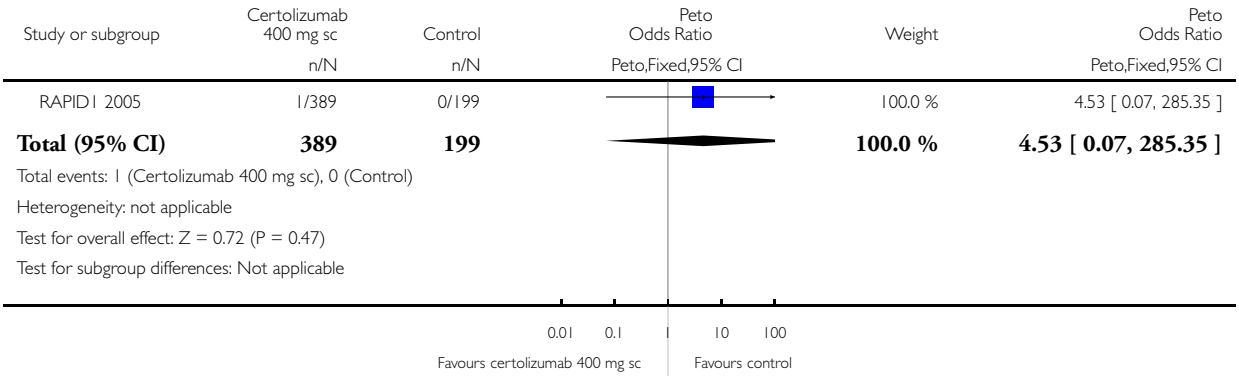


Analysis 9.37. Comparison 9 Safety certolizumab 400 mg sc, Outcome 37 Herpes viral infection.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 37 Herpes viral infection

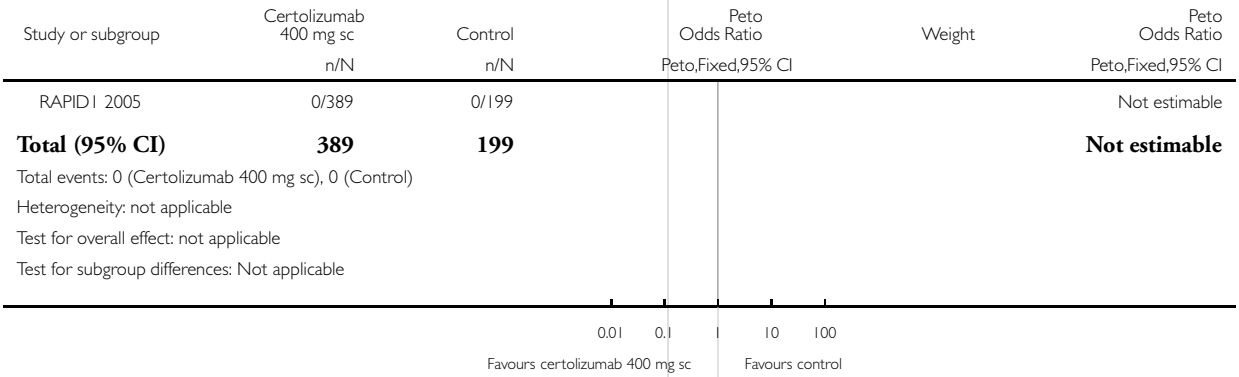


Analysis 9.38. Comparison 9 Safety certolizumab 400 mg sc, Outcome 38 Bacterial peritonitis.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 38 Bacterial peritonitis



Analysis 9.39. Comparison 9 Safety certolizumab 400 mg sc, Outcome 39 Opportunistic infections.

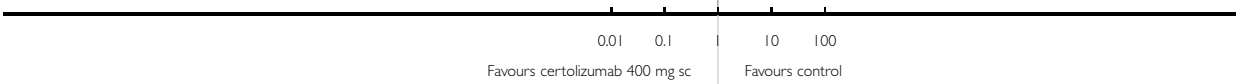
Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 39 Opportunistic infections

Study or subgroup	Certolizumab 400 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
RAPID1 2005	0/389	0/199			Not estimable
Total (95% CI)	**389**	**199**			**Not estimable**

Total events: 0 (Certolizumab 400 mg sc), 0 (Control)
Heterogeneity: not applicable
Test for overall effect: not applicable
Test for subgroup differences: Not applicable



Analysis 9.40. Comparison 9 Safety certolizumab 400 mg sc, Outcome 40 Infections and infestations.

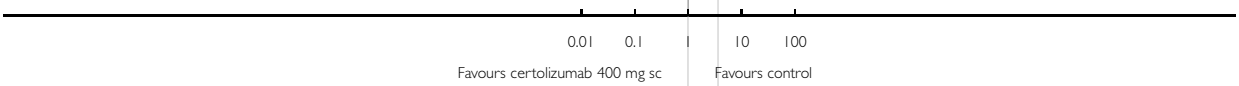
Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 40 Infections and infestations

Study or subgroup	Certolizumab 400 mg sc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
CDP870-014 2009	33/124	17/119		14.4 %	1.86 [1.10, 3.16]
RAPID1 2005	184/389	52/199		57.0 %	1.81 [1.40, 2.34]
RAPID2 2007	53/246	26/125		28.6 %	1.04 [0.68, 1.57]
Total (95% CI)	**759**	**443**		**100.0 %**	**1.60 [1.31, 1.95]**

Total events: 270 (Certolizumab 400 mg sc), 95 (Control)
Heterogeneity: $Chi^2 = 5.39$, $df = 2$ ($P = 0.07$); $I^2 = 63\%$
Test for overall effect: $Z = 4.58$ ($P < 0.00001$)



Analysis 9.41. Comparison 9 Safety certolizumab 400 mg sc, Outcome 41 Nasopharyngitis.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 41 Nasopharyngitis

Study or subgroup	Certolizumab 400 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
RAPID1 2005	30/389	3/199		86.3 %	3.22 [1.53, 6.76]
RAPID2 2007	4/246	1/125		13.7 %	1.86 [0.29, 11.99]
Total (95% CI)	**635**	**324**		**100.0 %**	**2.99 [1.50, 5.95]**

Total events: 34 (Certolizumab 400 mg sc), 4 (Control)

Heterogeneity: $Chi^2 = 0.29$, df = 1 (P = 0.59); $I^2 = 0.0\%$

Test for overall effect: Z = 3.11 (P = 0.0019)

Test for subgroup differences: Not applicable

Analysis 9.42. Comparison 9 Safety certolizumab 400 mg sc, Outcome 42 Gastrointestinal disorders.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 42 Gastrointestinal disorders

Study or subgroup	Certolizumab 400 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
CDP870-014 2009	22/124	19/119		97.4 %	1.13 [0.58, 2.22]
RAPID1 2005	0/389	1/199		2.6 %	0.05 [0.00, 3.28]
Total (95% CI)	**513**	**318**		**100.0 %**	**1.05 [0.54, 2.03]**

Total events: 22 (Certolizumab 400 mg sc), 20 (Control)

Heterogeneity: $Chi^2 = 2.07$, df = 1 (P = 0.15); $I^2 = 52\%$

Test for overall effect: Z = 0.14 (P = 0.89)

Test for subgroup differences: Not applicable

Analysis 9.43. Comparison 9 Safety certolizumab 400 mg sc, Outcome 43 Hematologic abnormalities.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 43 Hematologic abnormalities

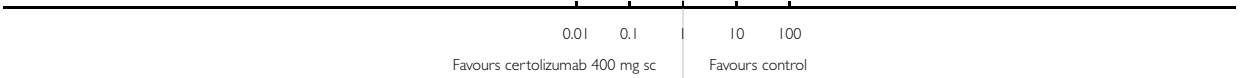
Study or subgroup	Certolizumab 400 mg sc n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
RAPID1 2005	3/389	2/199		100.0 %	0.76 [0.12, 4.86]
Total (95% CI)	**389**	**199**		**100.0 %**	**0.76 [0.12, 4.86]**

Total events: 3 (Certolizumab 400 mg sc), 2 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 0.29 (P = 0.77)

Test for subgroup differences: Not applicable

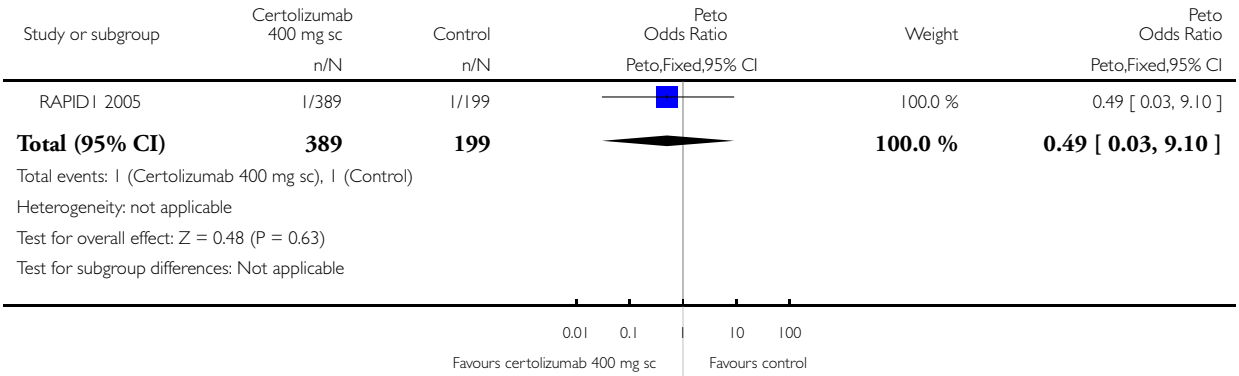


Analysis 9.44. Comparison 9 Safety certolizumab 400 mg sc, Outcome 44 Decreased Haemoglobin.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 44 Decreased Haemoglobin

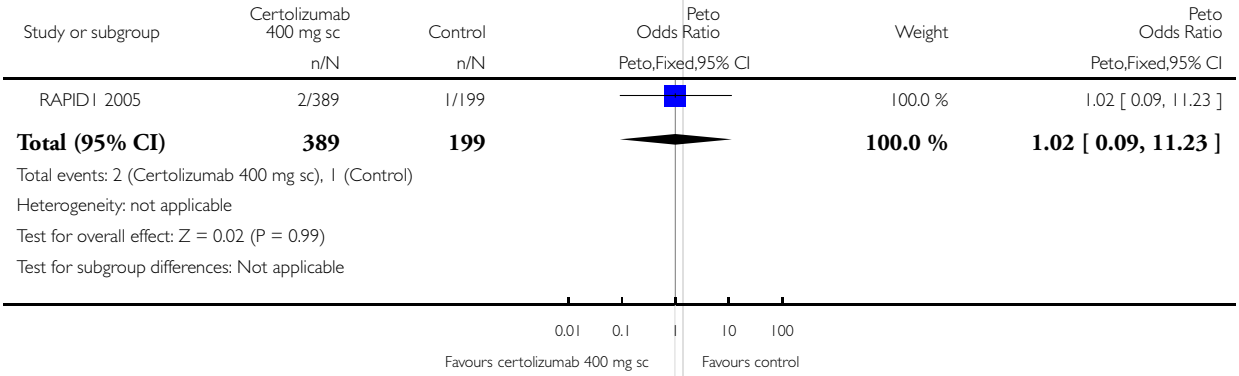


Analysis 9.45. Comparison 9 Safety certolizumab 400 mg sc, Outcome 45 Increased platelet count.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 9 Safety certolizumab 400 mg sc

Outcome: 45 Increased platelet count



Analysis 10.1. Comparison 10 Mean HAQ-DI from baseline at week 24, Outcome 1 certolizumab 200 mg sc.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 10 Mean HAQ-DI from baseline at week 24

Outcome: 1 certolizumab 200 mg sc

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	393	-0.58 (0.59)	199	-0.17 (0.56)		50.3 %	-0.41 [-0.51, -0.31]
RAPID2 2007	246	-0.5 (0.47)	127	-0.14 (0.45)		49.7 %	-0.36 [-0.46, -0.26]
Total (95% CI)	**639**		**326**			**100.0 %**	**-0.39 [-0.45, -0.32]**

Heterogeneity: Chi^2 = 0.50, df = 1 (P = 0.48); I^2 =0.0%

Test for overall effect: Z = 10.94 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 10.2. Comparison 10 Mean HAQ-DI from baseline at week 24, Outcome 2 certolizumab 400 mg sc.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 10 Mean HAQ-DI from baseline at week 24

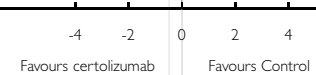
Outcome: 2 certolizumab 400 mg sc

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
FAST4WARD 2005 (1)	111	-0.36 (0.51)	109	0.13 (0.51)		20.8 %	-0.49 [-0.62, -0.36]
RAPID1 2005	390	-0.6 (0.59)	199	-0.17 (0.56)		39.8 %	-0.43 [-0.53, -0.33]
RAPID2 2007	246	-0.5 (0.47)	127	-0.14 (0.45)		39.4 %	-0.36 [-0.46, -0.26]
Total (95% CI)	**747**		**435**			**100.0 %**	**-0.41 [-0.48, -0.35]**

Heterogeneity: Chi^2 = 2.49, df = 2 (P = 0.29); I^2 =20%

Test for overall effect: Z = 13.24 (P < 0.00001)

Test for subgroup differences: Not applicable



(1) In FAST4WARD we have obtained standard deviations from p values according to the Handbook section 7.7.3.7

Analysis 11.1. Comparison 11 HAQ-Di at 24 weeks, any dose, Outcome 1 Change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 11 HAQ-Di at 24 weeks, any dose

Outcome: 1 Change from baseline

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 certolizumab 200 mg sc							
RAPID1 2005	393	-0.58 (0.59)	100	-0.17 (0.56)		20.8 %	-0.41 [-0.53, -0.29]
RAPID2 2007	246	-0.5 (0.47)	64	-0.14 (0.45)		20.6 %	-0.36 [-0.48, -0.24]
Subtotal (95% CI)	**639**		**164**			**41.4 %**	**-0.39 [-0.47, -0.30]**
Heterogeneity: Chi^2 = 0.31, df = 1 (P = 0.58); I^2 =0.0%							
Test for overall effect: Z = 8.57 (P < 0.00001)							
2 certolizumab 400 mg sc							
FAST4WARD 2005	111	-0.36 (0.51)	109	0.13 (0.51)		17.7 %	-0.49 [-0.62, -0.36]
RAPID1 2005	390	-0.6 (0.59)	99	-0.17 (0.56)		20.6 %	-0.43 [-0.55, -0.31]
RAPID2 2007	246	-0.5 (0.47)	63	-0.14 (0.45)		20.3 %	-0.36 [-0.49, -0.23]
Subtotal (95% CI)	**747**		**271**			**58.6 %**	**-0.42 [-0.50, -0.35]**
Heterogeneity: Chi^2 = 1.93, df = 2 (P = 0.38); I^2 =0.0%							
Test for overall effect: Z = 11.22 (P < 0.00001)							
Total (95% CI)	**1386**		**435**			**100.0 %**	**-0.41 [-0.46, -0.35]**
Heterogeneity: Chi^2 = 2.67, df = 4 (P = 0.61); I^2 =0.0%							
Test for overall effect: Z = 14.10 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 0.43, df = 1 (P = 0.51), I^2 =0.0%							

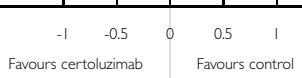
Analysis 12.1. Comparison 12 HAQ-Di at 52 weeks, any dose, Outcome 1 Change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 12 HAQ-Di at 52 weeks, any dose

Outcome: 1 Change from baseline

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 certolizumab 200 mg sc							
RAPID1 2005	393	-0.6 (0.59)	100	-0.18 (0.56)		50.2 %	-0.42 [-0.54, -0.30]
Subtotal (95% CI)	**393**		**100**			**50.2 %**	**-0.42 [-0.54, -0.30]**
Heterogeneity: not applicable							
Test for overall effect: Z = 6.62 (P < 0.00001)							
2 certolizumab 400 mg sc							
RAPID1 2005	390	-0.63 (0.59)	99	-0.18 (0.56)		49.8 %	-0.45 [-0.57, -0.33]
Subtotal (95% CI)	**390**		**99**			**49.8 %**	**-0.45 [-0.57, -0.33]**
Heterogeneity: not applicable							
Test for overall effect: Z = 7.06 (P < 0.00001)							
Total (95% CI)	**783**		**199**			**100.0 %**	**-0.43 [-0.52, -0.35]**
Heterogeneity: Chi^2 = 0.11, df = 1 (P = 0.74); I^2 =0.0%							
Test for overall effect: Z = 9.68 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 0.11, df = 1 (P = 0.74), I^2 =0.0%							



Analysis 13.1. Comparison 13 SF-36 Physical Component Summary (PCS) week 24, Outcome 1 certolizumab 200 mg sc.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 13 SF-36 Physical Component Summary (PCS) week 24

Outcome: 1 certolizumab 200 mg sc

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	393	7.7 (7.93)	199	1.8 (8.46)		60.2 %	5.90 [4.49, 7.31]
RAPID2 2007	246	5.23 (8.31)	127	0.93 (8)		39.8 %	4.30 [2.56, 6.04]
Total (95% CI)	**639**		**326**			**100.0 %**	**5.26 [4.17, 6.36]**

Heterogeneity: Chi^2 = 1.96, df = 1 (P = 0.16); I^2 =49%

Test for overall effect: Z = 9.41 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 13.2. Comparison 13 SF-36 Physical Component Summary (PCS) week 24, Outcome 2 certolizumab 400 mg sc.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 13 SF-36 Physical Component Summary (PCS) week 24

Outcome: 2 certolizumab 400 mg sc

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	390	8.3 (7.9)	199	1.8 (8.46)		60.2 %	6.50 [5.09, 7.91]
RAPID2 2007	246	5.46 (8.31)	127	0.93 (8)		39.8 %	4.53 [2.79, 6.27]
Total (95% CI)	**636**		**326**			**100.0 %**	**5.72 [4.62, 6.81]**

Heterogeneity: Chi^2 = 2.98, df = 1 (P = 0.08); I^2 =66%

Test for overall effect: Z = 10.22 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 14.1. Comparison 14 SF-36 Mental Component Summary (MCS) week 24, Outcome 1 certolizumab 200 mg sc.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 14 SF-36 Mental Component Summary (MCS) week 24

Outcome: 1 certolizumab 200 mg sc

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	393	6.3 (11.89)	199	2.3 (11.29)		56.9 %	4.00 [2.04, 5.96]
RAPID2 2007	246	6.05 (10.82)	127	1.63 (10.36)		43.1 %	4.42 [2.17, 6.67]
Total (95% CI)	**639**		**326**			**100.0 %**	**4.18 [2.70, 5.66]**

Heterogeneity: Chi^2 = 0.08, df = 1 (P = 0.78); I^2 =0.0%

Test for overall effect: Z = 5.54 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 14.2. Comparison 14 SF-36 Mental Component Summary (MCS) week 24, Outcome 2 certolizumab 400 mg sc.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 14 SF-36 Mental Component Summary (MCS) week 24

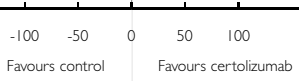
Outcome: 2 certolizumab 400 mg sc

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	390	6.5 (11.85)	199	2.3 (11.29)		57.2 %	4.20 [2.24, 6.16]
RAPID2 2007	246	6.28 (10.98)	127	1.63 (10.36)		42.8 %	4.65 [2.39, 6.91]
Total (95% CI)	**636**		**326**			**100.0 %**	**4.39 [2.91, 5.88]**

Heterogeneity: $Chi^2 = 0.09$, df = 1 (P = 0.77); $I^2 = 0.0\%$

Test for overall effect: Z = 5.81 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 15.1. Comparison 15 SF-36 Mental Component Summary (MCS) week 52, Outcome 1 certolizumab 200 mg sc.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 15 SF-36 Mental Component Summary (MCS) week 52

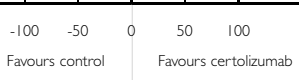
Outcome: 1 certolizumab 200 mg sc

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	393	6.35 (11.1)	199	2.05 (11.14)		100.0 %	4.30 [2.40, 6.20]
Total (95% CI)	**393**		**199**			**100.0 %**	**4.30 [2.40, 6.20]**

Heterogeneity: not applicable

Test for overall effect: Z = 4.44 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 15.2. Comparison 15 SF-36 Mental Component Summary (MCS) week 52, Outcome 2 certolizumab 400 mg sc.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 15 SF-36 Mental Component Summary (MCS) week 52

Outcome: 2 certolizumab 400 mg sc

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	390	6.35 (11.06)	199	2.05 (11.14)		100.0 %	4.30 [2.40, 6.20]
Total (95% CI)	**390**		**199**			**100.0 %**	**4.30 [2.40, 6.20]**

Heterogeneity: not applicable

Test for overall effect: Z = 4.44 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 16.1. Comparison 16 SF-36 Physical Component Summary (PCS) week 52, Outcome 1 certolizumab 200 mg sc.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 16 SF-36 Physical Component Summary (PCS) week 52

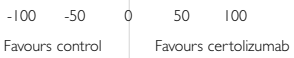
Outcome: 1 certolizumab 200 mg sc

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	393	7.79 (8.72)	199	1.73 (8.61)		100.0 %	6.06 [4.59, 7.53]
Total (95% CI)	**393**		**199**			**100.0 %**	**6.06 [4.59, 7.53]**

Heterogeneity: not applicable

Test for overall effect: Z = 8.05 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 16.2. Comparison 16 SF-36 Physical Component Summary (PCS) week 52, Outcome 2 certolizumab 400 mg sc.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 16 SF-36 Physical Component Summary (PCS) week 52

Outcome: 2 certolizumab 400 mg sc

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	390	8.61 (8.49)	199	1.73 (8.61)		100.0 %	6.88 [5.42, 8.34]
Total (95% CI)	**390**		**199**			**100.0 %**	**6.88 [5.42, 8.34]**

Heterogeneity: not applicable

Test for overall effect: Z = 9.22 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 17.1. Comparison 17 SF-36 Physical Component Summary (PCS) week 24, any dose, Outcome 1 Change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 17 SF-36 Physical Component Summary (PCS) week 24, any dose

Outcome: 1 Change from baseline

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 certolizumab 200 mg sc							
RAPID1 2005	393	7.7 (7.93)	100	1.8 (8.46)		29.8 %	5.90 [4.07, 7.73]
RAPID2 2007	246	5.23 (8.31)	64	0.93 (8)		20.4 %	4.30 [2.08, 6.52]
Subtotal (95% CI)	**639**		**164**			**50.2 %**	**5.25 [3.84, 6.66]**
Heterogeneity: Chi^2 = 1.19, df = 1 (P = 0.28); I^2 =16%							
Test for overall effect: Z = 7.28 (P < 0.00001)							
2 certolizumab 400 mg sc							
RAPID1 2005	390	8.3 (7.9)	99	1.8 (8.46)		29.6 %	6.50 [4.66, 8.34]
RAPID2 2007	246	5.46 (8.31)	63	0.93 (8)		20.2 %	4.53 [2.30, 6.76]
Subtotal (95% CI)	**636**		**162**			**49.8 %**	**5.70 [4.28, 7.12]**
Heterogeneity: Chi^2 = 1.78, df = 1 (P = 0.18); I^2 =44%							
Test for overall effect: Z = 7.87 (P < 0.00001)							
Total (95% CI)	**1275**		**326**			**100.0 %**	**5.47 [4.47, 6.48]**
Heterogeneity: Chi^2 = 3.16, df = 3 (P = 0.37); I^2 =5%							
Test for overall effect: Z = 10.71 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 0.20, df = 1 (P = 0.66), I^2 =0.0%							

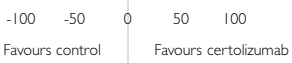
Analysis 18.1. Comparison 18 SF-36 Mental Component Summary (MCS) week 24, any dose, Outcome 1 Change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 18 SF-36 Mental Component Summary (MCS) week 24, any dose

Outcome: 1 Change from baseline

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 certolizumab 200 mg sc							
RAPID1 2005	393	6.3 (11.89)	100	2.3 (11.29)		28.6 %	4.00 [1.49, 6.51]
RAPID2 2007	246	6.05 (10.82)	64	1.63 (10.36)		21.7 %	4.42 [1.54, 7.30]
Subtotal (95% CI)	**639**		**164**			**50.3 %**	**4.18 [2.29, 6.07]**
Heterogeneity: Chi^2 = 0.05, df = 1 (P = 0.83); I^2 =0.0%							
Test for overall effect: Z = 4.34 (P = 0.000014)							
2 certolizumab 400 mg sc							
RAPID1 2005	390	6.5 (11.85)	99	2.3 (11.29)		28.4 %	4.20 [1.68, 6.72]
RAPID2 2007	246	6.28 (10.98)	63	1.63 (10.36)		21.3 %	4.65 [1.75, 7.55]
Subtotal (95% CI)	**636**		**162**			**49.7 %**	**4.39 [2.49, 6.29]**
Heterogeneity: Chi^2 = 0.05, df = 1 (P = 0.82); I^2 =0.0%							
Test for overall effect: Z = 4.53 (P < 0.00001)							
Total (95% CI)	**1275**		**326**			**100.0 %**	**4.29 [2.95, 5.63]**
Heterogeneity: Chi^2 = 0.12, df = 3 (P = 0.99); I^2 =0.0%							
Test for overall effect: Z = 6.27 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 0.02, df = 1 (P = 0.88), I^2 =0.0%							



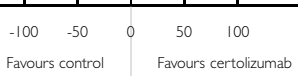
Analysis 19.1. Comparison 19 SF-36 Physical Component Summary (PCS) week 52, any dose, Outcome 1 Change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 19 SF-36 Physical Component Summary (PCS) week 52, any dose

Outcome: 1 Change from baseline

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 certolizumab 200 mg sc							
RAPID1 2005	393	7.79 (8.72)	100	1.73 (8.61)		50.0 %	6.06 [4.17, 7.95]
Subtotal (95% CI)	**393**		**100**			**50.0 %**	**6.06 [4.17, 7.95]**
Heterogeneity: not applicable							
Test for overall effect: Z = 6.27 (P < 0.00001)							
2 certolizumab 400 mg sc							
RAPID1 2005	390	8.61 (8.49)	99	1.73 (8.61)		50.0 %	6.88 [4.99, 8.77]
Subtotal (95% CI)	**390**		**99**			**50.0 %**	**6.88 [4.99, 8.77]**
Heterogeneity: not applicable							
Test for overall effect: Z = 7.12 (P < 0.00001)							
Total (95% CI)	**783**		**199**			**100.0 %**	**6.47 [5.13, 7.81]**
Heterogeneity: Chi^2 = 0.36, df = 1 (P = 0.55); I^2 =0.0%							
Test for overall effect: Z = 9.47 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 0.36, df = 1 (P = 0.55), I^2 =0.0%							



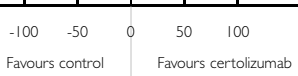
Analysis 20.1. Comparison 20 SF-36 Mental Component Summary (MCS) week 52, any dose, Outcome 1 Change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 20 SF-36 Mental Component Summary (MCS) week 52, any dose

Outcome: 1 Change from baseline

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 certolizumab 200 mg sc							
RAPID1 2005	393	6.35 (11.1)	100	2.05 (11.14)		50.2 %	4.30 [1.86, 6.74]
Subtotal (95% CI)	**393**		**100**			**50.2 %**	**4.30 [1.86, 6.74]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.45 (P = 0.00056)							
2 certolizumab 400 mg sc							
RAPID1 2005	390	6.35 (11.06)	99	2.05 (11.14)		49.8 %	4.30 [1.85, 6.75]
Subtotal (95% CI)	**390**		**99**			**49.8 %**	**4.30 [1.85, 6.75]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.43 (P = 0.00059)							
Total (95% CI)	**783**		**199**			**100.0 %**	**4.30 [2.57, 6.03]**
Heterogeneity: Chi^2 = 0.0, df = 1 (P = 1.00); I^2 =0.0%							
Test for overall effect: Z = 4.87 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 0.0, df = 1 (P = 1.00), I^2 =0.0%							



Analysis 21.1. Comparison 21 Disease Activity Score (DAS28) (ESR) remission (< 2.6), Outcome 1 Proportion of patients achieving remission 24 weeks certolizumab 200 mg.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 21 Disease Activity Score (DAS28) (ESR) remission (< 2.6)

Outcome: 1 Proportion of patients achieving remission 24 weeks certolizumab 200 mg

Study or subgroup	Certolizumab 200 mg n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
RAPID1 2005 (1)	45/391	3/196		66.1 %	3.77 [2.02, 7.04]
RAPID2 2007 (2)	23/245	1/125		33.9 %	4.10 [1.71, 9.83]
Total (95% CI)	**636**	**321**		**100.0 %**	**3.88 [2.33, 6.45]**

Total events: 68 (Certolizumab 200 mg), 4 (Control)

Heterogeneity: $Chi^2 = 0.02$, df = 1 (P = 0.88); $I^2 = 0.0\%$

Test for overall effect: Z = 5.22 (P < 0.00001)

Test for subgroup differences: Not applicable

(1) UCB report for NICE quote Certolizumab n=391

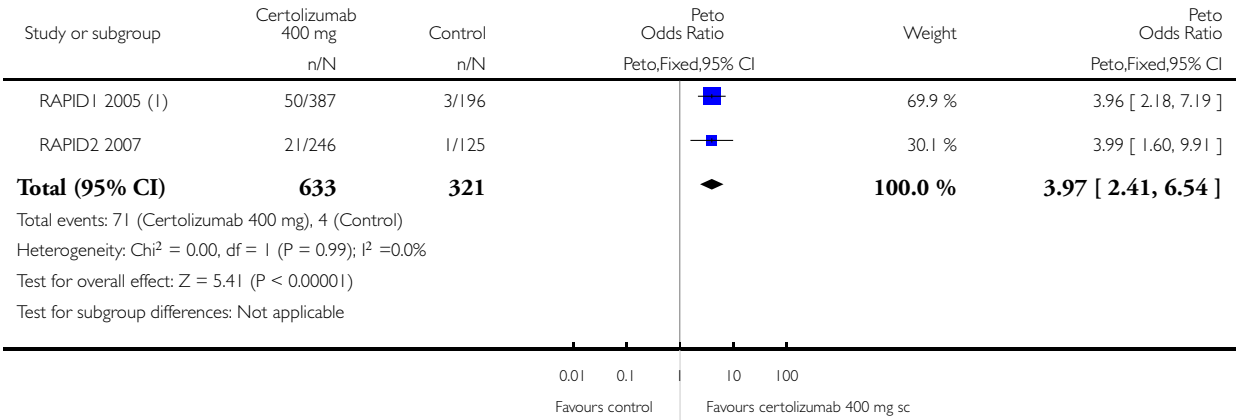
(2) UCB report for NICE quote Certolizumab n=245

Analysis 21.2. Comparison 21 Disease Activity Score (DAS28) (ESR) remission (< 2.6), Outcome 2 Proportion of patients achieving remission 24 weeks certolizumab 400 mg.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 21 Disease Activity Score (DAS28) (ESR) remission (< 2.6)

Outcome: 2 Proportion of patients achieving remission 24 weeks certolizumab 400 mg



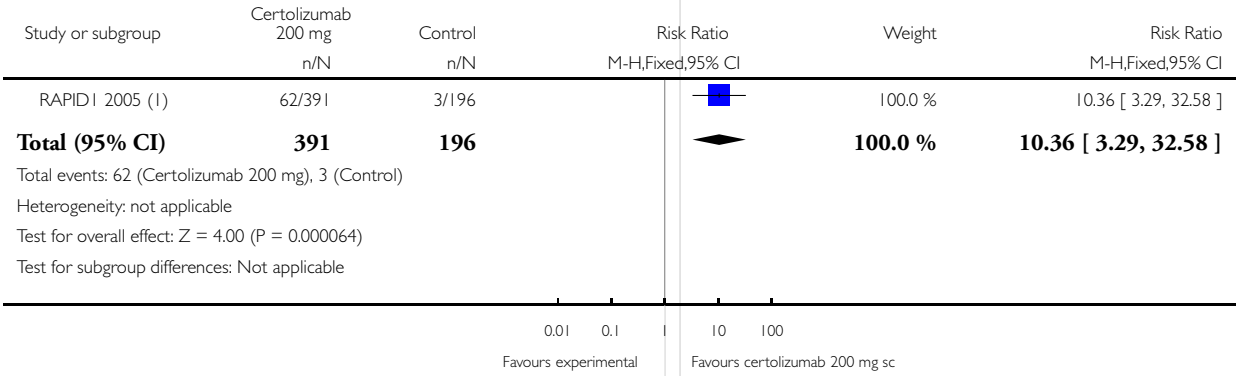
(1) UCB report for NICE quote Certolizumab n=387

Analysis 21.3. Comparison 21 Disease Activity Score (DAS28) (ESR) remission (< 2.6), Outcome 3 Proportion of patients achieving remission 52 weeks certolizumab 200 mg.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 21 Disease Activity Score (DAS28) (ESR) remission (< 2.6)

Outcome: 3 Proportion of patients achieving remission 52 weeks certolizumab 200 mg



(1) UCB report for NICE quote Certolizumab n=391

Analysis 21.4. Comparison 21 Disease Activity Score (DAS28) (ESR) remission (< 2.6), Outcome 4 Proportion of patients achieving remission 52 weeks certolizumab 400 mg.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 21 Disease Activity Score (DAS28) (ESR) remission (< 2.6)

Outcome: 4 Proportion of patients achieving remission 52 weeks certolizumab 400 mg

Study or subgroup	Certolizumab 400 mg n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
RAPID1 2005 (1)	74/387	3/196		100.0 %	12.49 [3.99, 39.12]
Total (95% CI)	**387**	**196**		**100.0 %**	**12.49 [3.99, 39.12]**
Total events: 74 (Certolizumab 400 mg), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.34 (P = 0.000015)					
Test for subgroup differences: Not applicable					

(1) UCB report for NICE quote Certolizumab n=387

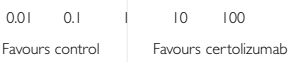
Analysis 22.1. Comparison 22 Disease Activity Score (DAS28) (ESR) remission (< 2.6) any doses, 24 weeks, Outcome 1 Proportion of patients achieving remission 24 weeks.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 22 Disease Activity Score (DAS28) (ESR) remission (< 2.6) any doses, 24 weeks

Outcome: 1 Proportion of patients achieving remission 24 weeks

Study or subgroup	Certolizumab n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 certolizumab 200 mg sc					
RAPID1 2005 (1)	45/391	3/100		37.5 %	3.84 [1.22, 12.09]
RAPID2 2007 (2)	23/245	1/64		12.5 %	6.01 [0.83, 43.65]
Subtotal (95% CI)	**636**	**164**		**50.0 %**	**4.38 [1.62, 11.82]**
Total events: 68 (Certolizumab), 4 (Control)					
Heterogeneity: Chi^2 = 0.15, df = 1 (P = 0.70); I^2 =0.0%					
Test for overall effect: Z = 2.91 (P = 0.0036)					
2 certolizumab 400 mg sc					
RAPID1 2005 (3)	50/387	3/99		37.5 %	4.26 [1.36, 13.38]
RAPID2 2007 (4)	21/246	1/63		12.5 %	5.38 [0.74, 39.22]
Subtotal (95% CI)	**633**	**162**		**50.0 %**	**4.54 [1.69, 12.24]**
Total events: 71 (Certolizumab), 4 (Control)					
Heterogeneity: Chi^2 = 0.04, df = 1 (P = 0.84); I^2 =0.0%					
Test for overall effect: Z = 2.99 (P = 0.0028)					
Total (95% CI)	**1269**	**326**		**100.0 %**	**4.46 [2.21, 9.00]**
Total events: 139 (Certolizumab), 8 (Control)					
Heterogeneity: Chi^2 = 0.19, df = 3 (P = 0.98); I^2 =0.0%					
Test for overall effect: Z = 4.18 (P = 0.000030)					
Test for subgroup differences: Chi^2 = 0.0, df = 1 (P = 0.0), I^2 =0.0%					



(1) UCB report for NICE quoted Certolizumab n=391 and placebo n=196

(2) In NICE report UCB quoted certoluzimab n= 245 and placebo n =125

(3) In NICE report UCB quoted Certolizumab n= 387 and placebo n = 196

(4) In NICE report UCB quoted placebo n =125

Analysis 23.1. Comparison 23 Disease Activity Score (DAS28) (ESR) remission (< 2.6) any doses, 52 weeks, Outcome 1 Proportion of patients achieving remission 52 weeks.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 23 Disease Activity Score (DAS28) (ESR) remission (< 2.6) any doses, 52 weeks

Outcome: 1 Proportion of patients achieving remission 52 weeks

Study or subgroup	Certolizumab n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 certolizumab 200 mg sc					
RAPID1 2005 (1)	62/391	3/100		50.0 %	5.29 [1.69, 16.49]
Subtotal (95% CI)	**391**	**100**		**50.0 %**	**5.29 [1.69, 16.49]**
Total events: 62 (Certolizumab), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.87 (P = 0.0041)					
2 certolizumab 400 mg sc					
RAPID1 2005 (2)	74/387	3/99		50.0 %	6.31 [2.03, 19.59]
Subtotal (95% CI)	**387**	**99**		**50.0 %**	**6.31 [2.03, 19.59]**
Total events: 74 (Certolizumab), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.19 (P = 0.0014)					
Total (95% CI)	**778**	**199**		**100.0 %**	**5.80 [2.60, 12.94]**
Total events: 136 (Certolizumab), 6 (Control)					
Heterogeneity: Chi^2 = 0.05, df = 1 (P = 0.83); I^2 =0.0%					
Test for overall effect: Z = 4.29 (P = 0.000018)					
Test for subgroup differences: Chi^2 = 0.0, df = 1 (P = 0.0), I^2 =0.0%					

(1) In NICE report UCB quoted placebo certoluzimab n= 391 and placebo n =196

(2) UCB report for NICE quoted Certolizumab n=387

Analysis 24.1. Comparison 24 DAS-28 at 24 weeks 200 mg sc certolizumab, Outcome 1 DAS 28 (ESR) change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 24 DAS-28 at 24 weeks 200 mg sc certolizumab

Outcome: 1 DAS 28 (ESR) change from baseline

Study or subgroup	Certolizumab 200 mg N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID2 2007	246	-2.27 (1.38)	127	-0.5 (1.05)		100.0 %	-1.77 [-2.02, -1.52]
Total (95% CI)	**246**		**127**			**100.0 %**	**-1.77 [-2.02, -1.52]**

Heterogeneity: not applicable

Test for overall effect: Z = 13.81 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 25.1. Comparison 25 DAS-28 at 24 weeks 400 mg sc certolizumab, Outcome 1 DAS 28 (ESR) change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 25 DAS-28 at 24 weeks 400 mg sc certolizumab

Outcome: 1 DAS 28 (ESR) change from baseline

Study or subgroup	Certolizumab 400 mg N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
FAST4WARD 2005	111	-1.5 (2)	109	-0.6 (2)		17.7 %	-0.90 [-1.43, -0.37]
RAPID2 2007	246	-2.46 (1.31)	127	-0.5 (1.05)		82.3 %	-1.96 [-2.21, -1.71]
Total (95% CI)	**357**		**236**			**100.0 %**	**-1.77 [-1.99, -1.55]**

Heterogeneity: Chi^2 = 12.71, df = 1 (P = 0.00036); I^2 =92%

Test for overall effect: Z = 15.61 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 26.1. Comparison 26 DAS-28 at week 52, certolizumab 200 mg, Outcome 1 DAS 28 (ESR) Change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 26 DAS-28 at week 52, certolizumab 200 mg

Outcome: 1 DAS 28 (ESR) Change from baseline

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	393	-3.3 (1.3)	199	-2.4 (1.3)		100.0 %	-0.90 [-1.12, -0.68]
Total (95% CI)	**393**		**199**			**100.0 %**	**-0.90 [-1.12, -0.68]**

Heterogeneity: not applicable

Test for overall effect: Z = 7.96 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 27.1. Comparison 27 DAS-28 at week 52, certolizumab 400 mg, Outcome 1 DAS 28 (ESR) Change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 27 DAS-28 at week 52, certolizumab 400 mg

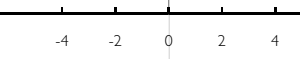
Outcome: 1 DAS 28 (ESR) Change from baseline

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	390	-3.4 (1.4)	199	-2.4 (1.3)		100.0 %	-1.00 [-1.23, -0.77]
Total (95% CI)	**390**		**199**			**100.0 %**	**-1.00 [-1.23, -0.77]**

Heterogeneity: not applicable

Test for overall effect: Z = 8.60 (P < 0.00001)

Test for subgroup differences: Not applicable



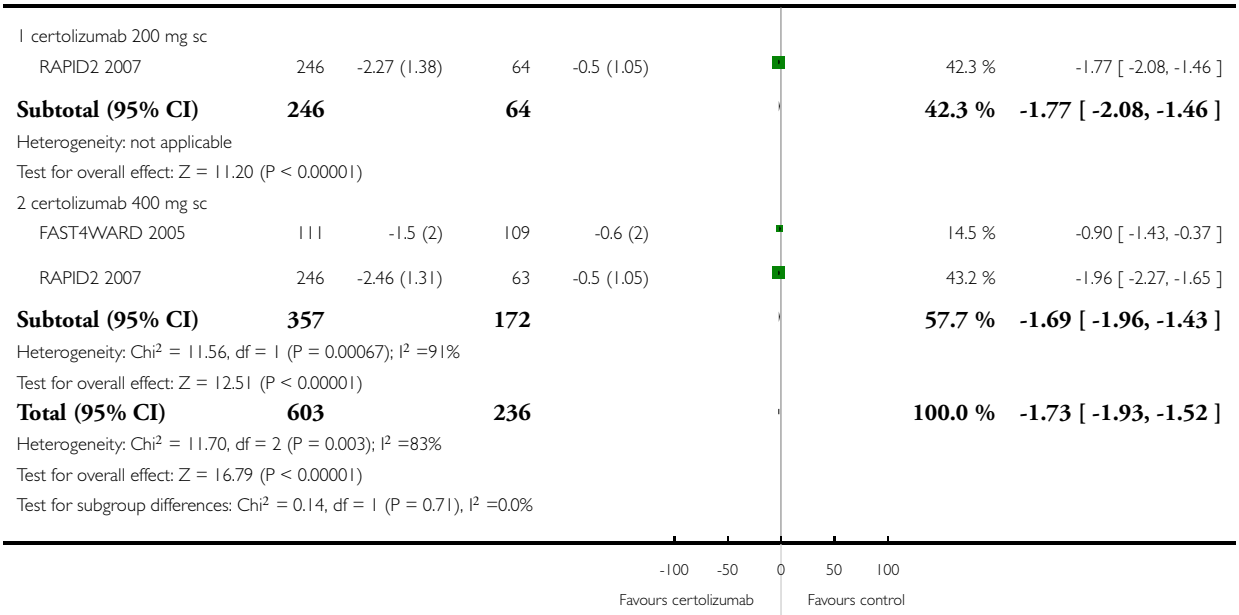
Analysis 28.1. Comparison 28 DAS-28 at 24 weeks, any dose, Outcome 1 Change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 28 DAS-28 at 24 weeks, any dose

Outcome: 1 Change from baseline

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 certolizumab 200 mg sc							
RAPID2 2007	246	-2.27 (1.38)	64	-0.5 (1.05)		42.3 %	-1.77 [-2.08, -1.46]
Subtotal (95% CI)	**246**		**64**			**42.3 %**	**-1.77 [-2.08, -1.46]**
Heterogeneity: not applicable							
Test for overall effect: Z = 11.20 (P < 0.00001)							
2 certolizumab 400 mg sc							
FAST4WARD 2005	111	-1.5 (2)	109	-0.6 (2)		14.5 %	-0.90 [-1.43, -0.37]
RAPID2 2007	246	-2.46 (1.31)	63	-0.5 (1.05)		43.2 %	-1.96 [-2.27, -1.65]
Subtotal (95% CI)	**357**		**172**			**57.7 %**	**-1.69 [-1.96, -1.43]**
Heterogeneity: Chi^2 = 11.56, df = 1 (P = 0.00067); I^2 =91%							
Test for overall effect: Z = 12.51 (P < 0.00001)							
Total (95% CI)	**603**		**236**			**100.0 %**	**-1.73 [-1.93, -1.52]**
Heterogeneity: Chi^2 = 11.70, df = 2 (P = 0.003); I^2 =83%							
Test for overall effect: Z = 16.79 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 0.14, df = 1 (P = 0.71), I^2 =0.0%							



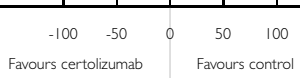
Analysis 29.1. Comparison 29 DAS-28 at 52 weeks, any dose, Outcome 1 Change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 29 DAS-28 at 52 weeks, any dose

Outcome: 1 Change from baseline

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 certolizumab 200 mg sc							
RAPID1 2005	393	-3.3 (1.3)	100	-2.4 (1.3)		51.0 %	-0.90 [-1.19, -0.61]
Subtotal (95% CI)	**393**		**100**			**51.0 %**	**-0.90 [-1.19, -0.61]**
Heterogeneity: not applicable							
Test for overall effect: Z = 6.18 (P < 0.00001)							
2 certolizumab 400 mg sc							
RAPID1 2005	390	-3.4 (1.4)	99	-2.4 (1.3)		49.0 %	-1.00 [-1.29, -0.71]
Subtotal (95% CI)	**390**		**99**			**49.0 %**	**-1.00 [-1.29, -0.71]**
Heterogeneity: not applicable							
Test for overall effect: Z = 6.73 (P < 0.00001)							
Total (95% CI)	**783**		**199**			**100.0 %**	**-0.95 [-1.15, -0.75]**
Heterogeneity: Chi^2 = 0.23, df = 1 (P = 0.63); I^2 =0.0%							
Test for overall effect: Z = 9.12 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 0.23, df = 1 (P = 0.63), I^2 =0.0%							



Analysis 30.1. Comparison 30 Modified total Sharp scores (mTSS), Outcome 1 Change from the baseline mean mTSS 24 weeks 200 mg certolizumab..

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 30 Modified total Sharp scores (mTSS)

Outcome: 1 Change from the baseline mean mTSS 24 weeks 200 mg certolizumab.

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	353	0.2 (3.2)	180	1.3 (3.8)		62.8 %	-1.10 [-1.75, -0.45]
RAPID2 2007	214	0.2 (2.7)	112	1.2 (4.1)		37.2 %	-1.00 [-1.84, -0.16]
Total (95% CI)	**567**		**292**			**100.0 %**	**-1.06 [-1.58, -0.55]**

Heterogeneity: $Chi^2 = 0.03$, df = 1 (P = 0.85); $I^2 = 0.0\%$

Test for overall effect: Z = 4.06 (P = 0.000049)

Test for subgroup differences: Not applicable

Analysis 30.2. Comparison 30 Modified total Sharp scores (mTSS), Outcome 2 Change from the baseline mean mTSS 24 weeks 400 mg certolizumab..

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 30 Modified total Sharp scores (mTSS)

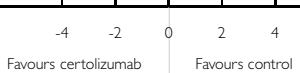
Outcome: 2 Change from the baseline mean mTSS 24 weeks 400 mg certolizumab.

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	355	0.2 (4.2)	180	1.3 (3.8)		56.7 %	-1.10 [-1.81, -0.39]
RAPID2 2007	222	-0.4 (2.1)	112	1.2 (4.1)		43.3 %	-1.60 [-2.41, -0.79]
Total (95% CI)	**577**		**292**			**100.0 %**	**-1.32 [-1.85, -0.78]**

Heterogeneity: $Chi^2 = 0.83$, df = 1 (P = 0.36); $I^2 = 0.0\%$

Test for overall effect: Z = 4.85 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 30.3. Comparison 30 Modified total Sharp scores (mTSS), Outcome 3 Change from the baseline mean mTSS 52 weeks 200 mg certolizumab sc.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 30 Modified total Sharp scores (mTSS)

Outcome: 3 Change from the baseline mean mTSS 52 weeks 200 mg certolizumab sc

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	364	0.4 (5.7)	181	2.8 (7.8)		100.0 %	-2.40 [-3.68, -1.12]
Total (95% CI)	**364**		**181**			**100.0 %**	**-2.40 [-3.68, -1.12]**

Heterogeneity: not applicable

Test for overall effect: Z = 3.68 (P = 0.00023)

Test for subgroup differences: Not applicable

Analysis 30.4. Comparison 30 Modified total Sharp scores (mTSS), Outcome 4 Change from the baseline mean mTSS 52 weeks 400 mg certolizumab sc.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 30 Modified total Sharp scores (mTSS)

Outcome: 4 Change from the baseline mean mTSS 52 weeks 400 mg certolizumab sc

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	363	0.2 (4.8)	181	2.8 (7.8)		100.0 %	-2.60 [-3.84, -1.36]
Total (95% CI)	**363**		**181**			**100.0 %**	**-2.60 [-3.84, -1.36]**

Heterogeneity: not applicable

Test for overall effect: Z = 4.11 (P = 0.000039)

Test for subgroup differences: Not applicable

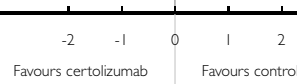
Analysis 31.1. Comparison 31 Modified total Sharp scores (mTSS) at 24 weeks, any dose, Outcome 1 Change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 31 Modified total Sharp scores (mTSS) at 24 weeks, any dose

Outcome: 1 Change from baseline

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 certolizumab 200 mg sc							
RAPID1 2005	353	0.2 (3.2)	90	1.3 (3.8)		32.6 %	-1.10 [-1.95, -0.25]
RAPID2 2007	214	0.2 (2.7)	56	1.2 (4.1)		18.5 %	-1.00 [-2.13, 0.13]
Subtotal (95% CI)	**567**		**146**			**51.1 %**	**-1.06 [-1.75, -0.38]**
Heterogeneity: Chi^2 = 0.02, df = 1 (P = 0.89); I^2 =0.0%							
Test for overall effect: Z = 3.06 (P = 0.0022)							
2 certolizumab 400 mg sc							
RAPID1 2005	355	0.2 (4.2)	91	1.3 (3.8)		29.6 %	-1.10 [-1.99, -0.21]
RAPID2 2007	222	-0.4 (2.1)	56	1.2 (4.1)		19.3 %	-1.60 [-2.71, -0.49]
Subtotal (95% CI)	**577**		**147**			**48.9 %**	**-1.30 [-1.99, -0.60]**
Heterogeneity: Chi^2 = 0.47, df = 1 (P = 0.49); I^2 =0.0%							
Test for overall effect: Z = 3.65 (P = 0.00026)							
Total (95% CI)	**1144**		**293**			**100.0 %**	**-1.18 [-1.67, -0.69]**
Heterogeneity: Chi^2 = 0.71, df = 3 (P = 0.87); I^2 =0.0%							
Test for overall effect: Z = 4.74 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 0.22, df = 1 (P = 0.64), I^2 =0.0%							



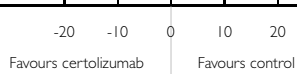
Analysis 32.1. Comparison 32 Modified total Sharp scores (mTSS) at 52 weeks, any dose, Outcome 1 Change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 32 Modified total Sharp scores (mTSS) at 52 weeks, any dose

Outcome: 1 Change from baseline

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 certolizumab 200 mg sc							
RAPID1 2005	364	0.4 (5.7)	91	2.8 (7.8)		49.4 %	-2.40 [-4.11, -0.69]
Subtotal (95% CI)	**364**		**91**			**49.4 %**	**-2.40 [-4.11, -0.69]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.76 (P = 0.0058)							
2 certolizumab 400 mg sc							
RAPID1 2005	363	0.2 (4.8)	90	2.8 (7.8)		50.6 %	-2.60 [-4.29, -0.91]
Subtotal (95% CI)	**363**		**90**			**50.6 %**	**-2.60 [-4.29, -0.91]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.02 (P = 0.0025)							
Total (95% CI)	**727**		**181**			**100.0 %**	**-2.50 [-3.70, -1.30]**
Heterogeneity: Chi^2 = 0.03, df = 1 (P = 0.87); I^2 =0.0%							
Test for overall effect: Z = 4.09 (P = 0.000043)							
Test for subgroup differences: Chi^2 = 0.03, df = 1 (P = 0.87), I^2 =0.0%							



Analysis 33.1. Comparison 33 Erosion score (ES), Outcome 1 Change from the baseline mean ES at week 24, 200 mg certolizumab..

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 33 Erosion score (ES)

Outcome: 1 Change from the baseline mean ES at week 24, 200 mg certolizumab.

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	353	0 (1.5)	180	0.7 (2.1)		71.9 %	-0.70 [-1.04, -0.36]
RAPID2 2007	214	0.1 (2)	112	0.7 (2.6)		28.1 %	-0.60 [-1.15, -0.05]
Total (95% CI)	**567**		**292**			**100.0 %**	**-0.67 [-0.96, -0.38]**

Heterogeneity: $Chi^2 = 0.09$, df = 1 (P = 0.76); $I^2 = 0.0\%$

Test for overall effect: Z = 4.51 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 33.2. Comparison 33 Erosion score (ES), Outcome 2 Change from the baseline mean ES at week 24, 400 mg certolizumab..

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 33 Erosion score (ES)

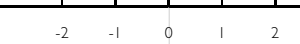
Outcome: 2 Change from the baseline mean ES at week 24, 400 mg certolizumab.

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	355	0.1 (2.4)	180	0.7 (2.1)		64.8 %	-0.60 [-1.00, -0.20]
RAPID2 2007	222	-0.3 (1.8)	112	0.7 (2.6)		35.2 %	-1.00 [-1.54, -0.46]
Total (95% CI)	**577**		**292**			**100.0 %**	**-0.74 [-1.06, -0.42]**

Heterogeneity: $Chi^2 = 1.38$, df = 1 (P = 0.24); $I^2 = 28\%$

Test for overall effect: Z = 4.56 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 33.3. Comparison 33 Erosion score (ES), Outcome 3 Change from the baseline mean ES at week 52, 200 mg certolizumab..

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 33 Erosion score (ES)

Outcome: 3 Change from the baseline mean ES at week 52, 200 mg certolizumab.

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	364	0.1 (2.5)	180	1.5 (4.3)		100.0 %	-1.40 [-2.08, -0.72]
Total (95% CI)	**364**		**180**			**100.0 %**	**-1.40 [-2.08, -0.72]**

Heterogeneity: not applicable

Test for overall effect: Z = 4.04 (P = 0.000053)

Test for subgroup differences: Not applicable

Analysis 33.4. Comparison 33 Erosion score (ES), Outcome 4 Change from the baseline mean ES at week 52, 400 mg certolizumab..

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 33 Erosion score (ES)

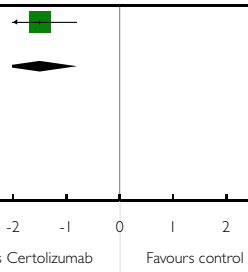
Outcome: 4 Change from the baseline mean ES at week 52, 400 mg certolizumab.

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	363	0 (3)	180	1.5 (4.3)		100.0 %	-1.50 [-2.20, -0.80]
Total (95% CI)	**363**		**180**			**100.0 %**	**-1.50 [-2.20, -0.80]**

Heterogeneity: not applicable

Test for overall effect: Z = 4.20 (P = 0.000027)

Test for subgroup differences: Not applicable



Analysis 34.1. Comparison 34 Erosion score (ES) at 24 weeks, any dose, Outcome 1 Change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 34 Erosion score (ES) at 24 weeks, any dose

Outcome: 1 Change from baseline

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 certolizumab 200 mg sc							
RAPID1 2005	353	0 (1.5)	91	0.7 (2.1)		37.9 %	-0.70 [-1.16, -0.24]
RAPID2 2007	214	0.1 (2)	56	0.7 (2.6)		14.9 %	-0.60 [-1.33, 0.13]
Subtotal (95% CI)	**567**		**147**			**52.8 %**	**-0.67 [-1.06, -0.28]**
Heterogeneity: Chi² = 0.05, df = 1 (P = 0.82); I² =0.0%							
Test for overall effect: Z = 3.39 (P = 0.00071)							
2 certolizumab 400 mg sc							
RAPID1 2005	355	0.1 (2.4)	90	0.7 (2.1)		31.9 %	-0.60 [-1.10, -0.10]
RAPID2 2007	222	-0.3 (1.8)	56	0.7 (2.6)		15.4 %	-1.00 [-1.72, -0.28]
Subtotal (95% CI)	**577**		**146**			**47.2 %**	**-0.73 [-1.14, -0.32]**
Heterogeneity: Chi² = 0.80, df = 1 (P = 0.37); I² =0.0%							
Test for overall effect: Z = 3.48 (P = 0.00050)							
Total (95% CI)	**1144**		**293**			**100.0 %**	**-0.70 [-0.98, -0.42]**
Heterogeneity: Chi² = 0.89, df = 3 (P = 0.83); I² =0.0%							
Test for overall effect: Z = 4.85 (P < 0.00001)							
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.84), I² =0.0%							

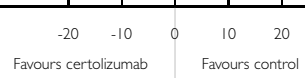
Analysis 35.1. Comparison 35 Erosion score (ES) at 52 weeks, any dose, Outcome 1 Change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 35 Erosion score (ES) at 52 weeks, any dose

Outcome: 1 Change from baseline

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 certolizumab 200 mg sc							
RAPID1 2005	364	0.1 (2.5)	91	1.5 (4.3)		51.1 %	-1.40 [-2.32, -0.48]
Subtotal (95% CI)	**364**		**91**			**51.1 %**	**-1.40 [-2.32, -0.48]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.98 (P = 0.0029)							
2 certolizumab 400 mg sc							
RAPID1 2005	363	0 (3)	90	1.5 (4.3)		48.9 %	-1.50 [-2.44, -0.56]
Subtotal (95% CI)	**363**		**90**			**48.9 %**	**-1.50 [-2.44, -0.56]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.13 (P = 0.0018)							
Total (95% CI)	**727**		**181**			**100.0 %**	**-1.45 [-2.11, -0.79]**
Heterogeneity: Chi^2 = 0.02, df = 1 (P = 0.88); I^2 =0.0%							
Test for overall effect: Z = 4.32 (P = 0.000016)							
Test for subgroup differences: Chi^2 = 0.02, df = 1 (P = 0.88), I^2 =0.0%							



Analysis 36.1. Comparison 36 Joint space narrowing (JSN), Outcome 1 Change from the baseline mean JSN 24 weeks 200 mg certolizumab..

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 36 Joint space narrowing (JSN)

Outcome: 1 Change from the baseline mean JSN 24 weeks 200 mg certolizumab.

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	355	0.2 (2.5)	180	0.7 (2.4)		53.2 %	-0.50 [-0.94, -0.06]
RAPID2 2007	214	0.1 (1.4)	112	0.5 (2.3)		46.8 %	-0.40 [-0.87, 0.07]
Total (95% CI)	**569**		**292**			**100.0 %**	**-0.45 [-0.77, -0.13]**

Heterogeneity: Chi^2 = 0.09, df = 1 (P = 0.76); I^2 =0.0%

Test for overall effect: Z = 2.79 (P = 0.0053)

Test for subgroup differences: Not applicable

Analysis 36.2. Comparison 36 Joint space narrowing (JSN), Outcome 2 Change from the baseline mean JSN 24 weeks 400 mg certolizumab..

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 36 Joint space narrowing (JSN)

Outcome: 2 Change from the baseline mean JSN 24 weeks 400 mg certolizumab.

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	355	0.2 (2.4)	180	0.7 (2.4)		51.8 %	-0.50 [-0.93, -0.07]
RAPID2 2007	222	-0.1 (1)	112	0.5 (2.3)		48.2 %	-0.60 [-1.05, -0.15]
Total (95% CI)	**577**		**292**			**100.0 %**	**-0.55 [-0.86, -0.24]**

Heterogeneity: Chi^2 = 0.10, df = 1 (P = 0.75); I^2 =0.0%

Test for overall effect: Z = 3.47 (P = 0.00052)

Test for subgroup differences: Not applicable

Analysis 36.3. Comparison 36 Joint space narrowing (JSN), Outcome 3 Change from the baseline mean JSN 52 weeks 200 mg certolizumab..

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 36 Joint space narrowing (JSN)

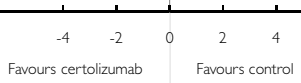
Outcome: 3 Change from the baseline mean JSN 52 weeks 200 mg certolizumab.

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	367	0.4 (4.2)	181	1.4 (5)		100.0 %	-1.00 [-1.85, -0.15]
Total (95% CI)	**367**		**181**			**100.0 %**	**-1.00 [-1.85, -0.15]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.32 (P = 0.020)

Test for subgroup differences: Not applicable



Analysis 36.4. Comparison 36 Joint space narrowing (JSN), Outcome 4 Change from the baseline mean JSN 52 weeks 400 mg certolizumab.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 36 Joint space narrowing (JSN)

Outcome: 4 Change from the baseline mean JSN 52 weeks 400 mg certolizumab

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	363	0.2 (2.8)	181	1.4 (5)		100.0 %	-1.20 [-1.98, -0.42]
Total (95% CI)	**363**		**181**			**100.0 %**	**-1.20 [-1.98, -0.42]**

Heterogeneity: not applicable

Test for overall effect: Z = 3.00 (P = 0.0027)

Test for subgroup differences: Not applicable

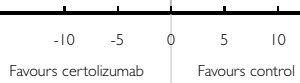
Analysis 37.1. Comparison 37 Joint space narrowing (JSN) at 24 weeks, any dose, Outcome 1 Change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 37 Joint space narrowing (JSN) at 24 weeks, any dose

Outcome: 1 Change from baseline

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 certolizumab 200 mg sc							
RAPID1 2005	355	0.2 (2.5)	91	0.7 (2.4)		27.7 %	-0.50 [-1.06, 0.06]
RAPID2 2007	214	0.1 (1.4)	56	0.5 (2.3)		21.6 %	-0.40 [-1.03, 0.23]
Subtotal (95% CI)	**569**		**147**			**49.4 %**	**-0.46 [-0.87, -0.04]**
Heterogeneity: Chi^2 = 0.05, df = 1 (P = 0.82); I^2 =0.0%							
Test for overall effect: Z = 2.14 (P = 0.032)							
2 certolizumab 400 mg sc							
RAPID1 2005	355	0.2 (2.4)	90	0.7 (2.4)		28.0 %	-0.50 [-1.06, 0.06]
RAPID2 2007	222	-0.1 (1)	56	0.5 (2.3)		22.7 %	-0.60 [-1.22, 0.02]
Subtotal (95% CI)	**577**		**146**			**50.6 %**	**-0.54 [-0.96, -0.13]**
Heterogeneity: Chi^2 = 0.06, df = 1 (P = 0.81); I^2 =0.0%							
Test for overall effect: Z = 2.59 (P = 0.0097)							
Total (95% CI)	**1146**		**293**			**100.0 %**	**-0.50 [-0.79, -0.21]**
Heterogeneity: Chi^2 = 0.20, df = 3 (P = 0.98); I^2 =0.0%							
Test for overall effect: Z = 3.35 (P = 0.00082)							
Test for subgroup differences: Chi^2 = 0.09, df = 1 (P = 0.77), I^2 =0.0%							



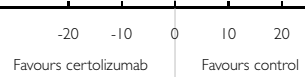
Analysis 38.1. Comparison 38 Joint space narrowing (JSN) at 52 weeks, any dose, Outcome 1 Change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 38 Joint space narrowing (JSN) at 52 weeks, any dose

Outcome: 1 Change from baseline

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 certolizumab 200 mg sc							
RAPID1 2005	367	0.4 (4.2)	91	1.4 (5)		48.1 %	-1.00 [-2.11, 0.11]
Subtotal (95% CI)	**367**		**91**			**48.1 %**	**-1.00 [-2.11, 0.11]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.76 (P = 0.078)							
2 certolizumab 400 mg sc							
RAPID1 2005	363	0.2 (2.8)	90	1.4 (5)		51.9 %	-1.20 [-2.27, -0.13]
Subtotal (95% CI)	**363**		**90**			**51.9 %**	**-1.20 [-2.27, -0.13]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.19 (P = 0.028)							
Total (95% CI)	**730**		**181**			**100.0 %**	**-1.10 [-1.88, -0.33]**
Heterogeneity: Chi^2 = 0.06, df = 1 (P = 0.80); I^2 =0.0%							
Test for overall effect: Z = 2.80 (P = 0.0051)							
Test for subgroup differences: Chi^2 = 0.06, df = 1 (P = 0.80), I^2 =0.0%							



Analysis 39.1. Comparison 39 Patient's assessment of arthritis pain (VAS score 0 to 100 mm), Outcome 1 Mean change at 24 weeks certolizumab 200 mg.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 39 Patient's assessment of arthritis pain (VAS score 0 to 100 mm)

Outcome: 1 Mean change at 24 weeks certolizumab 200 mg

Study or subgroup	Certolizumab 200 mg sc N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	393	-29.6 (21.81)	199	-8.1 (22.57)		59.7 %	-21.50 [-25.31, -17.69]
RAPID2 2007	246	-23.7 (22)	127	-4.7 (21.41)		40.3 %	-19.00 [-23.63, -14.37]
Total (95% CI)	**639**		**326**			**100.0 %**	**-20.49 [-23.43, -17.55]**

Heterogeneity: Chi² = 0.67, df = 1 (P = 0.41); I² =0.0%

Test for overall effect: Z = 13.66 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 39.2. Comparison 39 Patient's assessment of arthritis pain (VAS score 0 to 100 mm), Outcome 2 Mean change at 24 weeks certolizumab 400 mg.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 39 Patient's assessment of arthritis pain (VAS score 0 to 100 mm)

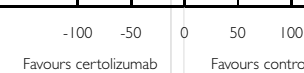
Outcome: 2 Mean change at 24 weeks certolizumab 400 mg

Study or subgroup	Certolizumab 400 mg sc N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
FAST4WARD 2005 (1)	111	-20.6 (42)	109	1.7 (42)		6.6 %	-22.30 [-33.40, -11.20]
RAPID1 2005 (2)	390	-31.7 (21.72)	199	-8.1 (22.57)		55.8 %	-23.60 [-27.41, -19.79]
RAPID2 2007	246	-26.1 (22)	127	-4.7 (21.41)		37.7 %	-21.40 [-26.03, -16.77]
Total (95% CI)	**747**		**435**			**100.0 %**	**-22.69 [-25.53, -19.84]**

Heterogeneity: Chi² = 0.52, df = 2 (P = 0.77); I² =0.0%

Test for overall effect: Z = 15.65 (P < 0.00001)

Test for subgroup differences: Not applicable



(1) In FAST4WARD we have obtained standard deviations from p values according to the Handbook section 7.7.3.7

(2) Data in RAPID1 from NICE report

Analysis 39.3. Comparison 39 Patient's assessment of arthritis pain (VAS score 0 to 100 mm), Outcome 3 Mean change at 52 weeks certolizumab 200 mg.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 39 Patient's assessment of arthritis pain (VAS score 0 to 100 mm)

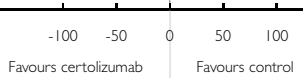
Outcome: 3 Mean change at 52 weeks certolizumab 200 mg

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	393	-31 (22.57)	199	-8.8 (23.79)		100.0 %	-22.20 [-26.19, -18.21]
Total (95% CI)	**393**		**199**			**100.0 %**	**-22.20 [-26.19, -18.21]**

Heterogeneity: not applicable

Test for overall effect: Z = 10.91 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 39.4. Comparison 39 Patient's assessment of arthritis pain (VAS score 0 to 100 mm), Outcome 4 Mean change at 52 weeks certolizumab 400 mg.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 39 Patient's assessment of arthritis pain (VAS score 0 to 100 mm)

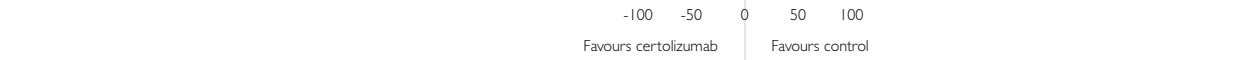
Outcome: 4 Mean change at 52 weeks certolizumab 400 mg

Study or subgroup	Certolizumab N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	390	-33.5 (23.7)	199	-8.8 (22.57)		100.0 %	-24.70 [-28.62, -20.78]
Total (95% CI)	**390**		**199**			**100.0 %**	**-24.70 [-28.62, -20.78]**

Heterogeneity: not applicable

Test for overall effect: Z = 12.35 (P < 0.00001)

Test for subgroup differences: Not applicable



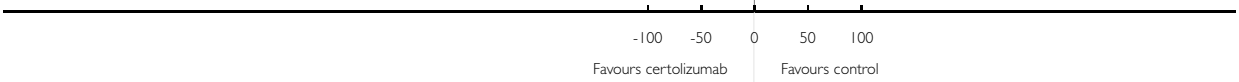
Analysis 40.1. Comparison 40 Patient's assessment of arthritis pain (VAS score 0 to 100 mm) at 24 weeks, any dose, Outcome 1 Change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 40 Patient's assessment of arthritis pain (VAS score 0 to 100 mm) at 24 weeks, any dose

Outcome: 1 Change from baseline

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 certolizumab 200 mg sc							
RAPID1 2005 (1)	393	-29.6 (21.81)	100	-8.1 (22.57)		28.1 %	-21.50 [-26.42, -16.58]
RAPID2 2007	246	-23.7 (22)	64	-4.7 (21.41)		19.4 %	-19.00 [-24.92, -13.08]
Subtotal (95% CI)	**639**		**164**			**47.5 %**	**-20.48 [-24.26, -16.69]**
Heterogeneity: Chi² = 0.40, df = 1 (P = 0.52); I² =0.0%							
Test for overall effect: Z = 10.60 (P < 0.00001)							
2 certolizumab 400 mg sc							
FAST4WARD 2005	111	-20.6 (42)	109	1.7 (42)		5.5 %	-22.30 [-33.40, -11.20]
RAPID1 2005	390	-31.7 (21.72)	99	-8.1 (22.57)		27.9 %	-23.60 [-28.54, -18.66]
RAPID2 2007	246	-26.1 (22)	63	-4.7 (21.41)		19.2 %	-21.40 [-27.36, -15.44]
Subtotal (95% CI)	**747**		**271**			**52.5 %**	**-22.66 [-26.26, -19.06]**
Heterogeneity: Chi² = 0.31, df = 2 (P = 0.85); I² =0.0%							
Test for overall effect: Z = 12.34 (P < 0.00001)							
Total (95% CI)	**1386**		**435**			**100.0 %**	**-21.63 [-24.23, -19.02]**
Heterogeneity: Chi² = 1.39, df = 4 (P = 0.85); I² =0.0%							
Test for overall effect: Z = 16.25 (P < 0.00001)							
Test for subgroup differences: Chi² = 0.67, df = 1 (P = 0.41), I² =0.0%							



(1) Data in RAPID1 from NICE report

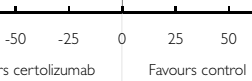
Analysis 41.1. Comparison 41 Patient's assessment of arthritis pain (VAS score 0 to 100 mm) at 52 weeks, any dose, Outcome 1 Change from baseline.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 41 Patient's assessment of arthritis pain (VAS score 0 to 100 mm) at 52 weeks, any dose

Outcome: 1 Change from baseline

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 certolizumab 200 mg sc							
RAPID1 2005 (1)	393	-31 (22.57)	100	-8.8 (23.79)		48.6 %	-22.20 [-27.37, -17.03]
Subtotal (95% CI)	**393**		**100**			**48.6 %**	**-22.20 [-27.37, -17.03]**
Heterogeneity: not applicable							
Test for overall effect: Z = 8.42 (P < 0.00001)							
2 certolizumab 400 mg sc							
RAPID1 2005	390	-33.5 (23.7)	99	-8.8 (22.57)		51.4 %	-24.70 [-29.73, -19.67]
Subtotal (95% CI)	**390**		**99**			**51.4 %**	**-24.70 [-29.73, -19.67]**
Heterogeneity: not applicable							
Test for overall effect: Z = 9.62 (P < 0.00001)							
Total (95% CI)	**783**		**199**			**100.0 %**	**-23.48 [-27.09, -19.88]**
Heterogeneity: Chi^2 = 0.46, df = 1 (P = 0.50); I^2 =0.0%							
Test for overall effect: Z = 12.77 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 0.46, df = 1 (P = 0.50), I^2 =0.0%							



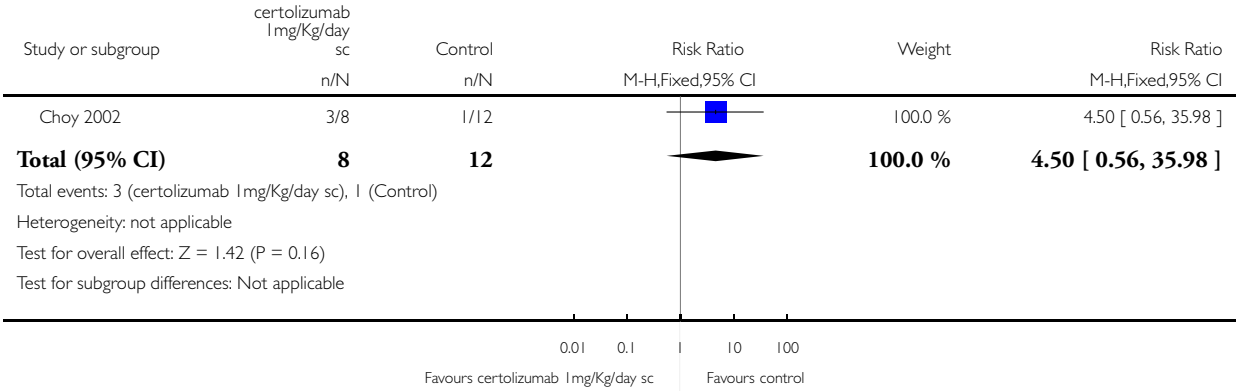
(1) Data in RAPID1 from NICE report

Analysis 42.1. Comparison 42 Certolizumab 1mg/kg/day sc, Outcome 1 Headache.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 42 Certolizumab 1mg/kg/day sc

Outcome: 1 Headache

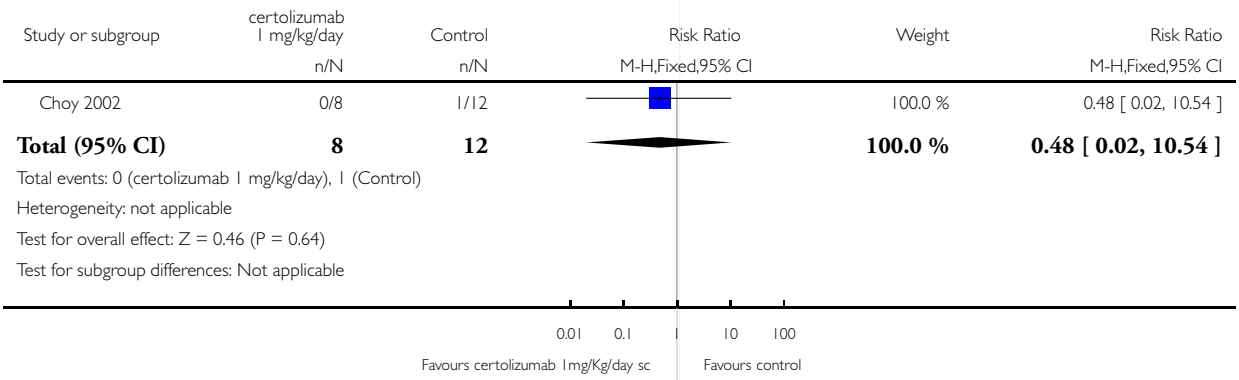


Analysis 42.2. Comparison 42 Certolizumab 1mg/kg/day sc, Outcome 2 Lower respiratory tract infection.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 42 Certolizumab 1mg/kg/day sc

Outcome: 2 Lower respiratory tract infection



Analysis 42.3. Comparison 42 Certolizumab 1mg/kg/day sc, Outcome 3 Adverse events Intensity severe.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 42 Certolizumab 1mg/kg/day sc

Outcome: 3 Adverse events Intensity severe

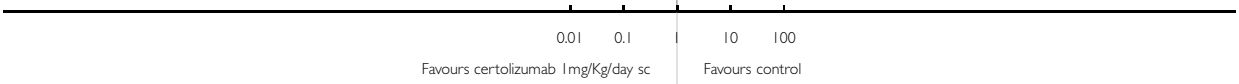
Study or subgroup	certolizumab 1 mg/kg/day n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Choy 2002	1/8	0/12		100.0 %	4.33 [0.20, 94.83]
Total (95% CI)	**8**	**12**		**100.0 %**	**4.33 [0.20, 94.83]**

Total events: 1 (certolizumab 1 mg/kg/day), 0 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 0.93 (P = 0.35)

Test for subgroup differences: Not applicable



Analysis 42.4. Comparison 42 Certolizumab 1mg/kg/day sc, Outcome 4 Antinuclear antibodies (ANA).

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 42 Certolizumab 1mg/kg/day sc

Outcome: 4 Antinuclear antibodies (ANA)

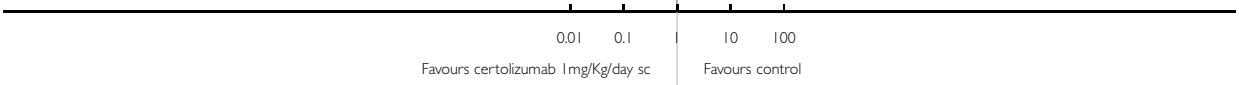
Study or subgroup	certolizumab 1 mg/kg/day n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Choy 2002	2/8	1/12		100.0 %	3.00 [0.32, 27.83]
Total (95% CI)	**8**	**12**		**100.0 %**	**3.00 [0.32, 27.83]**

Total events: 2 (certolizumab 1 mg/kg/day), 1 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 0.97 (P = 0.33)

Test for subgroup differences: Not applicable

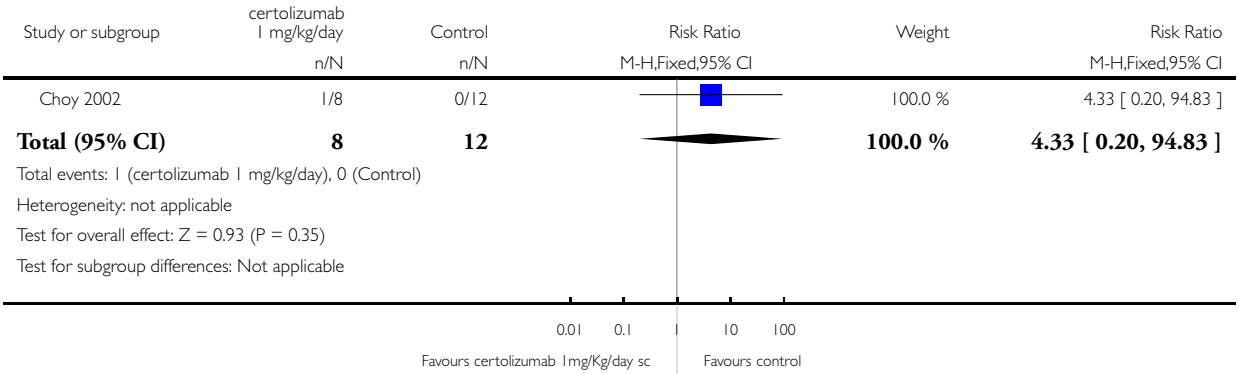


Analysis 42.5. Comparison 42 Certolizumab 1mg/kg/day sc, Outcome 5 Urinary tract infection.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 42 Certolizumab 1mg/kg/day sc

Outcome: 5 Urinary tract infection

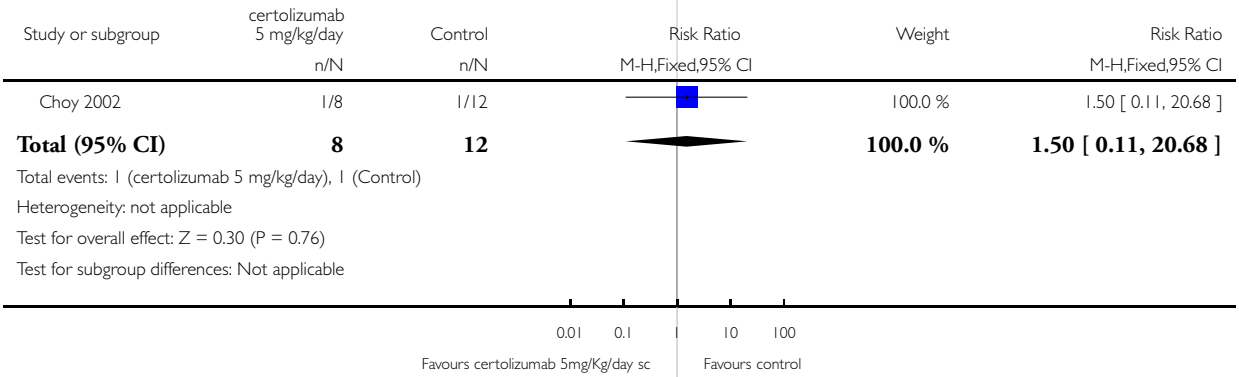


Analysis 43.1. Comparison 43 Certolizumab 5 mg/kg/day sc, Outcome 1 Lower respiratory tract infection.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 43 Certolizumab 5 mg/kg/day sc

Outcome: 1 Lower respiratory tract infection

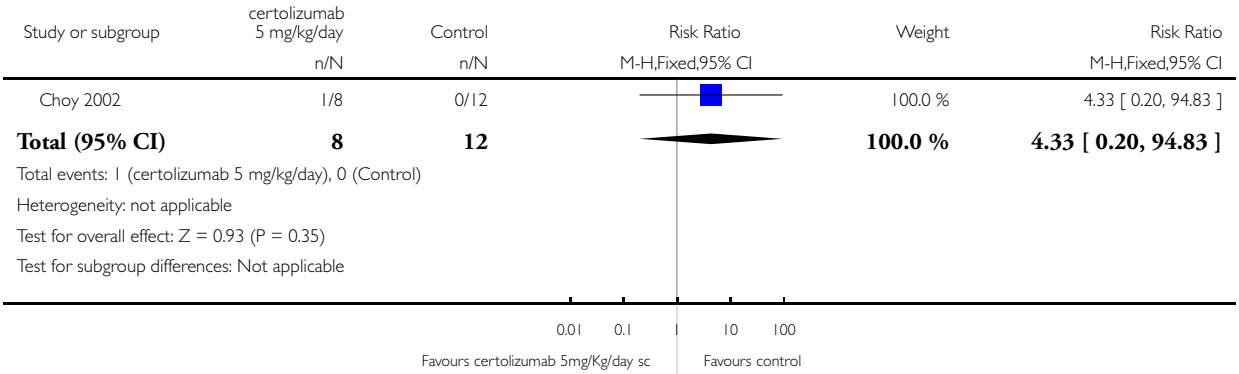


Analysis 43.2. Comparison 43 Certolizumab 5 mg/kg/day sc, Outcome 2 Urinary tract infection.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 43 Certolizumab 5 mg/kg/day sc

Outcome: 2 Urinary tract infection

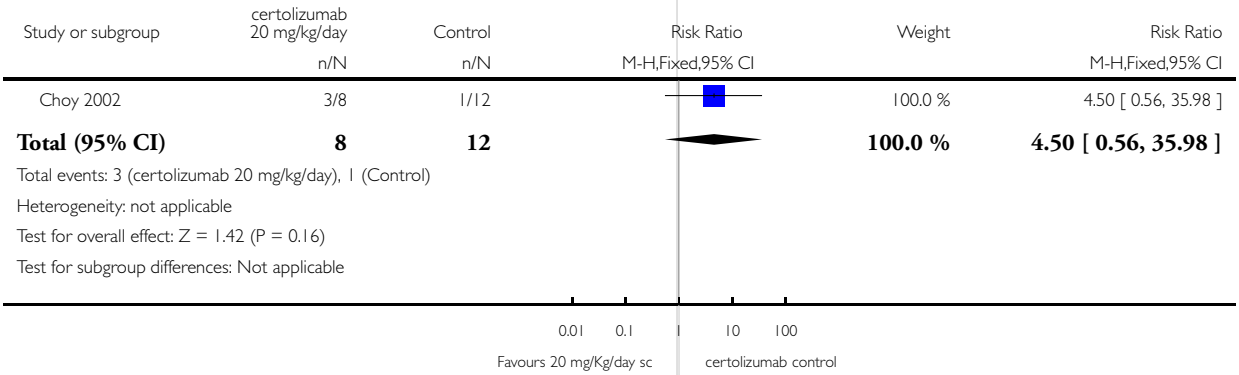


Analysis 44.1. Comparison 44 Certolizumab 20 mg/kg/day sc, Outcome 1 Headache.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 44 Certolizumab 20 mg/kg/day sc

Outcome: 1 Headache



Analysis 44.2. Comparison 44 Certolizumab 20 mg/kg/day sc, Outcome 2 Lower respiratory tract infection.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 44 Certolizumab 20 mg/kg/day sc

Outcome: 2 Lower respiratory tract infection

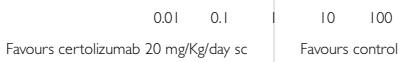
Study or subgroup	certolizumab 20 mg/kg/day n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Choy 2002	2/8	1/12		100.0 %	3.00 [0.32, 27.83]
Total (95% CI)	**8**	**12**		**100.0 %**	**3.00 [0.32, 27.83]**

Total events: 2 (certolizumab 20 mg/kg/day), 1 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 0.97 (P = 0.33)

Test for subgroup differences: Not applicable



Analysis 44.3. Comparison 44 Certolizumab 20 mg/kg/day sc, Outcome 3 Death.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 44 Certolizumab 20 mg/kg/day sc

Outcome: 3 Death

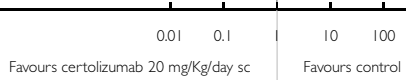
Study or subgroup	certolizumab 20 mg/kg/day n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Choy 2002	1/8	0/12		100.0 %	4.33 [0.20, 94.83]
Total (95% CI)	**8**	**12**		**100.0 %**	**4.33 [0.20, 94.83]**

Total events: 1 (certolizumab 20 mg/kg/day), 0 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 0.93 (P = 0.35)

Test for subgroup differences: Not applicable

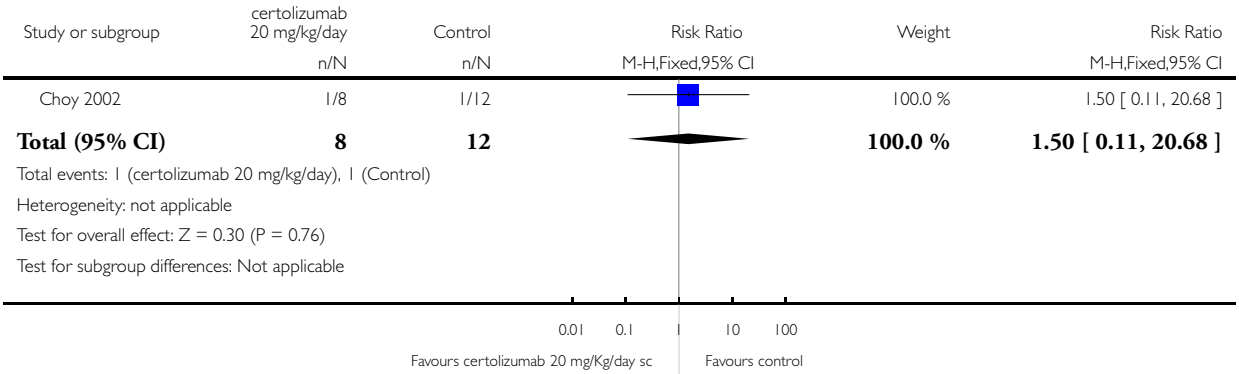


Analysis 44.4. Comparison 44 Certolizumab 20 mg/kg/day sc, Outcome 4 Antinuclear antibodies (ANA).

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 44 Certolizumab 20 mg/kg/day sc

Outcome: 4 Antinuclear antibodies (ANA)

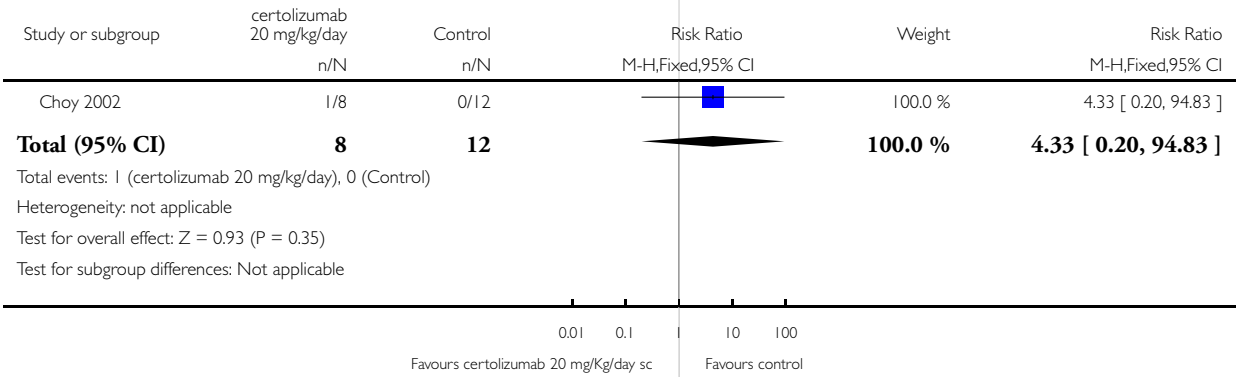


Analysis 44.5. Comparison 44 Certolizumab 20 mg/kg/day sc, Outcome 5 Urinary tract infection.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 44 Certolizumab 20 mg/kg/day sc

Outcome: 5 Urinary tract infection



Analysis 45.1. Comparison 45 Withdrawals, Outcome 1 All Withdrawn: any doses any follow up.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 45 Withdrawals

Outcome: 1 All Withdrawn: any doses any follow up

Study or subgroup	Certolizumab n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
CDP870-014 2009	28/125	56/125		9.8 %	0.50 [0.34, 0.73]
Choy 2002	2/24	6/12		1.4 %	0.17 [0.04, 0.71]
FAST4WARD 2005	35/111	81/109		14.4 %	0.42 [0.32, 0.57]
RAPID1 2005	254/783	156/199		43.7 %	0.41 [0.37, 0.47]
RAPID2 2007	137/492	110/127		30.7 %	0.32 [0.27, 0.38]
Total (95% CI)	**1535**	**572**		**100.0 %**	**0.39 [0.36, 0.43]**

Total events: 456 (Certolizumab), 409 (Control)

Heterogeneity: $Chi^2 = 9.99$, $df = 4$ ($P = 0.04$); $I^2 = 60\%$

Test for overall effect: $Z = 19.39$ ($P < 0.00001$)

Test for subgroup differences: Not applicable

Analysis 45.2. Comparison 45 Withdrawals, Outcome 2 Withdrawn due to lack of efficacy: any doses any follow up.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 45 Withdrawals

Outcome: 2 Withdrawn due to lack of efficacy: any doses any follow up

Study or subgroup	Certolizumab n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
CDP870-014 2009	16/125	45/125		9.4 %	0.36 [0.21, 0.59]
FAST4WARD 2005	24/111	75/109		15.7 %	0.31 [0.22, 0.46]
RAPID1 2005	151/783	125/199		41.5 %	0.31 [0.26, 0.37]
RAPID2 2007	95/492	101/127		33.4 %	0.24 [0.20, 0.30]
Total (95% CI)	**1511**	**560**		**100.0 %**	**0.29 [0.26, 0.33]**
Total events: 286 (Certolizumab), 346 (Control)					
Heterogeneity: Chi^2 = 4.22, df = 3 (P = 0.24); I^2 =29%					
Test for overall effect: Z = 19.02 (P < 0.00001)					
Test for subgroup differences: Not applicable					

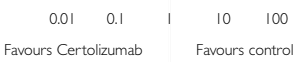
Analysis 45.3. Comparison 45 Withdrawals, Outcome 3 Withdrawn due to adverse events: any doses any follow up.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 45 Withdrawals

Outcome: 3 Withdrawn due to adverse events: any doses any follow up

Study or subgroup	Certolizumab n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
CDP870-014 2009	7/125	6/125		37.5 %	1.17 [0.40, 3.37]
FAST4WARD 2005	5/111	2/109		12.6 %	2.45 [0.49, 12.39]
RAPID1 2005	39/783	3/199		29.9 %	3.30 [1.03, 10.58]
RAPID2 2007	17/492	2/127		19.9 %	2.19 [0.51, 9.37]
Total (95% CI)	**1511**	**560**		**100.0 %**	**2.17 [1.15, 4.10]**
Total events: 68 (Certolizumab), 13 (Control)					
Heterogeneity: Chi^2 = 1.84, df = 3 (P = 0.61); I^2 =0.0%					
Test for overall effect: Z = 2.40 (P = 0.016)					
Test for subgroup differences: Not applicable					



Analysis 46.1. Comparison 46 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX), Outcome 1 ACR 50 200 mg certolizumab 24 weeks.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 46 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX)

Outcome: 1 ACR 50 200 mg certolizumab 24 weeks

Study or subgroup	Certolizumab 200 mg sc n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
RAPID1 2005	144/393	15/199		79.1 %	4.86 [2.94, 8.04]
RAPID2 2007	80/246	4/127		20.9 %	10.33 [3.87, 27.54]
Total (95% CI)	**639**	**326**		**100.0 %**	**6.01 [3.84, 9.40]**

Total events: 224 (Certolizumab 200 mg sc), 19 (Placebo)

Heterogeneity: Chi^2 = 1.85, df = 1 (P = 0.17); I^2 =46%

Test for overall effect: Z = 7.84 (P < 0.00001)

Analysis 46.2. Comparison 46 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX), Outcome 2 HAQ change from baseline 200 mg certolizumab 24 weeks.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 46 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX)

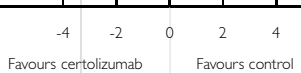
Outcome: 2 HAQ change from baseline 200 mg certolizumab 24 weeks

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
RAPID1 2005	393	-0.58 (0.59)	199	-0.17 (0.56)		50.3 %	-0.41 [-0.51, -0.31]
RAPID2 2007	246	-0.5 (0.47)	127	-0.14 (0.45)		49.7 %	-0.36 [-0.46, -0.26]
Total (95% CI)	**639**		**326**			**100.0 %**	**-0.39 [-0.45, -0.32]**

Heterogeneity: Chi^2 = 0.50, df = 1 (P = 0.48); I^2 =0.0%

Test for overall effect: Z = 10.94 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 46.3. Comparison 46 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX), Outcome 3 Serious adverse events certolizumab 200 mg sc.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 46 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX)

Outcome: 3 Serious adverse events certolizumab 200 mg sc

Study or subgroup	Certolizumab n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 certolizumab 200 mg					
RAPID1 2005	45/392	11/199		71.0 %	2.00 [1.12, 3.58]
RAPID2 2007	18/248	4/125		29.0 %	2.07 [0.83, 5.16]
Total (95% CI)	**640**	**324**		**100.0 %**	**2.02 [1.24, 3.30]**
Total events: 63 (Certolizumab), 15 (Control)					
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.95); I^2 =0.0%					
Test for overall effect: Z = 2.81 (P = 0.0050)					
Test for subgroup differences: Not applicable					

Analysis 46.4. Comparison 46 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX), Outcome 4 Proportion of patients achieving DAS <2.6 (Remission) 200 mg certolizumab 24 weeks.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 46 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX)

Outcome: 4 Proportion of patients achieving DAS <2.6 (Remission) 200 mg certolizumab 24 weeks

Study or subgroup	Certolizumab n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 certolizumab 200 mg sc 24 weeks					
RAPID1 2005 (1)	45/391	3/196		66.1 %	3.77 [2.02, 7.04]
RAPID2 2007 (2)	23/245	1/125		33.9 %	4.10 [1.71, 9.83]
Total (95% CI)	**636**	**321**		**100.0 %**	**3.88 [2.33, 6.45]**
Total events: 68 (Certolizumab), 4 (Control)					
Heterogeneity: Chi^2 = 0.02, df = 1 (P = 0.88); I^2 =0.0%					
Test for overall effect: Z = 5.22 (P < 0.00001)					
Test for subgroup differences: Not applicable					

(1) UCB report for NICE quoted Certolizumab n=391 and placebo n=196

(2) In NICE report UCB quoted certoluzimab n= 245 and placebo n =125

Analysis 46.5. Comparison 46 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX), Outcome 5 Radiological changes: Erosion Scores (ES) 200 mg certolizumab 200 mg sc.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 46 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX)

Outcome: 5 Radiological changes: Erosion Scores (ES) 200 mg certolizumab 200 mg sc

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 certolizumab 200 mg sc 24 weeks							
RAPID1 2005	353	0 (1.5)	180	0.7 (2.1)		71.9 %	-0.70 [-1.04, -0.36]
RAPID2 2007	214	0.1 (2)	112	0.7 (2.6)		28.1 %	-0.60 [-1.15, -0.05]
Total (95% CI)	**567**		**292**			**100.0 %**	**-0.67 [-0.96, -0.38]**

Heterogeneity: $Chi^2 = 0.09$, df = 1 (P = 0.76); $I^2 = 0.0\%$

Test for overall effect: Z = 4.51 (P < 0.00001)

Test for subgroup differences: Not applicable

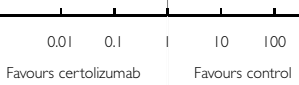
Analysis 46.6. Comparison 46 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX), Outcome 6 All Withdrawals:.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 46 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX)

Outcome: 6 All Withdrawals:

Study or subgroup	Certolizumab n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
CDP870-014 2009	28/125	56/125		9.8 %	0.50 [0.34, 0.73]
Choy 2002	2/24	6/12		1.4 %	0.17 [0.04, 0.71]
FAST4WARD 2005	35/111	81/109		14.4 %	0.42 [0.32, 0.57]
RAPID1 2005	254/783	156/199		43.7 %	0.41 [0.37, 0.47]
RAPID2 2007	137/492	110/127		30.7 %	0.32 [0.27, 0.38]
Total (95% CI)	**1535**	**572**		**100.0 %**	**0.39 [0.36, 0.43]**
Total events: 456 (Certolizumab), 409 (Control)					
Heterogeneity: Chi^2 = 9.99, df = 4 (P = 0.04); I^2 =60%					
Test for overall effect: Z = 19.39 (P < 0.00001)					
Test for subgroup differences: Not applicable					

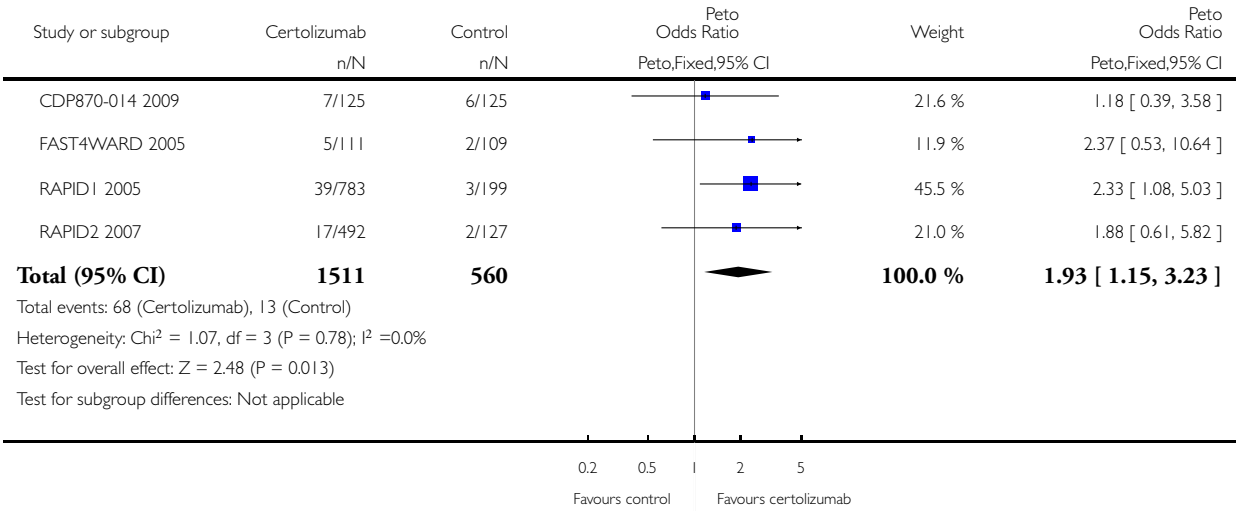


Analysis 46.7. Comparison 46 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX), Outcome 7 Withdrawals due to adverse events.

Review: Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

Comparison: 46 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX)

Outcome: 7 Withdrawals due to adverse events



ADDITIONAL TABLES

Table 1. Demographic and disease characteristics of the retrieved phase III trials

Study	FAST4WARD n = 220	CDP870-014 n = 247	RAPID1 n = 982	RAPID2 n = 619
Age (years) Mean SD	53.8 (12.2) Cer 400mg 52.7 (12.7) Placebo 54.0 (11.6)	54.3 (12.05)	52.0 (11.6) Cer 200mg 51.4 (11.6) Cer 400 mg 52.4 (11.7) Placebo 52.2 (11.2)	51.9 (11.5) Cer 200mg 52.2 (11.1) Cer 400 mg 51.9 (11.8) Placebo 51.5 (11.8)
Female n (%)	83.6%	69.2%	83.2% Cer 200mg 324 (82.4%) Cer 400 mg 326 (83.6%) Placebo 167 (83.9%)	81.6% Cer 200mg 206 (83.7%) Cer 400 mg 192 (78%) Placebo 107 (84.3%)
Disease duration (years) Mean (SD)	9.5 (NC) Cer 400mg 8.7 (8.2) Placebo 10.4 (9.6)	9.6 (NC)	6.1 (4.3) Cer 200mg 6.1 (4.2) Cer 400 mg 6.2 (4.4)	6.2 (4.2) Cer 200mg 6.1 (4.1) Cer 400 mg 6.5 (4.3)

Table 1. Demographic and disease characteristics of the retrieved phase III trials (*Continued*)

			Placebo 6.2 (4.4)	Placebo 5.6 (3.9)
RF positive ([≥ 14 IU/ml] (%)	100% Cer 400mg 110 (99.9%) Placebo 109 (100%)	78%	81.8% Cer 200mg 312 (79.6%) Cer 400 mg 326 (83. 6%) Placebo 164 (82.8%)	76.9% Cer 200mg 186 (77.5%) Cer 400 mg 179 (75. 5%) Placebo 97 (78.2%)
MTX concomitant dose (mg/Week) Mean(SD)	N/A	16.8	13.6 Cer 200mg 13.6 (4.3) Cer 400 mg 13.6 (4) Placebo 13.4 (4.2)	12.5 Cer 200mg 12.5 (3.6) Cer 400 mg 12.6 (3.7) Placebo 12.2 (3.3)
Prednisolone dose allowed	prednisone equivalent (≤10 mg/day)	prednisone equivalent (≤10 mg/day)	prednisone equivalent (≤10 mg/day)	prednisone equivalent (≤10 mg/day)
Number of previous DMARDS Mean (SD)	2.0 Cer 400mg 2.0 (1.2) Placebo 2.0 (1.3)	1.3	1.3 Cer 200mg 1.3 (1.3) Cer 400 mg 1.3 (1.3) Placebo 1.4 (1.4)	1.2 Cer 200mg 1.2 (1.3) Cer 400 mg 1.3 (1.2) Placebo 1.2 (1.2)
Tender Joint count Mean (SD)	29.0 (13.13)	30.0 (12.28)	30.7 (12.9)	30.2 (14.0)
Swollen Joint Count Mean (SD)	20.5 (9.67)	22.5 (9.48)	21.5 (9.8)	21.0 (9.8)
HAQ-DI mean (SD)	1.5 (0.64)	1.4 (0.63)	1.7 (0.60)	1.6 (0.59)
CRP (mg/L) Geometric mean (CV)	11.5 (NC)	12.4 (NC)	14.7 (144.2)	13.6 (180.9)
DAS28(ESR) Mean (SD)	6.3 (1.00)	6.2 (0.99)	6.9 (0.8)	6.8 (0.83)

Cer= Certolizumab; CV = coefficient of variation; DAS = disease activity score; DMARD = disease-modifying antirheumatic drug; ESR = erythrocyte sedimentation rate; IU = international units; L = littre; mg = milligrams; mL = millilitre; RF= rheumatoid factor; SD = standard deviation; y = years; NC= not calculated; N/A=not applicable All randomised subjects; the actual numbers vary slightly across parameters

Table 2. Intention to treat and per protocol patients

Study	Placebo		Certolizumabl 200 mg		Certolizumabl 200 mg		Total	
	ITT	PP	ITT	PP	ITT	PP	ITT	PP

Table 2. Intention to treat and per protocol patients (*Continued*)

FAST4WARD	109	81	N/A	N/A	111	89	220	170
CDP870-014	119	79	N/A	N/A	124	92	243	171
RAPID1	199	43	393	274	390	255	982	572
RAPID2	127	17	246	172	246	181	619	370

ITT Intention-to-treat; PP per protocol populations
In studies RAPID1 and RAPID2, the number of withdrawals was high in the placebo groups, possibly due to the early escape option at Week 16

Table 3. Effectiveness ACR

	Follow up	Doses/study	Response rate certolizumab	Response rate placebo	RR	% RAR	NNT (close)
ACR20							
	24 weeks	200 mg/ RAPID1, RAPID2	58.2%	11.1%	4.95 (3.65 to 6.72)	46.5 (37.3 to 55.1)	2
	24 weeks	400 mg/ RAPID1, RAPID2, FAST4WARD, CDP870-014	55.3%	13.5%	4.09 (3.27 to 5.13)	41.7 (30.6 to 51.7)	2
	52 weeks	200 mg/ RAPID1,	53.2%	13.1%	4.05 (2.80 to 5.87)	40.1 (28.7 to 51.1)	3
	52 weeks	400 mg/ RAPID1	54.1%	13.1%	4.18 (2.89 to 6.05)	40.9 (29.7 to 51.9)	3
ACR50							
	24 weeks	200 mg/ RAPID1, RAPID2	35.4%	5.8%	6.01 (3.84 to 9.40)	29.8 (19.4 to 41.7)	3
	24 weeks	400 mg/ RAPID1, RAPID2, FAST4WARD, CDP870-014	32.4%	5.4%	5.68 (3.93 to 8.20)	25.3 (15.8 to 38.8)	4

Table 3. Effectiveness ACR (*Continued*)

	52 weeks	200 mg/ RAPID1,	37.9%	7.5%	5.03 (3.04 to 8. 32)	30.5 (18.2 to 44.4)	3
	52 weeks	400 mg/ RAPID1	40%	7.5%	5.27 (3.19 to 8. 71)	32.6 (20 to 46. 6)	3
ACR70							
	24 weeks	200 mg/ RAPID1, RAPID2	19.2%	2.1%	8.87 (4.20 to 18.75)	17.4 (7.9 to 32. 6)	6
	24 weeks	400 mg/ RAPID1, RAPID2, FAST4WARD, CDP870-014	12.8%	1.6%	6.39 (3.32 to 12.27)	8.7 (3.8 to 18.2)	12
	52 weeks	200 mg/ RAPID1,	21.1%	3.5%	6.00 (2.83 to 12.74)	17.6 (7.3 to 33. 7)	5
	52 weeks	400 mg/ RAPID1,	23.1%	3.5%	6.56 (3.10 to 13.89)	19.6 (8.4 to 36. 3)	5

Table 4. Adverse events

	Doses/study	Response rate in % (number of events) certolizumab	Response rate in % (number of events) placebo	RR	RAR	NNTH (close)
Serious adverse events				**Peto OR**		
	200 mg/ RAPID1, RAPID2	9.8% (63)	4.6% (15)	2.02 (1.24 to 3. 30)	0.052 (0.01 to 0. 12)	24 (11-96)
	400 mg/ RAPID1, RAPID2, FAST4WARD	10.3 % (90)	4.4 % (30)	1.92 (1.30 to 2. 83)	0.05 (0.02 to 0. 10)	27 (15-81)
Adverse events leading to withdrawal				**Peto OR**		

Table 4. Adverse events (*Continued*)

	200 mg/ RAPID1, RAPID2	4.5% (29)	1.6% (5)	2.40 (1.16 to 4. 95)	0.03 (0.002 to 0. 95)	47 (18-398)
	400 mg/ RAPID1, RAPID2, FAST4WARD	4.6 % (34)	1.6 % (7)	2.41 (1.26 to 4. 63)	0.03(0.004 to 0. 88)	47 (19-246)
Adverse events, severe intensity				**Peto OR**		
	200 mg/ RAPID1, RAPID2	7.7% (49)	5.3% (18)	1.21 (1 to 1.47).	0.021 (-0.010 to 0.074)	NS
	400 mg/ RAPID1, RAPID2, FAST4WARD	8% (60)	6.5% (29)	1.24 (0.79 to 1. 95)	0.015 (-0.014 to 0.192)	NS
Adverse events leading to death				**Peto OR**		
	200 mg/ RAPID1, RAPID2	0.5% (3)	0.3% (1)	1.47 (0.18 to 11. 76)	0.001 (-0.003 to 0.021)	NS
	400 mg/ RAPID1, RAPID2, FAST4WARD	0.7% (5)	0% (1)	2.16 (0.4 to 11. 79)	0.002 (-0.002 to 0.024)	NS
Death				**Peto OR**		
	200 mg/ RAPID1, RAPID2	0.6% (4)	0.3% (1)	1.85 (0.29 to 11. 86)	(-0.01 to 0.01)	NS
	400 mg/ RAPID1, RAPID2, FAST4WARD	0.6% (5)	0.1% (1)	2.16 (0.40 to 11. 79)	(0.00 to 0.01)	NS
Malignancies (neoplasias including lymphoma)				**Peto OR**		

Table 4. Adverse events (*Continued*)

	200 mg/ RAPID1, RAPID2	1.3% (8)	0.7% (2)	1.85 (0.50 to 6. 93)	0.006 (-0.004 to 0.050)	NS
	400 mg/ RAPID1, RAPID2, FAST4WARD	0.7 % (5)	0.5 % (2)	1.26 (0.25 to 6. 54)	0.001 (-0.003 to 0.26)	NS
Infections and infestations				**RR**		
	200 mg/ RAPID1, RAPID2	39.4% (197)	27.1% (121)	1.37 (1.10 to 1. 69)	0.10 (0.04 to 0. 16)	10
	400 mg/ CDP870-14, RAPID1, RAPID2	35.5 % (270)	21.2% (95)	1.60 (1.31 to 1. 95)	0.18 (0.09 to 0. 28)	8
Tuberculosis				**Peto OR**		
	200 mg/ RAPID1, RAPID2	0.8% (5)	0% (0)	4.53 (0.71 to 29. 11)	Not calculated	NS
	400 mg/ RAPID1, RAPID2, FAST4WARD	0.7% (5)	0% (0)	4.55(0.71 to 29. 11)	Not calculated	NS

Table 5. Health-related quality of life

	Follow up	Doses/study	Mean differences	NNT(close)
HAQ (0-3) (Best= 0; Worst 3)				
	24 weeks	200 mg/ RAPID1, RAPID2	-0.39 (-0.45 to -0.32)	
	24 weeks	400 mg/ RAPI1, RAPID2, FAST4WARD	-0.41 (-0.48 to -0.35)	

Table 5. Health-related quality of life (*Continued*)

	52 weeks	200 mg/RAPID1	-0.42 (-0.54 to -0.32)	
	52 weeks	400 mg/RAPID1	-0.45 (-0.57 to -0.33)	
SF-36 PCS (0-100) (Worst =0; Best=100)				
	24 weeks	200 mg/ RAPID1, RAPID2	5.26 (4.17 to 6.36)	
	24 weeks	400 mg/ RAPID1,RAPID2	5.72 (4.62 to 6.81).	
SF-36 MCS (0-100) (Worst =0; Best=100)				
	24 weeks	200 mg/ RAPID1 RAPID2	4.18 (2.70 to 5.66)	
	24 weeks	400 mg/ RAPID1, RAPID2	4.39 (2.91 to 5.88)	
SF-36 PCS				
	52 weeks	200 mg/ RAPID1	6.06 (4.59 to 7.53)	
	52 weeks	400 mg/ RAPID1	6.88 (5.42 to 8.34)	
SF-36 MCS (0-100) (Worst =0; Best=100)				
	52 weeks	200 mg/ RAPID1	4.3 (2.4 to 6.2)	
	52 weeks	400 mg/ RAPID1	4.3 (2.4 to 6.2)	
Patients VAS score (0-100)				
	24 weeks	200 mg/RAPID2	-19.00 (-23.63 to -14.37)	
		400 mg/RAPID2, FAST4WARD	-21.53 (-25.81 to -17.26)	
	52 weeks			
DAS28 remission (< 2.6)		Peto Odds Ratio		
	24 weeks	200 mg/RAPID1, RAPID2	3.88 (2.33 to 6.45)	31 (17 to 65)
		400 mg/RAPID1,RAPID2,	3.97 (2.41 to 6.54)	30 (17 to 61)
		Risk Ratio		

Table 5. Health-related quality of life (*Continued*)

	52 weeks	200 mg/RAPID1	10.36 (3.29 to 32.58)	8 (3 to 30)
		400 mg/RAPID1	12.49 (3.99 to 39.12)	6(2 to 23)

Table 6. Radiological changes

	Follow up	Doses/study	Mean differences
Modified Total Sharp Scores (mTTS) is the sum of the erosion score (ES) and the joint space narrowing (JSN) score and has a range of 0 to 398			
	24 weeks	200 mg/ RAPID1, RAPID2	-1.06 (-1.58 to -0.55)
	24 weeks	400 mg/ RAPID1, RAPID2	-1.32 (-1.85 to -0.78)
	52 weeks	200 mg/RAPID1	-2.4 (-3.68 to -1.12)
	52 weeks	400 mg/RAPID1	-2.6 (-3.84 to -1.36)
Erosion Score is the sum of joint scores collected for 46 joints and has a range of 0 to 230			
	24 weeks	200 mg/ RAPID1, RAPID2	-0.67 (-0.96 to -0.38)
	24 weeks	400 mg/ RAPID1, RAPID2	-0.74 (-1.06 to -0.42)
	52 weeks	200 mg/RAPID1	-1.4 (-2.08 to -0.72)
	52 weeks	400 mg/RAPID1	-1.5 (-2.20 to -0.80)
Joint Space Narrowing (JSN) is the sum of joint scores collected for 42 joints and has a range of 0 to 168			
	24 weeks	200 mg/ RAPID1, RAPID2	-0.45 (-0.77 to -0.13)
	24 weeks	400 mg/ RAPID1, RAPID2	-0.55 (- 0.86 to -0.24)
	52 weeks	200 mg/RAPID1	-1 (-1.85 to -0.15)
	52 weeks	400 mg/RAPID1	-1.2 (-1.98 to -0.42)

APPENDICES

Appendix 1. MEDLINE search strategy

Search strategy for effectiveness:
1. (CDP870 or CDP 870 or "certolizumab pegol" or certolizumab or CDP-870 or cimzia).mp.
2. . ("Rheumatoid Arthritis" or (Caplan$ and Syndrome?) or (Felty$ and S?ndrome) or (Rheumatoid and Nodule?) or (Sjogren$ and S?ndrome?) or (Sicca$ and S?ndrome?) or (Ankylos$ and Spondylit$) or (Spondylarthritis and Ankylopoietica) or (Rheumatoid$ and Spondylit$) or (Bechterew$ and Disease?) or (Marie-Struempell and Disease?) or (Adult and Onset and Still$ and Disease?)).mp.
3.. exp Arthritis, Rheumatoid/
4. (2 OR 3)
5. 1 AND 4
6. Clinical trial.pt.
7. randomized.ab.
8. Placebo.ab.
9. dt.fs.
10. randomly.ab.
11. trial.ab.
12. groups.ab.
13. or/ 6-12
14. 5 and 13
Search strategy for Safety:
#1. Exp Headache/ci OR Exp Nasopharyngitis/ci OR Exp Arthritis, Rheumatoid/ci OR Exp Nausea/ci OR Exp Infection/ci OR Exp Respiratory Tract Infections/ci OR Exp Urinary Tract Infections/ci OR Exp Neck Pain/ci OR Exp Antibodies, Antinuclear/ci OR Exp Granulomatous Disease, Chronic/ci OR Exp Granulomatous Disease, Chronic/ci OR Exp Tuberculosis/ci OR Exp Histoplasmosis/ci OR Exp Neoplasms/ci OR Exp Skin Neoplasms/ci OR Exp Hematologic Neoplasms/ci OR Exp Death/ci OR Exp Sepsis/ci OR Exp Abdominal Pain/ci OR Exp Heart Failure, Congestive/ci OR Exp Fever/ci OR Exp Pruritus/ci OR Exp Melanoma/ci OR Exp Lymphoma/ci OR Exp Pneumonia/ci OR Exp Lupus/ci OR Exp Lupus Erythematosus, Systemic/ci OR Exp Anaphylaxis/ci OR "blood disorders".ab,ti. OR "laboratory test abnormalities".ab,ti. OR Headache.ab,ti. OR Nasopharyngitis.ab,ti. OR "Rheumatoid Arthritis".ab,ti. OR Nausea.ab,ti. OR Infection.ab,ti. OR "Respiratory Tract Infections".ab,ti. OR "Urinary Tract Infections" .ab,ti. OR "Neck Pain".ab,ti. OR "Antinuclear Antibodies".ab,ti. OR "Chronic Granulomatous Disease" .ab,ti. OR Tuberculosis.ab,ti. OR Histoplasmosis.ab,ti. OR Neoplasms.ab,ti. OR "Skin Neoplasms".ab,ti. OR "Hematologic Neoplasms".ab,ti. OR Death.ab,ti. OR Sepsis.ab,ti. OR "Abdominal Pain" .ab,ti. OR "Heart Failure".ab,ti. OR Fever.ab,ti. OR Pruritus.ab,ti. OR Melanoma.ab,ti. OR Lymphoma.ab,ti. OR Pneumonia.ab,ti. OR Lupus.ab,ti. OR "Lupus Erythematosus".ab,ti. OR Anaphylaxis.ab,ti.
#2. ae.fs OR po.fs OR to.fs OR de.fs OR co.fs
#3. (advers$.ab,ti. OR untoward$.ab,ti. OR avers$.ab,ti. OR detrimental$.ab,ti. OR damage$.ab,ti. OR harmful$.ab,ti. OR cripple$.ab,ti. OR prejudicial$.ab,ti. OR disruptiv$.ab,ti. OR destructive$.ab,ti. OR deleter$.ab,ti. OR untoward$.ab,ti. OR unexpect$.ab,ti. OR side$.ab,ti. OR serious$.ab,ti. OR severe$.ab,ti. OR unlikely$.ab,ti. OR malignan$.ab,ti.) AND (consequenc$.ab,ti. OR implication$.ab,ti. OR result$.ab,ti. OR outgrowth$.ab,ti. OR repercussion$.ab,ti. OR episod$ .ab,ti. OR happen$.ab,ti. OR reaction$.ab,ti. OR effect$.ab,ti. OR experience$.ab,ti.) OR complication$.tw.
#4. Exp Drug Toxicity
#5. 1 OR 2 OR 3 OR 4
#6. CDP870 OR CDP870 or CDP 870 or "certolizumab pegol" or certolizumab or CDP-870 or cimzia.mp.
#8. 5 AND 6
Last search on November 2009
Ovid MEDLINE(R) <1950 to November Week 3 2009>
1 (certolizumab or cimzia or cdp870 or cdp 870).mp.

2 rheumatoid arthritis.mp.

3 exp Arthritis, Rheumatoid/

4 2 or 3

5 1 and 4

6 limit 5 to humans

7 from 6 keep 1-31
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <November 30, 2009>
1 (certolizumab or cimzia or cdp870 or cdp 870).mp.

2 rheumatoid arthritis.mp.

3 1 and 2

4 from 3 keep 1-15

Appendix 2. EMBASE search strategy

Search strategy for effectiveness:
1. 'rheumatoid arthritis'/exp/
2. 'certolizumab pegol'/exp/
3. (CDP870 OR 'CDP 870' OR CDP-870 OR 'certolizumab pegol' OR certolizumab OR cimzia).mp.
4. 2 OR 3
5. 4 AND 1
6. random:.tw.
7. clinical trial:.mp.
8. exp health care quality
9. or/6-8
10. 5 AND 9
Search strategy for safety:
#1 exp Headache/si or exp Nasopharyngitis/si or exp Arthritis, Rheumatoid/si or exp Nausea/si or exp Infection/si or exp Respiratory Tract Infections/si or exp Urinary Tract Infections/si or exp Neck Pain/si or exp Antibodies, Antinuclear/si or exp Granulomatous Disease, Chronic/si or exp Granulomatous Disease, Chronic/si or exp Tuberculosis/si or exp Histoplasmosis/si or exp Neoplasms/si or exp Skin Neoplasms/si or exp Hematologic Neoplasms/si or exp Death/si or exp Sepsis/si or exp Abdominal Pain/si or exp Heart Failure, Congestive/si or exp Fever/si or exp Pruritus/si or exp Melanoma/si or exp Lymphoma/si or exp Pneumonia/si or exp Lupus/si or exp Lupus Erythematosus, Systemic/si or exp Anaphylaxis/si or "blood disorders".ab,ti. or "laboratory test abnormalities".ab,ti. or Headache.ab,ti. or Nasopharyngitis.ab,ti. or "Rheumatoid Arthritis".ab,ti. or Nausea.ab,ti. or Infection.ab,ti. or "Respiratory Tract Infections".ab,ti. or "Urinary Tract Infections".ab,ti. or "Neck Pain".ab,ti. or "Antinuclear Antibodies".ab,ti. or "Chronic Granulomatous Disease".ab,ti. or Tuberculosis.ab,ti. or Histoplasmosis.ab,ti. or Neoplasms.ab,ti. or "Skin Neoplasms".ab,ti. or "Hematologic Neoplasms".ab,ti. or Death.ab,ti. or Sepsis.ab,ti. or "Abdominal Pain".ab,ti. or "Heart Failure".ab,ti. or Fever.ab,ti. or Pruritus.ab,ti. or Melanoma.ab,ti. or Lymphoma.ab,ti. or Pneumonia.ab,ti. or Lupus.ab,ti. or "Lupus Erythematosus".ab,ti. or Anaphylaxis.ab,ti.
#2 (ae or to or co).fs.
#3 (((advers$ or untoward$ or avers$ or detrimental$ or damage$ or harmful$ or cripple$ or prejudicial$ or disruptiv$ or destructive$ or deleter$ or untoward$ or unexpect$ or side$ or serious$ or severe$ or unlikely$ or malignan$) and (consequenc$ or implication$ or result$ or outgrowth$ or repercussion$ or episod$ or happen$ or reaction$ or effect$ or experience$)) or complication$).tw.
#4 exp Adverse drug reaction/ or exp Side-effect/ or exp Drug Toxicity
#5 or/1-4
#6 CDP870.rn OR (CDP870 or CDP 870 or "certolizumab pegol" or certolizumab or CDP-870 or cimzia).mp.
#7 5 AND 6
Last search on November 2009
EMBASE (Ovid) 1980 - 2009 Week 48

1 (certolizumab or cimzia or cdp870 or cdp 870).mp.

2 rheumatoid arthritis.mp.
3 exp rheumatoid arthritis/
4 2 or 3
5 1 and 4
6 limit 5 to human

Appendix 3. CINAHL search strategy

Search strategy for effectiveness:
1.'rheumatoid arthritis'/exp/
2."rheumatoid arthritis".mp.
3. (CDP870 OR 'CDP 870' OR CDP-870 OR 'certolizumab pegol' OR certolizumab OR cimzia).mp.
4.(1 or 2) and 3
5.exp prognosis
6.exp study design
7.random:.mp.
8.or/ 5-7
9.4 and 8
Last search on November 2009
S1 certolizumab or cimzia or cdp870 or "cdp 870"
S2 (MH "arthritis, rheumatoid") or "rheumatoid arthritis"
S3 S1 and S2

Appendix 4. Search strategy for CDSR and CENTRAL, HTA, DARE, NHS EED

Search strategy for effectiveness:
Cochrane Database of Systematic Reviews, Health Technology Assessment (HTA), The Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED) from Ovid:
1.'rheumatoid arthritis'.mp.
2.(CDP870 OR 'CDP 870' OR CDP-870 OR 'certolizumab pegol' OR certolizumab OR cimzia).mp.
3.1 and 2
Search strategy for safety:
DARE, CDSR and CENTRAL from OVID platform (version 10.5.1), will be searched up to October 2007, The search strategy will combine text and index terms for CDP870 and adverse effects reported in RCTs of certolizumab Pegol and another anti-TNF alpha with a strategy based on that by Golder (a) 2006 Golder (b) 2006.
#1 Drug and (hypersensitive$ or tocit$).tw.
#2 ((safe$ or advers$ or tolerabilit$ or toxic$ or adr$ or tolera$ or harm$ or complicat$ or risk$) adj20 objective$).tw.
#3 (side adj3 effect$ adj20 objective$).tw.
#4 (undesirable adj3 effect$ adj20 objetive$).tw.
#5 (treatment adj3 emergent adj20 objective$).tw.
#6 or/1-5
#7 (CDP870 or CDP 870 or certolizumab pegol or certolizumab or CDP-870 or cimzia).tw.
#8 6 and 7
Last search on November 2009
#1 certolizumab or cimzia
#2 cdp870
#3 cdp next 870
#4 (#1 OR #2 OR #3)
#5 rheumatoid next arthritis
#6 MeSH descriptor Arthritis, Rheumatoid explode all trees
#7 (#5 OR #6)
#8 (#4 AND #7)

Appendix 5. SCOPUS search strategy

Search strategy for effectiveness:
SCOPUS will be searched up to August of 2007, without limits of years:
KEY((certolizumab OR cimzia OR CDP-870 OR CDP870 OR "CDP 870") AND ("rheumatoid arthritis"))
Web of Knowledge (WOK), was searched up to August of 2007, without limits of years. The search strategy is as follows:
topic=((certolizumab OR cimzia OR CDP-870 OR CDP870 OR "CDP 870") AND ("rheumatoid arthritis")
Databases=MEDLINE, Current Contents Connect, Web of Science, Derwent Innovations Index, ISI Proceedings; Timespan=All Years

Appendix 6. TOXLINE (TOXNET) search strategy

Search strategy for safety:
TOXLINE (TOXNET) will be searched up to October 2007. The search strategy will combine index and text terms for CDP870:
#1. certolizumab OR "certolizumab pegol" OR CDP870 OR CDP-870 OR "CDP 870" OR cimzia
Last search on November 2009
Last Search Query: certolizumab OR cimzia OR cdp870

Appendix 7. Web of Knowledge

Last search on November 2009
Web of Knowledge (Science Citation Index and Social Science Citation Index) 1900 - Nov 2009

Search terms: TS= (certolizumab OR cimzia OR or CDP870 OR cdp 870) and ("rheumatoid arthritis")

Appendix 8. Demographic and disease characteristics of the retrieved phase III trials

Study	FAST4WARD n = 220	CDP870-014 n = 247	RAPID1 n = 982	RAPID2 n = 619
Age (years) Mean SD	53.8 (12.2) Cer 400mg 52.7 (12.7) Placebo 54.0 (11.6)	54.3 (12.05)	52.0 (11.6) Cer 200mg 51.4 (11.6) Cer 400 mg 52.4 (11.7) Placebo 52.2 (11.2)	51.9 (11.5) Cer 200mg 52.2 (11.1) Cer 400 mg 51.9 (11.8) Placebo 51.5 (11.8)
Follow up	24 weeks	24 weeks	52 weeks	24 weeks
Female n (%)	83.6%	69.2%	83.2% Cer 200mg 324 (82.4%) Cer 400 mg 326 (83.6%) Placebo 167 (83.9%)	81.6% Cer 200mg 206 (83.7%) Cer 400 mg 192 (78%) Placebo 107 (84.3%)
Disease duration (years) Mean (SD)	9.5 (NC) Cer 400mg 8.7 (8.2) Placebo 10.4 (9.6)	9.6 (NC)	6.1 (4.3) Cer 200mg 6.1 (4.2) Cer 400 mg 6.2 (4.4) Placebo 6.2 (4.4)	6.2 (4.2) Cer 200mg 6.1 (4.1) Cer 400 mg 6.5 (4.3) Placebo 5.6 (3.9)

(*Continued*)

RF positive ([³ 14 IU/ml] (%)	100% Cer 400mg 110 (99.9%) Placebo 109 (100%)	78%	81.8% Cer 200mg 312 (79.6%) Cer 400 mg 326 (83.6%) Placebo 164 (82.8%)	76.9% Cer 200mg 186 (77.5%) Cer 400 mg 179 (75.5%) Placebo 97 (78.2%)
MTX concomitant dose (mg/Week) Mean(SD)	N/A	16.8	13.6 Cer 200mg 13.6 (4.3) Cer 400 mg 13.6 (4) Placebo 13.4 (4.2)	12.5 Cer 200mg 12.5 (3.6) Cer 400 mg 12.6 (3.7) Placebo 12.2 (3.3)
Number of previous DMARDS Mean (SD)	2.0 Cer 400mg 2.0 (1.2) Placebo 2.0 (1.3)	1.3	1.3 Cer 200mg 1.3 (1.3) Cer 400 mg 1.3 (1.3) Placebo 1.4(1.4)	1.2 Cer 200mg 1.2 (1.3) Cer 400 mg 1.3 (1.2) Placebo 1.2 (1.2)
Tender Joint count Mean (SD)	29.0 (13.13)	30.0 (12.28)	30.7 (12.9)	30.2 (14.0)
Swollen Joint Count Mean (SD)	20.5 (9.67)	22.5 (9.48)	21.5 (9.8)	21.0 (9.8)
HAQ-DI mean (SD)	1.5 (0.64)	1.4 (0.63)	1.7 (0.60)	1.6 (0.59)
CRP (mg/L) Geometric mean (CV)	11.5 (NC)	12.4 (NC)	14.7 (144.2)	13.6 (180.9)
DAS28(ESR) Mean (SD)	6.3 (1.00)	6.2 (0.99)	6.9 (0.8)	6.8 (0.83)

Notes: Cer= Certolizumab; CV = coefficient of variation; DAS = disease activity score; DMARD = disease-modifying antirheumatic drug; ESR = erythrocyte sedimentation rate; IU = international units; L = liter; mg = milligrams; mL = millilitres; RF= rheumatoid factor; SD = standard deviation; y = years; NC= not calculated; N/A=not applicable All randomised subjects; the actual numbers vary slightly across parameters

Appendix 9. Flow of patients in the phase III studies retrieved

Study	Placebo	Certolizumab 200mg	Certolizumab 400mg
RAPID1 n = 982	ITT n = 199 Safety n = 199	ITT n = 393 Safety [a] n = 392	ITT n = 390 Safety n = 389
	Withdrawn at week 16 due to lack of efficacy n = 125 (62.8%)	Withdrawn at week 16 due to lack of efficacy n = 83 (21.1%)	Withdrawn at week 16 due to lack of efficacy n = 68 (17.4%)

(*Continued*)

	All withdrawn n = 156 (78.4%)	All withdrawn n = 138 (35.1)	All withdrawn n = 116 (39.7%)
	Completed n = 43 (21.6%)	Completed n = 255 (64.9%)	Completed n = 274 (70.3%)
RAPID2 n = 619	ITT n = 127[c] Safety n = 125	ITT n = 246 Safety n = 248	ITT n = 246 Safety n = 246
	Withdrawn at week 16 due to lack of efficacy n = 103 (81%)	Withdrawn at week 16 due to lack of efficacy n = 52 (21.1%)	Withdrawn at week 16 due to lack of efficacy n = 52 (21.1%)
	All withdrawn n = 110 (86%)	All withdrawn n = 72 (29.3%)	All withdrawn n = 65 (26.4%)
	Completed n = 17 (13.4%)	Completed n = 174 (70.7%)	Completed n = 181 (73.6%)
FAST4WARD	ITT n = 109 Safety n = 109		ITT n = 111 Safety n = 111
	All withdrawn n = 81 (74%) 75 (68.8%) Lack of efficacy 2 (1.8%) Adverse event 1 (0.9%) Protocol violation 3 (2.8) Lost to follow-up		All withdrawn n = 35 (31.5%) 24 (21.6%) Lack of efficacy 5 (4.5%) Adverse event 4 (3.6%) Protocol violation 2 (1.8%) Consent withdrawn
	Completed n = 28(25.7%)		Completed n = 76(68.5%)
CDP870-014	ITT n = 121[d] Safety n = 119		ITT n = 126 [d] Safety n = 124
	All withdrawn n = 56 (46.3%) 45 (37.2%) Lack of efficacy 6 (5%) Adverse event 5 (4.1%) Other reasons		All withdrawn n = 28 (22.2%) 16 (12.7%) Lack of efficacy 7 (5.6%) Adverse event 5 (4%) Other reasons

(*Continued*)

	Completed n = 65 (53.7%)		Completed n = 98 (77.8%)

a One patient withdrew by her own decision
b One patient was discontinued due to the ESR/CRP not meeting criteria
c Two patients in the placebo group received certolizumab and were included for safety in the 200 mg Group
d Two patients in the each of treatment groups did not take study medication. Manufactures reported efficacy calculations from Placebo n = 119 and Certol n = 124

HISTORY

Protocol first published: Issue 1, 2009

Review first published: Issue 2, 2011

Date	Event	Description
3 April 2008	Amended	CMSG ID: C001-R

CONTRIBUTIONS OF AUTHORS

Design the protocol: Juan Cabello; Vicente Ruiz; Amanda Burls

Write up the background: Saiz E; Gosalvez J; P Jobanputra

Develop the search strategy: Anne Fry Smith

Trial search (2 people): Vicente Ruiz; P Jobanputra

Obtain copies of the trials: Anne Fry Smith

Selection of trials for inclusion (2 + 1) : Vicente Ruiz; P Jobanputra. If data discrepancies will be resolved by involvement of a third person: Saiz E

Retrieval of trial data on effectiveness (two people): Vicente Ruiz; P Jobanputra. If data discrepancies will be resolved by involvement of a third person: Saiz E

Data input in Revman: STATA: Vicente Ruiz

Carry out analyses: Vicente Ruiz; P Jobanputra

Interpret analyses: Juan Cabello; Amanda Burls

Write up results: Juan Cabello; Vicente Ruiz; Amanda Burls; Gosalvez J; P Jobanputra

Update effectiveness review: Vicente Ruiz; Juan Cabello; Amanda Burls; Gosalvez J

DECLARATIONS OF INTEREST

Dr Paresh Jobanputra has previously been involved in industry sponsored clinical trials of the TNF inhibitors adalimumab and etanercept. He has also received funding for educational purposes from Wyeth and Abbott Laboratories, the manufacturers of these drugs.

Dr Jose Galvez and Dr Encarnación Saez have, in the past, been involved in two randomised clinical trials, one phase III with etoricoxib sponsored by MSD and a phase IV study with etanercept sponsored by Wyeth.

SOURCES OF SUPPORT

Internal sources

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External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Subgroup analyses were planned for the duration of the illness (approximately of three years evolution), patients' sex, drug dose, administration and methodological quality, but only subgroup analysis regarding the dose of certolizumab pegol was performed. All phase III trials were performed in patients with a high mean duration of RA (from 6.1 to 9.5 years) and we could not obtain any data categorized by sex. All phase III trials allowed previous DMARD treatments (mean from 1.2 to 2 years). All phase III trials used in the meta-analysis were rated as high quality, and so we did not perform more subgroup analysis.

INDEX TERMS

Medical Subject Headings (MeSH)

Antibodies, Monoclonal, Humanized; Antirheumatic Agents [*therapeutic use]; Arthritis, Rheumatoid [*drug therapy]; Immunoglobulin Fab Fragments [*therapeutic use]; Polyethylene Glycols [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans