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

Ruiz Garcia V, Burls A, Cabello JB, Vela Casasempere P, Bort-Marti S, Bernal JA

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[Intervention Review]

Certolizumab pegol (CDP870) for rheumatoid arthritis in adults

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ABSTRACT

Background

Tumour necrosis factor (TNF)-alpha inhibitors are beneficial for the treatment of rheumatoid arthritis (RA) for reducing the risk of joint damage, improving physical function and improving the quality of life. This review is an update of the 2014 Cochrane Review of the treatment of RA with certolizumab pegol.

Objectives

To assess the clinical benefits and harms of certolizumab pegol (CZP) in people 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 (CENTRAL: Cochrane Library 2016, Issue 9), MEDLINE, Embase, Web of Knowledge, reference lists of articles, clinicaltrials.gov and ICTRP of WHO. The searches were updated from 2014 (date of the last search for the previous version) to 26 September 2016.

Selection criteria

Randomised controlled trials that compared certolizumab pegol with any other agent, including placebo or methotrexate (MTX), in adults with active RA, regardless of current or prior treatment with conventional disease-modifying anti-rheumatic drugs (DMARDs), such as MTX.

Data collection and analysis

Two review authors independently checked search results, extracted data and assessed trial quality. We resolved disagreements by discussion or referral to a third review author.

Main results

We included 14 trials in this update, three more than previously. Twelve trials (5422 participants) included measures of benefit. We pooled 11 of them, two more than previously. Thirteen trials included information on harms, (5273 participants). The duration of follow-up varied from 12 to 52 weeks and the range of doses of certolizumab pegol varied from 50 to 400 mg given subcutaneously. In Phase III trials, the comparator was placebo plus MTX in seven trials and placebo in five. In the two Phase II trials the comparator was only placebo.

The approved dose of certolizumab pegol, 200 mg every other week, produced clinically important improvements at 24 weeks for the following outcomes:

- American College of Rheumatology (ACR) 50% improvement (pain, function and other symptoms of RA): 25% absolute improvement (95% confidence interval (CI) 20% to 33%); number need to treat for an additional beneficial outcome (NNTB) of 4 (95% CI 3 to 5); risk ratio (RR) 3.80 (95% CI 2.42 to 5.95), 1445 participants, 5 studies.

- The Health Assessment Questionnaire (HAQ): -12% absolute improvement (95% CI -9% to -14%); NNTB of 8 (95% CI 7 to 11); mean difference (MD) - 0.35 (95% CI -0.43 to -0.26; 1268 participants, 4 studies) (scale 0 to 3; lower scores mean better function).

- Proportion of participants achieving remission (Disease Activity Score (DAS) < 2.6) absolute improvement 10% (95% CI 8% to 16%); NNTB of 8 (95% CI 6 to 12); risk ratio (RR) 2.94 (95% CI 1.64 to 5.28), 2420 participants, six studies.

- Radiological changes: erosion score (ES) absolute improvement -0.29% (95% CI -0.42% to -0.17%); NNTB of 6 (95% CI 4 to 10); MD -0.67 (95% CI -0.96 to -0.38); 714 participants, two studies (scale 0 to 230), but not a clinically important difference.

-Serious adverse events (SAEs) were statistically but not clinically significantly more frequent for certolizumab pegol (200 mg every other week) with an absolute rate difference of 3% (95% CI 1% to 4%); number needed to treat for an additional harmful outcome (NNTH) of 33 (95% CI 25 to 100); Peto odds ratio (OR) 1.47 (95% CI 1.13 to 1.91); 3927 participants, nine studies.

There was a clinically significant increase in all withdrawals in the placebo groups (for all doses and at all follow-ups) with an absolute rate difference of -29% (95% CI -16% to -42%), NNTH of 3 (95% CI 2 to 6), RR 0.47 (95% CI 0.39 to 0.56); and there was a clinically significant increase in withdrawals due to adverse events in the certolizumab groups (for all doses and at all follow-ups) with an absolute rate difference of 2% (95% CI 0% to 3%); NNTH of 58 (95% CI 28 to 329); Peto OR 1.45 (95% CI 1.09 to 1.94) 5236 participants Twelve studies.

We judged the quality of evidence to be high for ACR50, DAS remission, SAEs and withdrawals due to adverse events, and moderate for HAQ and radiological changes, due to concerns about attrition bias. For all withdrawals we judged the quality of evidence to be moderate, due to inconsistency.

Authors' conclusions

The results and conclusions did not change from the previous review. There is a moderate to high certainty of evidence from randomised controlled trials that certolizumab pegol, alone or combined with methotrexate, is beneficial in the treatment of RA for improved ACR50 and health-related quality of life, an increased chance of remission of RA, and reduced joint damage as seen on x-ray. Fewer people stopped taking their treatment, but most of these who did stopped due to serious adverse events. Adverse events were more frequent with active treatment. We found a clinically but not statistically significant risk of serious adverse events.

PLAIN LANGUAGE SUMMARY

Certolizumab pegol for treating adults with rheumatoid arthritis

We conducted an updated review of the benefits and harms of certolizumab pegol (CZP) for adults with active rheumatoid arthritis (RA). We searched for all relevant studies until September 2016 and found 14 trials with 5499 people.

The length of follow-up in most of the trials was 24 weeks; most participants were women.

What is rheumatoid arthritis and what is certolizumab pegol?

When you have RA, your immune system becomes overactive and attacks the lining of your joints. This makes your joints swollen, stiff and painful.

Certolizumab pegol is a biologic medication for the treatment of RA. It works by blocking a substance produced by the body known as tumour necrosis factor alpha (TNFα). Certolizumab pegol is given by injections under the skin. The approved dose is 200 mg.

What happens to people with rheumatoid arthritis who take certolizumab pegol 200 mg every other week after six months?

ACR50 (standard: a 50% improvement in the number of tender or swollen joints and other outcomes such as pain and disability):

- 25 more people out of 100 experienced improvements in the symptoms of their rheumatoid arthritis after six months with certolizumab pegol (absolute improvement 25%).

- 36 people out of 100 who took certolizumab pegol experienced improvements compared to nine people out of 100 who took a placebo (a fake injection).

We rate the quality of evidence for ACR50 as high.

Health-related quality of life (**Health Assessment Questionnaire, HAQ: 0 to 3 scale, where a lower score means improvement):**

- people who took certolizumab pegol scored 0.35 points lower than people who took placebo (absolute improvement 12%).

- people on certolizumab pegol scored 0.48 points lower compared to 0.13 points lower for people who took a placebo.

We rate the quality of evidence for the HAQ as moderate, downgraded, due to concerns about the high number of people dropping out of the studies.

Remission (absence of clinical signs of inflammation):

- 10 people out of 100 experienced remission with certolizumab pegol (absolute improvement 10%).

- 22 people out of 100 who took certolizumab pegol experienced remission compared to 12 people out of 100 who took a placebo.

We rate the quality of evidence for the remission as high.

Radiological changes (x-rays of the joints, measured on a 0 to 230 unit scale):

- the joint damage in people who took certolizumab pegol was 0.67 units less (absolute improvement -0.29%).

- the damage to joints in people who took certolizumab pegol was 0.04 units less compared to people who took a placebo, whose joint damage was 0.7 units more.

We rate the quality of evidence for the findings in the radiological changes as moderate, downgraded, due to concerns about the high number of people dropping out of the studies.

Serious adverse events:

- three more people out of 100 experienced serious adverse events with certolizumab pegol (3% absolute harm).

- nine people out of 100 who took certolizumab pegol experienced serious adverse events compared to six people out of 100 who took a placebo.

We rate the quality of evidence for serious adverse events as high.

All Withdrawals

- 29 fewer people out of 100 experienced withdrawals with certolizumab pegol (absolute harm 29%).

- 23 people out of 100 who took certolizumab pegol experienced withdrawals compared to 52 people out of 100 who took a placebo.

We rate the quality of evidence for all withdrawals as moderate.

Withdrawals due to adverse events

- two more people out of 100 stopped treatment because of SAEs with certolizumab pegol (2% absolute harm).

- five people out of 100 who took certolizumab pegol estopped treatment because of SAEs compared to three people out of 100 who took a placebo.

We rate the quality of evidence for the withdrawals due to adverse events as high.

In summary:

- certolizumab pegol improves ACR50, health-related quality of life, and remission of RA.

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

- certolizumab pegol increases serious adverse events.

- with certolizumab pegol, fewer people stop taking their treatment, but those who stop do so because of serious adverse events.

Summary of findings for the main comparison. Certolizumab pegol 200 mg sc (with or without MTX) versus placebo (with or without MTX) for rheumatoid arthritis in adults

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
Intervention: 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 200 mg sc certolizumab pegol	**87 per 1000**	**359 per 1000** (328 to 391)	**RR 3.80** (2.42 to 5.95)	1445 (5 studies)	⊕⊕⊕⊕ **high**	Absolute risk difference = 25% (95% CI 20% to 33%). Relative per cent change = 280% (142% to 495%). NNTB = 4 (3 to 5)
HAQ change from baseline Scale from: 0 to 3. Follow-up: mean 24 weeks (lower scores means better function) 200 mg sc certolizumab pegol	The mean HAQ change from baseline in the control groups was **-0.13**	The mean HAQ change from baseline in the intervention groups was **0.35 lower** (0.43 to 0.26 lower)	**MD -0.35** (-0.43 to -0.26)	1268 (4 studies)	⊕⊕⊕⊖ **moderate** [1]	Absolute risk difference = -12% (95% CI -9% to -14%). Relative per cent change = -21% (-15% to -25%). NNT = 8 (7 to 11)
Proportion of patients achieving DAS < 2.6 (remission) Follow-up: mean 24 weeks	**123 per 1000**	**216 per 1000** (194 to 247)	**RR 2.94** (1.64 to 5.28)	2420 (6 studies)	⊕⊕⊕⊕ **high**	Absolute risk difference = 10% (95% CI 8% to 16%). Relative per cent change = 194% (64% to 428%)

200 mg sc certolizumab pegol						NNT = 8 (6 to 12)
Radiological changes: Erosion Scores (ES) Scale from: 0 to 230 Follow-up: 24 weeks 200 mg sc certolizumab pegol	The mean radiological changes: Erosion Scores (ES) in the control groups was **0.7**	The mean Radiological changes: Erosion Scores (ES) in the intervention groups was **0.67 lower** (0.96 to 0.38 lower)	**MD -0.67** (-0.96 to -0.28)	714 (2 studies)	⊕⊕⊕⊖ **moderate** [1]	Absolute risk difference = -0.29% (95% CI -0.42% to -0.17%). Relative per cent change = - 2.90% (-4.16% to -1.65%) NNT = 6 (4 to 10)
Serious adverse events Follow-up: 12 to 24 weeks 200 mg sc certolizumab pegol	**58 per 1000**	**85 per 1000** (59 to 120)	**Peto OR 1.47** (1.13 to 1.91)	3927 (9 studies)	⊕⊕⊕⊕ **high**	Absolute risk difference = 3% (95% CI 1% to 4%). Relative per cent change = 47% (13% to 91%). NNTH = 33 (25 to 100)
All Withdrawals: All doses of certolizumab pegol vs placebo Follow-up: 0 to 52 weeks	**524 per 1000**	**231 per 1000** (203 to 291)	**RR 0.47** (0.39 to 0.56)	5200 (13 studies)	⊕⊕⊕⊖ **moderate**[2]	Absolute risk difference = -29% (95% CI -16% to -42%). Relative per cent change= -53% (-44% to -61%). NNTH = 3 (2 to 6)
Withdrawals due to adverse events All doses of certolizumab pegol versus placebo Follow-up: 0 to 52 weeks	**38 per 1000**	**52 per 1000** (40 to 73)	**Peto OR 1.45** (1.09 to 1.94)	5236 (12 studies)	⊕⊕⊕⊕ **high**	Absolute risk difference = 2% (95% CI 0% to 3%). Relative per cent change = 45% (9% to 94%). NNTH = 58 (28 to 329)

*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; **NNTB:** number needed to treat for an additional beneficial outcome

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]We downgraded the quality of evidence by one level for risk of bias due to attrition bias analysed per protocol. We have rated all the trials at low risk for attrition bias since reasons for attrition/exclusions were reported in most of them, and reasons were similar. However, for HAQ-DI and radiological changes we can only conduct a per protocol analysis, as these are continuous outcomes that count the average number of participants still in the trials. For DAS remission, ACR50, SAEs, all withdrawals and withdrawals due to AEs we conducted an ITT analysis, which is a more conservative approach, not requiring downgrading.
[2]We downgraded the quality of evidence by one level for inconsistency, due to heterogeneity (not all the confidence intervals overlap, and I^2 is 79%).

BACKGROUND

Description of the condition

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterised by synovial inflammation of joints and other structures such as tendon sheaths and bursas, autoantibody production (rheumatoid factor and anti-citrullinated protein antibody (ACPA)), with both cartilage and bone destruction. RA typically causes a symmetrical polyarticular arthritis with pain, swelling and stiffness of the affected joints. If the disease is not controlled early, damage may become permanent, leading to significant disability. People with RA commonly experience fatigue and show changes in the blood, such as anaemia due to chronic inflammation, and an acute phase reaction. In some people 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 (Tureson 2013). RA is also associated with reduced life expectancy; in a Spanish cohort, the standardised mortality ratio was 1.89 (Abasolo 2016), specifically due to cardiovascular disease (Meune 2009).

Despite progress in understanding the pathogenesis of RA, its cause remains unknown. Important genetic influences are recognised, with more than 100 RA risk loci identified (Okada 2014). Based on twin studies, heritability is approximately 60% (MacGregor 2000), so environment also plays a key role in RA pathogenesis. Moreover, in recent years environmental factors have gained importance in explaining the development of RA: smoking has specifically been associated with the development of ACPA-positive RA (Lundberg 2013), and cumulative evidence from a large number of studies implicates the microbiome of the periodontium, lung, and gut in RA pathogenesis (Kharlamova 2016).

People of all ages are affected, but the disease begins most commonly between the ages of 40 and 70 years, with incidence rising with increasing age (Doran 2002). The global prevalence is 0.24%, with twice as many women as men affected (Cross 2014). Significant functional limitations occur in 15% of sufferers five years after disease onset, with around a third of those in paid work experiencing work disability (Young 2000). In Finland, the risk of disability is seven times higher in people with RA compared with the general population (Sokka 2003). Rapid induction of remission translates to the maintenance of work capacity (Puolakka 2005).

Description of the intervention

The management of RA has undergone dramatic changes during the last 15 years. The latest updated recommendations of both the American College of Rheumatology (Singh 2016) and the European League Against Rheumatism (Smolen 2014) emphasise the importance of starting therapy with disease-modifying anti-rheumatic drugs (DMARDs) as soon as the diagnosis of RA is made; the search for remission or low disease activity using a treat-to-target approach; and close monitoring by using composite measures of disease activity and appropriate switching of drug treatment when the objectives are not reached. Methotrexate (MTX) remains the drug of choice at the start of treatment of RA (Lopez-Olivo 2014), although leflunomide or triple therapy are considered excellent alternatives (Singh 2012).

People sometimes do not respond to or are unable to tolerate DMARDs (Yee 2003). The newer biological drugs that have been introduced and approved for the treatment of RA in recent decades have been associated with clinical outcome improvement (Singh 2009), but also with higher rates of adverse events (Singh 2011).

How the intervention might work

RA is characterised by immunological activation of many cell types and a network of cytokines, particularly tumour necrosis factor alpha (TNFα) (Brennan 2008). Inhibitors of TNFα have been a major development in the treatment of RA. Randomised trials have shown that these drugs are highly beneficial in people with RA who have not responded well to conventional DMARDs. TNFα inhibitors have been shown to reduce the risk of joint damage, improve physical function and quality of life (Chen 2006). Five TNFα inhibitors are currently licensed for use against RA in Europe and the USA. These are adalimumab (Navarro-Sarabia 2005), etanercept (Lethaby 2013), golimumab (Singh 2010), infliximab (Blumenauer 2002) and certolizumab pegol (Ruiz Garcia 2014). Comparative efficacy studies to evaluate variations between anti-TNF and non-anti-TNF biologics have shown little difference between them (Navarro-Millán 2013). One pragmatic, open-label controlled trial (Jobanputra 2012) has directly compared etanercept and adalimumab, and reported similar persistence rates, efficacy and safety over two years of treatment. Similar results have been obtained with certolizumab pegol in extension studies, with the American College of Rheumatology ACR20 at 57% and ACR50 at 27% at eight years (NCT00160693), and ACR20 at 81% and ACR50 at 58% at seven years (NCT00175877). An important limitation of the wider use of TNF inhibitors is the high cost, between USD 10,000 and USD 25,000 per person a year. However, the recent entry of bio similars is causing a significant drop in prices. Biosimilars are biological products that are copies of an approved innovator biopharmaceutical, developed after the expiration of the innovator's patent and submitted for separate marketing approval. The use of bio similars may dramatically increase in the near future, mainly due to cost savings (Dörner 2016).

A systematic review of infliximab and adalimumab has shown that the risks of malignancy and serious infection were increased, with odds ratios (ORs) 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). However, more recent data show that therapy with anti-TNF is not related to an increased risk of malignancies (skin cancer, melanoma, lymphoma or solid tumours) (Lopez-Olivo 2012). A second review of nine biologic drugs (the five TNF inhibitors etanercept, adalimumab, infliximab, golimumab and certolizumab pegol; the interleukin (IL)-1 antagonist anakinra; the IL-6 antagonist tocilizumab; the anti-CD28 abatacept; and anti-B cell rituximab) showed that biologics as a group were associated with a statistically significantly higher rate of total adverse events (OR 1.28, 95% CI 1.09 to 1.50) and withdrawals due to adverse events (OR 1.47, 95% CI 1.20 to 1.86), and an increased risk of tuberculosis (TB) reactivation (OR 4.68, 95% CI 1.18 to 18.60) compared to control (Singh 2011). Moreover, the risk of serious infection is increased in people with RA treated with biological therapies compared with conventional DMARDs (Singh 2015).

Certolizumab pegol (CZP) was approved by the US Food and Drug Administration (FDA) and the European Medicines Evaluation Agency (EMEA) in 2009 for adults suffering from moderate to severe RA. Certolizumab pegol is an anti-TNF consisting of a humanised

immunoglobulin fragment (Fab) conjugated to polyethylene glycol (PEG), also termed pegylation. This unique molecular structure yields a longer half-life and reduces the need for frequent dosing (Choy 2002). Certolizumab pegol in combination with MTX is indicated for the treatment of moderate to severe active RA in adults when the response to conventional DMARDs, including MTX, has been inadequate. It is also indicated in severe, active and progressive RA not treated previously with conventional DMARDs. In the case of intolerance, side effects or contraindications to MTX it also can be given as monotherapy. The drug has been shown to reduce the rate of progression of joint damage, as measured by x-ray, and to improve physical function. Long-term follow-up studies of commercially-sponsored randomised controlled trials (RCTs) show persistence rates of 59.9% at week 232 (Smolen 2015), with 46.7% of participants having low disease activity at two years (Keystone 2012). Whether such rates can be replicated in routine care remains to be seen.

Why it is important to do this review

Biological treatment has led to a radical change in the prognosis and quality of life of people with RA. However, clinicians need to take into account the potential risks associated with their use. This review summarises the current data available on the benefits and harms of certolizumab pegol, on its own and in combination with MTX, for the treatment of RA. New evidence about efficacy, safety and long-term persistence has become available since our previous update. It is important to be sure that clinicians choose the treatment for people with RA appropriately, using the best medical evidence available (Emparanza 2015).

OBJECTIVES

To assess the clinical benefits and harms of certolizumab pegol (CZP) in people with RA who have not responded well to conventional disease-modifying anti-rheumatic drugs (DMARDs).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Adults (18 years and older) with RA who have persistent disease activity.

People 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 had to have an active form of the disease as demonstrated by at least two of the following symptoms:

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

Types of interventions

Certolizumab pegol (CZP)) at any dose.

The comparators were placebo or any DMARD including other biologic agents used to treat RA.

Types of outcome measures

Major outcomes

- The proportion of participants achieving an ACR50
- Health-related quality of life, such as the Health Assessment Questionnaire (HAQ) or Short Form Health Survey (SF-36)
- Disease Activity Score (DAS28 or other versions of DAS)
- Radiological changes (erosion score (ES), modified total Sharp score, joint space narrowing)
- Serious adverse events (SAEs)
- All withdrawals
- Withdrawals due to adverse events

The 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.

Scores in the HAQ range from 0 to 3, with 3 indicating a worse health state, so a negative change indicates improvement. The SF-36 is a scale from 0 to 100 where 0 is the worst and 100 the best health state.

Serious adverse events are defined as malignancies and all infections, especially tuberculosis, and death.

We sought all causes of withdrawals from the medication.

Minor outcomes

- ACR20 and ACR70 (a 20% or 70% improvement respectively in the parameters described above)
- Frequency of adverse events
- Withdrawals due to lack of efficacy

We sought reports of the following adverse 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.

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), the best sensitivity filter developed by the Hedges Team (Wong 2006a; Wong 2006b), and followed the Cochrane Musculoskeletal Review Group (CMSG) recommendations. Searches included both MeSH headings and text terms for CDP870 and rheumatoid arthritis. Tamara Rader, Information Scientist of the CMSG, conducted the searches. These included: MEDLINE (Appendix 1); Embase (Appendix 2); CINAHL (Appendix 3); Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL), HTA, DARE, NHS EED (the Cochrane Library) (Appendix 4); SCOPUS (Appendix 5); TOXLINE (TOXNET) (Appendix 6).

Safety data were obtained from clinical trials.

We updated the searches in CENTRAL (the Cochrane Library 2014, Issue 5), MEDLINE (2009 to 5 June 2014), Embase (2009 to 5 June 2014), SCOPUS (2009 to 5 June 2014), TOXLINE (2009 to 5 June 2014), Web of Knowledge (2009 to 5 June 2014) and the websites of the FDA and EMEA (2009 to 5 June 2014).

For this updated review, we updated the searches of MEDLINE; Embase, Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL), HTA, DARE, NHS EED (the Cochrane Library), and WOK in January 2016 and again in September 2016 (see Appendix 10; Appendix 11; Appendix 12; Appendix 13).

Searching other resources

1. We examined the information made available by the main researchers and sponsors in ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (apps.who.int/trialsearch/).
2. We reviewed information on the clinical trial meta-register database (www.controlled-trials.com/mrct/).
3. We inspected the reference lists of all identified studies for more trials.
4. When published data were missing, incomplete, or inconsistent with the trial protocols, we sought further information from the authors and manufacturers (UCB).

Data collection and analysis

Selection of studies

Two review authors independently checked the search results for studies that potentially met the inclusion criteria, resolving disagreements by discussion or by referral to a third review author.

Inclusion criteria

1. RCTs that compared certolizumab pegol with any other agent including placebo in adults 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 they were published only as abstracts, we requested the trial reports from the manufacturers.
3. Studies having at least three months of follow-up to assess benefits.

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

Exclusion criteria

1. Trials of certolizumab pegol for juvenile arthritis, Crohn's disease, psoriatic arthritis and other forms of spondyloarthritis.
2. Trials of certolizumab pegol comparing different doses or routes of administration without another active or placebo control group (except for assessing harm 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 checked titles and abstracts of studies found by the search, to assess which studies might potentially meet the inclusion criteria; where there was doubt, we acquired the full article for further inspection. We then obtained studies identified by this process and two review authors independently screened them to see if they met the review criteria using a web interface.

We extracted data when possible for intention-to-treat populations, as raw numbers plus any summary measures with the standard deviations, confidence intervals and P values of the outcomes reported. We compiled them in an Excel spreadsheet. We would have resolved any differences of opinion and data discrepancies by reference to a third review author (SB) but this proved to be unnecessary.

Assessment of risk of bias in included studies

According to the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), we assessed the risks of bias by creating a 'Risk of bias' table for each study. We present a summary below as a 'Risk of bias' graph.

The main criteria used to assess the risks of bias included: random sequence generation, allocation concealment, blinding of participants, incomplete outcome data, selective reporting of outcomes, and other potential biases (such as fraud or imbalance in the groups, or the sponsor either owning the data or needing to approve the manuscript). We rated the risk of bias in each study on the basis of each criterion as: low risk of bias, high risk of bias, unclear risk of bias (either lack of information or uncertainty over the potential bias). We included these criteria in the tables, resolving disagreements by discussion between the two review authors with recourse to a third review author if necessary, but in the event there were no disagreements.

Measures of treatment effect

We used the risk difference to quantify the number needed to treat for an additional beneficial outcome (NNTB) (Laupacis 1988). We calculated the NNTB from the risk ratio according to the formula NNTB = 1/ACR*(1 - RR), where ACR is the assumed control risk and RR the risk ratio. When events were very rare (fewer than 10%) we used the Peto odds ratio (Peto OR). For continuous data we used mean differences (MDs) when the results were measured in the same way in the different studies. We used standardised mean differences (SMDs) when the results obtained were conceptually the same but used different measurement scales. We recorded the central estimate (mean) and standard deviation (SD). Where these were not directly stated we calculated them 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, we used the median as a proxy measure of the mean and we considered the difference between the first and third interquartile to be 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. The unit of analysis was not an issue for this review.

Dealing with missing data

We carried out an intention-to-treat analysis. Every individual 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 for the response to treatment because it assumes that those discontinuing the studies would not have responded. It is not conservative for adverse effects. However, assuming that all those leaving early had developed side effects could 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 excluded abstracts of studies only if they 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, with a 10% level of significance, and the I^2 statistic. We interpreted the ranges of I^2 according to the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions*:

0% to 40% might not be important;
30% to 60% may represent moderate heterogeneity;
50% to 90% may represent substantial heterogeneity;
75% to 100% represents considerable heterogeneity (Higgins 2011).

Assessment of reporting biases

We planned to explore reporting bias using funnel plots when doing a meta-analysis for 10 or more studies.

Data synthesis

We explored the need to pool the results according to a fixed-effect or random-effects model analysis (Laird 1990). We planned to use the fixed-effect model to pool the data because statistical heterogeneity in our preview review was not high. However, we decided finally to perform a random-effects model, despite the I^2 values being low. Although it was the same drug, there was clear clinical heterogeneity (different doses, allowing MTX or not, different follow-up, different duration of RA, etc.).

Subgroup analysis and investigation of heterogeneity

We planned subgroup analyses for the duration of the illness (approximately three years evolution), participants' sex, drug dose and administration, and methodological quality. If we had detected heterogeneity then we would have conducted a subgroup analysis (Yusuf 1991), or a meta-regression (Thompson 1999) to see if it could be explained.

Sensitivity analysis

We planned the following sensitivity analyses in order to explore effect size differences and the robustness of conclusions:

1. Effect of study quality, defined as random sequence generation, allocation concealment, blinding of participants, incomplete outcome data, selective outcome reporting and other potential sources of bias.

2. Effect of imputation, size of trials, use of concomitant methotrexate, and doses of certolizumab pegol.

'Summary of findings' table

We used the GRADE approach, developed by the GRADE working group, to provide an overall assessment of the quality of the evidence by outcome. The GRADE approach specifies four levels of quality, with the highest quality rating for RCTs. Review authors can, however, downgrade randomised trial evidence from 'high' to 'moderate', 'low' or even 'very low' quality evidence, depending on the presence of specific factors: design or implementation, imprecision, inconsistency, indirectness, or reporting bias (see *Cochrane Handbook for Systematic Reviews of Interventions* Chapter XII (section 12.2) (Higgins 2011)).

RESULTS

Description of studies

Results of the search

See the flow chart (Figure 1) and 'Results of searches' in Appendix 10; Appendix 11; Appendix 12; Appendix 13; Appendix 14; Appendix 15; Appendix 16; Appendix 17.

Figure 1. Update: Records identified through the databases: (n = 559) Additional records identified through other sources (Clinicaltrials.gov, ICRTP)

(n = 98) Flow diagram.

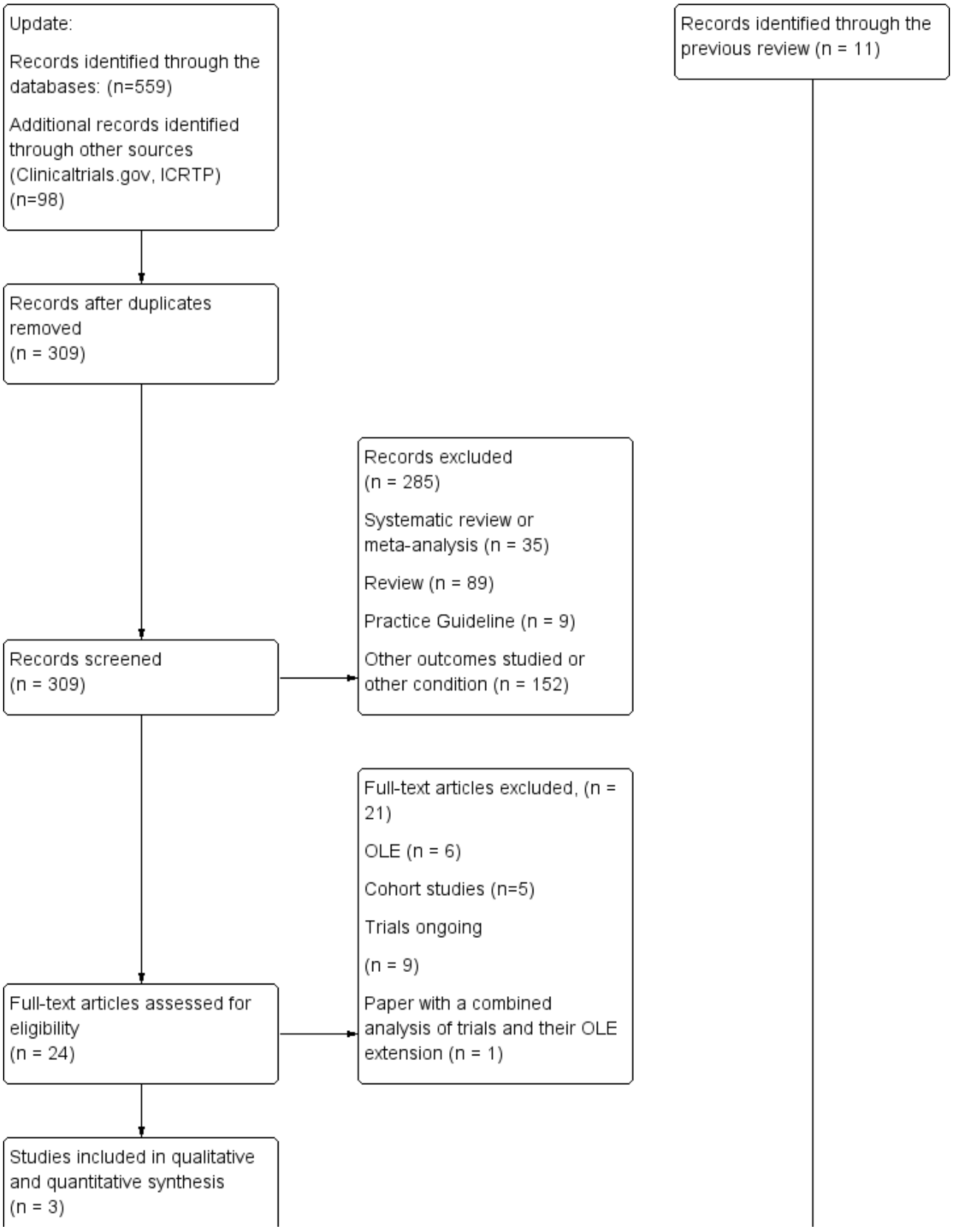
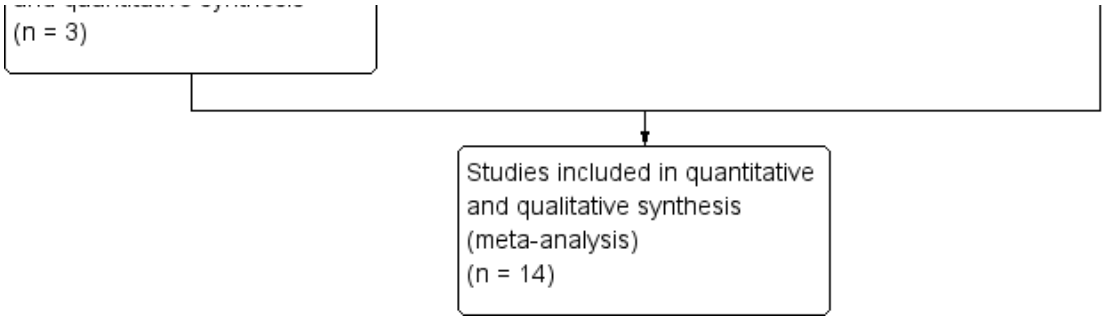


Figure 1. (Continued)



We include 14 trials in this update. Eleven (5422 participants) were included in the pooled analysis for benefits, two more than previously, and 13 (5273 participants) in the pooled analysis for safety. The duration of follow-up varied from 12 to 52 weeks and the range of doses of certolizumab pegol varied from 50 to 400 mg given subcutaneously (sc). In Phase III trials, the control was placebo plus MTX in seven trials and placebo alone in five trials. In Phase II the comparator was placebo. So summarising 7 trials compared certolizumab plus MTX and 7 trials certolizumab compared with placebo.

In accord with Cochrane MECIR standards, the Cochrane Musculoskeletal Group (CMSG) updated the searches on 25 January 2016 and reran them on 27 September, 2016.

Included studies

We include 14 trials, 12 in the assessment of benefits (CDP870-004 2001; Choy 2012; Smolen 2015; Fleischmann 2009; Yamamoto (a) 2014; Yamamoto (b) 2014; NCT00993317; Atsumi 2016; Emery 2015; Keystone 2008; Smolen 2009; Weinblatt 2012) and 14 trials in the assessment of harms (CDP870-004 2001; Choy 2012; Smolen 2015; Choy 2002; Fleischmann 2009; Yamamoto (a) 2014; Yamamoto (b) 2014; NCT00993317; Østergaard 2015; Atsumi 2016; Emery 2015; Keystone 2008; Smolen 2009; Weinblatt 2012). See Table 1. See the Characteristics of included studies and the demographics and flow of participants in Table 2 and Table 4 for details. Only Choy 2002 and CDP870-004 2001 were Phase II studies. We found a third Phase II study (Kaushik 2005) but we were advised by UCB that: "this publication refers to the 2 previous phase II". We used all the Phase III studies to assess both benefits and harms. CDP870-004 2001 only contributed data on benefits, as it did not report any data on harms.

Due to the short follow-up for assessing benefits, we only included Choy 2002 for safety data. The data from the two Phase II studies (CDP870-004 2001; Choy 2002) were not pooled with the rest of the studies, due to the different follow-ups and doses used.

We retrieved 12 Phase III trials (Choy 2012; Smolen 2015; Fleischmann 2009; Yamamoto (a) 2014; Yamamoto (b) 2014; NCT00993317; Østergaard 2015; Atsumi 2016; Emery 2015; Keystone 2008; Smolen 2009; Weinblatt 2012). All the trials were funded by UCB. Data from Choy 2012 were provided by UCB from the clinical study summary (www.clinicalstudyresults.org/documents/company-study_4348_0.pdf) and the EMA 2009 reports; they were finally published in 2012 (the study was completed in 2004).

Table 2 shows the demographic and baseline characteristics for the Phase III trials: age, gender, rheumatoid factor (RF) positivity, MTX concomitant dose, number of previous DMARDs, basal HAQ and basal DAS28, among other outcomes. Table 3 provides the flow chart of participants in the Phase III studies.

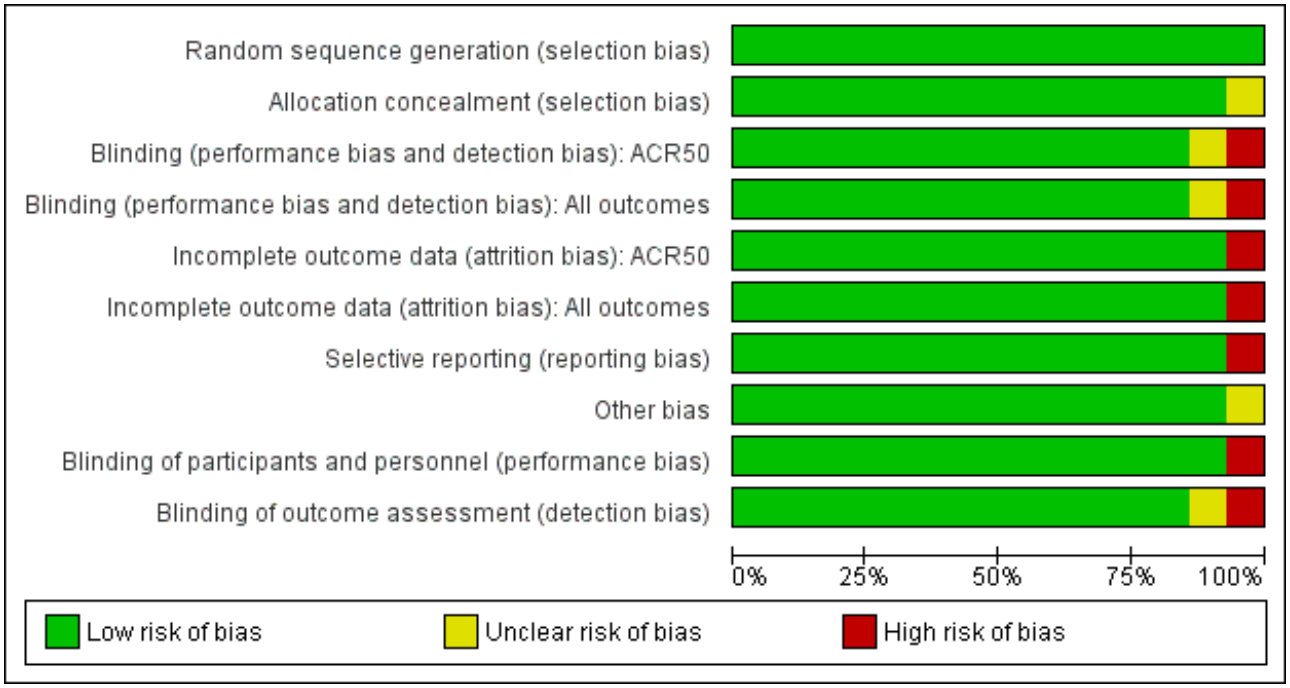
Excluded studies

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

Risk of bias in included studies

We present the judgements about each 'Risk of bias' item as percentages across all included studies (Figure 2). We rated most of the trials at low risk of bias. The overall likelihood of bias seemed to be low.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



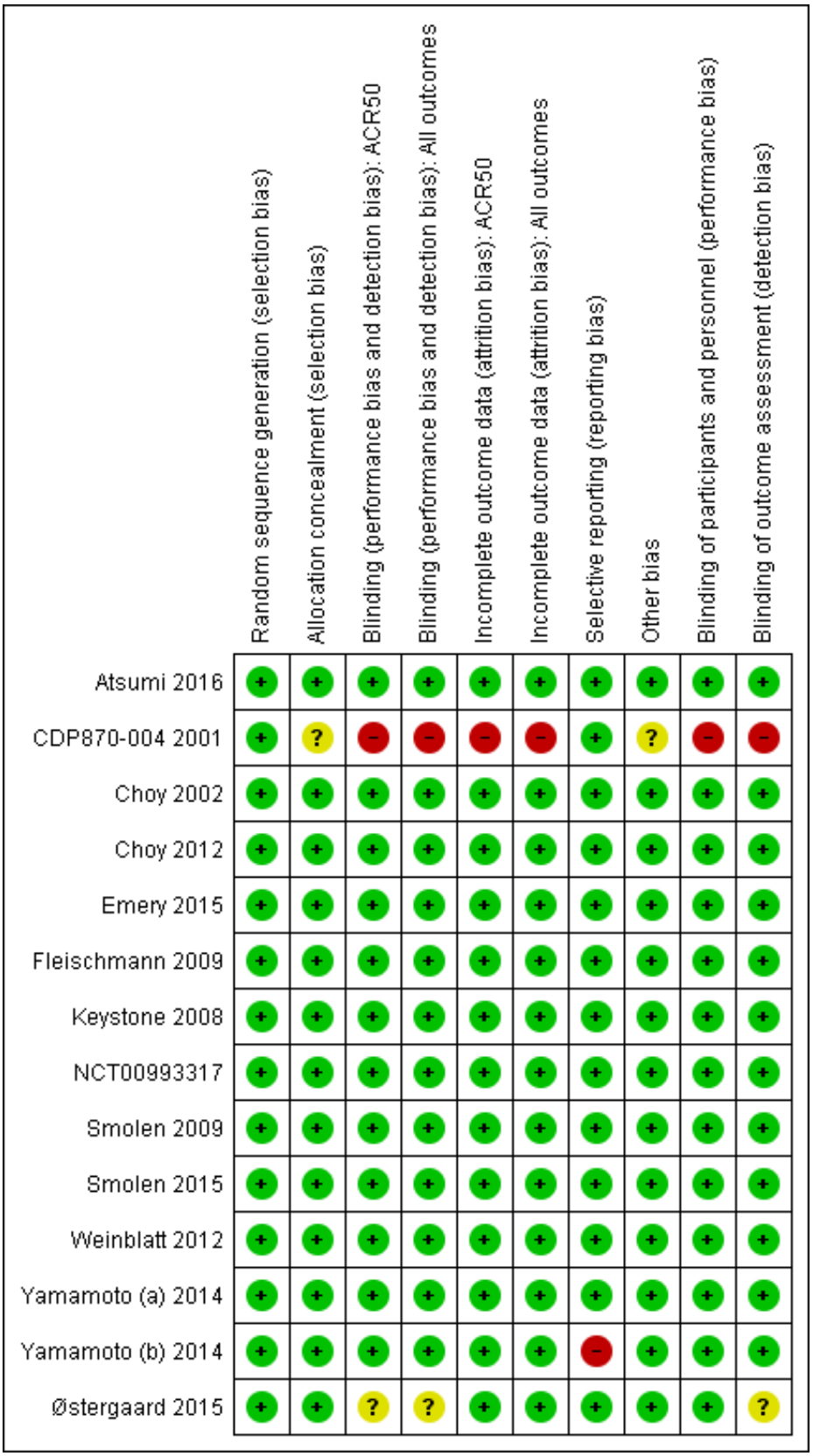
Allocation

All studies except CDP870-004 2001 reported adequate methods of randomisation and allocation concealment. Eight studies (Choy 2012; Smolen 2015; Fleischmann 2009; Atsumi 2016; Emery 2015; Keystone 2008; Smolen 2009; Weinblatt 2012) used the interactive voice response system (IVRS) method of allocation concealment. The Asian trials (Yamamoto (a) 2014; Yamamoto (b) 2014; NCT00993317) were described as: 'external randomisation' (NCT00993317) or randomisation by blocks (Yamamoto (a) 2014; Yamamoto (b) 2014), so the risk of bias seemed to be low.

Blinding

All studies except CDP870-004 2001 reported adequate blinding. Refer to Figure 3.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Phase II:

- CDP870-004 2001 did not disclose the methods of blinding, and UCB explained to us: "CPD-870 and the placebo utilized in this study (saline) did not have the same viscosity therefore full blinding was not possible. Study drug was to be prepared by a pharmacist having no other involvement in the study; injections of study medications were given by a nurse or physician who had no other involvement in the study...";
- Choy 2002 disclosed the methods of blinding: “Placebo (sodium acetate buffer) was given similarly as a single intravenous infusion of 100 ml over 60 min”. It was unlikely that the blinding could have been broken. UCB explained to us: "all data were entered and Database locked after completion of the clinical phase for the first study period and before ESR and CRP were entered into the database. ESR and CRP data were withheld from investigator and sponsor study personal during the course of the study because knowledge of patient’s profile could potentially unblind the study..., auto AB, anti CZP level, TNFalpha, IL6 and IL1b were transferred into the database after Database lock."

Phase III:

- UCB told us, "in Fleischmann 2009, Choy 2012, Keystone 2008, Smolen 2009, Smolen 2015, Weinblatt 2012, all the study staff, with the exception of the unblinded dispenser, was blind to the treatment. Each study center was required to have a written blinding plan in place signed by the Principal Investigator, which detailed the study center's steps for ensuring that the double blind nature of the study was maintained. All the studies were monitored by two different independent teams from the sponsor, one devoted to blind data and one devoted to possibly unblinded information (such as study medications related topics) and completely separate documentation/filing systems were maintained for the duration of the trials";
- Keystone 2008: "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";
- Smolen 2009: "Radiographs were read centrally and blinded (for treatment, visit and patient identification) and independently by two experienced readers";
- Fleischmann 2009 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".
- in the Japanese and Korean trials (Yamamoto (a) 2014; Yamamoto (b) 2014; NCT00993317) "All study staff with the exception of the unblinded dispenser were blind to the treatment, ... These unblinded personnel were not allowed to engage in any other study activities".
- in Østergaard 2015: "The personnel administering the injections had no involvement in the study other than performing the erythrocyte sedimentation rate analysis"
- in Atsumi 2016: "Drug administration was performed by dedicated non blinded persons due to distinguish ability of CZP from PBO; however, these personnel were not permitted to engage in other study activities to maintain blinding. All investigators and healthcare professionals involved in safety/efficacy assessments were blind to study medications"
- in Emery 2015: "Sponsor, investigator site and vendor staff involved will be blinded to the testaments assignment with the following exceptions: sponsor clinical study supplies coordinator and qualifier person unblinded site personnel involved in ESR determination" (UCB private files). We do not have any information about how the blinding was performed.

For these reasons, we rated the risk of bias for blinding as low.

Incomplete outcome data

All studies, except the small Phase II trial (CDP870-004 2001) reported adequate methods of handling missing outcome data. All other studies gave a full account of all withdrawals and reasons for withdrawals. Where possible, we extracted data to allow an intention-to-treat analysis in Choy 2012; Fleischmann 2009; NCT00993317. Eight out of 11 studies reported less than 80% completion rates. However, for ACR20, ACR50, ACR70 DAS remission, SAEs, withdrawals and withdrawals due to adverse events we conducted an ITT analysis. Only radiological scores and HAQ were analysed per protocol. In consequence for the overall estimation, we think the risk of bias is low. Refer to Figure 3.

The completion rates in the certolizumab pegol group ranged from 68% in Fleischmann 2009 to 90% in Weinblatt 2012 . In all trials, fewer participants in the placebo-treated group completed the trial compared to the treatment arm. More participants who were treated with placebo withdrew due to lack of efficacy. The percentage of those completing the trial in the placebo group ranged from 15% in the 12-month results of Yamamoto (a) 2014 to 86% in the 12-week results of Weinblatt 2012 . We imputed missing data using last observation carried forward (LOCF) in most trials. The new trials for this update (Atsumi 2016: Emery 2015) reported low rates of participants who finished the trials.

In the Atsumi 2016 trial, “Patients who did not achieve an improvement of RA symptoms (defined as the persistence of DAS28[ESR] ≥3.2 for4 weeks or longer) after Week 24 were eligible to withdraw from trial and move to rescue treatment with open label trial of CZP” so, 22.6% in the certolizumab pegol group and 44.6% in placebo group were withdrawn. We did not find this assumption in the protocol in clinicaltrials.gov/ct2/show/NCT01451203. Similary in Emery 2015 the participants “not achieving sufficient improvement defined as DAS 28 DAS28[ESR] ≥3.2 and or ≥ 1.2 point improvement in DAS28(ESR) from BL at weeks 20 and 24 were withdrawn to allow them to switch to a complementary medication”. In this trial 15% of people withdrew from the placebo arm and 8% from the certolizumab pegol arm, but people also withdrew for lack of efficacy, adverse events, protocol violation and being lost to follow-up. Total withdrawals in the placebo group amounted to 34% of participants and 24% from the certolizumab pegol group. We did not find in the protocol hold in clinicaltrials.gov again this assumption clinicaltrials.gov/ct2/show/NCT01519791?term=NCT01519791&rank=1. In Keystone 2008 “certolizumab pegol or placebo patients who were ACR20 non-responders at both weeks 12 and 14 in RCT, were required to withdraw at week 16” . One hundred-and-thirty-nine out of 199 left the placebo arm (70%) and 181 out of 783 in the certolizumab pegol arm (23%). In Østergaard 2015 three of 27 participants discontinued due to adverse events and lack of efficacy, while one of 17 in the placebo group discontinued for withdrawal of consent. Newly we did not find any assumption in the protocol. This trial was small (41 people) with very short follow-up of two weeks, focused only on radiological changes. In summary, higher rates of withdrawal in the certolizumab pegol arm with a long-term follow-up can introduce a serious bias into the interpretation of effectiveness of certolizumab

pegol. Moreover, the assumption that people could be withdrawn if they did not achieve a good response was not prespecified in the protocols.

Selective reporting

All studies reported their prespecified outcomes, except for Yamamoto (b) 2014. UCB gave ACR20/50/70 as a figure as well as providing the DAS, but we could not pool DAS data and we had no information about the modified Total Sharp Score (mTTS) for radiographic progression.

We changed our previous assessment of the bias in Fleischmann 2009, because all the primary outcomes were described in the paper.

In the previous version of the review Choy 2012 only reported ACR20, but the ACR50, HAQ disability index and acute-phase reactant (CRP) are now available, so we have revised our 'Risk of bias' assessment to low.

In summary, we think the risk of reporting bias in this update is low. Refer to Figure 3.

Other potential sources of bias

We did not detect potential threats to validity, such as fraud or imbalance in the groups (relating to the baseline characteristics). All studies included in this review were sponsored by the manufacturer of certolizumab pegol. There is evidence that industry-sponsored trials may overestimate the treatment effect (Bhandari 2004) and there is also evidence that most of the authors of published trials have a conflict of interest. However, there is a lack of consensus on whether these conflicts result in reduced quality of the trials and, in view of this, we have decided to rate the risk of bias for this domain as low.

We searched for more trials as well as for more information about unpublished trials (see Characteristics of ongoing studies table), but no information was available, either from the sponsors or from any publication.

In summary, we think the risk of other potential sources of bias is low for this update. Refer to Figure 3.

Summary assessment of risk of bias by outcomes

Figure 2 and Figure 3 provide a graphical summary of the results of the 'Risk of bias' assessments for the 14 included studies.

The main major outcomes

ACR 50 response at six months and 52 weeks: we rated six studies at six months and three studies at 52 weeks included in the meta-analysis at low risk for adequate allocation concealment, blinding and reporting of appropriate outcomes. Although there were high rates of withdrawals, we rated the trials at low risk of bias, since we were able to conduct an ITT analysis. Another concern was that all studies were sponsored by the manufacturer of certolizumab pegol.

HAQ change from baseline, response at six months and 52 weeks: we rated five studies at six months and two studies at 52 weeks included in the meta-analysis at low risk for adequate allocation concealment, blinding and reporting of appropriate outcomes. However, we had concerns about bias for incomplete outcome data due to the high dropout rates.This item was subject to a per protocol analysis, which we downgraded by one level. Another concern was that all studies were sponsored by the manufacturer of certolizumab pegol.

Proportion of participants achieving remission (DAS < 2.6) at 24 weeks: six studies. We rated them at low risk of bias for all the domains. Despite the rates of withdrawals, we conducted an ITT analysis for this outcome. Another concern was that all studies were sponsored by the manufacturer of certolizumab pegol.

Radiological changes (ES scores) at 24 weeks: two studies. We rated We rated all domains at low risk of bias. However, we had concerns about bias for incomplete outcome data, due to the dropout rates in both studies.This item was subject to per protocol analysis, and we downgraded it by one level. Another concern was that all studies were sponsored by the manufacturer of certolizumab pegol.

Serious adverse events with certolizumab pegol 200 mg at any follow-up: we rated nine studies included in the meta-analysis at low risk of bias for adequate allocation concealment, blinding and reporting of appropriate outcomes. We analysed all of them on an ITT basis for all randomised participants who received at least one dose, but in two out of the nine studies the analysis was per protocol: in Smolen 2009 "two patients in the placebo group received certolizumab pegol 200 mg and were included in the certolizumab pegol 200 mg group for safety evaluations", and in Weinblatt 2012 nine participants fewer were analysed in the certolizumab pegol arm and three participants fewer in the placebo group. In Atsumi 2016, an ITT analysis was performed. However, in Emery 2015, the analysis was per protocol, with two participants fewer in the control group and one less in the (CZP) group. We performed an ITT analysis In Østergaard 2015 trial. Another concern was that all studies were sponsored by the manufacturer of certolizumab pegol.

Withdrawals for all doses and follow-up to 52 weeks: we rated 13 studies at low risk of bias in all the domains. We conducted an ITT analysis for all the trials. Another concern was that all studies were sponsored by the manufacturer of certolizumab pegol.

Withdrawals due to adverse events for all doses and follow-up to 52 weeks: we rated 12 studies at low risk of bias in all the domains. We conducted an ITT analysis for all the trials. Another concern was that all studies were sponsored by the manufacturer of certolizumab pegol.

Effects of interventions

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

We conducted our analyses based on the doses used in the trials, i.e. the drug exposure time for subcutaneous (sc) doses of 200 mg and 400 mg. For 400 mg the most usual was at four-week intervals, and for 200 mg sc the most frequently-used was every other week, but in some trials such as Keystone 2008 and Smolen 2009 the interval was every two weeks for the 400 mg dose as well. As we had two periods of follow-up (six months and one year) in one study, we could not combine them, so we pooled each outcome at each follow-up. We also had studies with more than one dose, so we split the placebo arm to enable us to pool results. We did not find strong differences that could justify our not combining the results for benefits and harms. We decided to perform a random-effects

model, in spite of the low values of I^2. Although it was the same drug, there is clear clinical heterogeneity (different doses, allowing MTX or not, different follow-up, different duration of RA, etc.).

Major outcomes

ACR50

We noted significant improvements for all doses at any given time point for the ACR50 compared to placebo (see 'Benefits' tables, ACR Table 4, Data and analyses).

The ACR50 with 200 mg certolizumab pegol showed, at 24 weeks, a risk ratio (RR) of 3.80 (95% confidence interval (CI) 2.42 to 5.95), five studies, involving 1445 participants (Analysis 2.1); The ACR50 with 400 mg certolizumab pegol showed, at 24 weeks, a RR of 4.65 (95% CI 3.09 to 6.99), five studies, involving 1591 participants (Analysis 3.1). We judged the quality of evidence for ACR50 with 200 and 400 mg certolizumab pegol at 24 weeks to be **high** .

The ACR50 with 200 mg certolizumab pegol showed, at 52 weeks a RR of 1.54 (95% CI 1.38 to 1.73), three studies, involving 881 participants (Analysis 4.1). This analysis reported an High value of I^2. We explained this due to that the results of RAPID1 showed a very high values RR 5.02 whereas the remaining trials showed lowest values around RR of 1.41 or 1.21). Moreover the CI of RAPID1 did not overlap the remaining trials.

The ACR50 with 400 mg certolizumab pegol showed, at 52 weeks, a RR of 5.27 (95% CI 3.19 to 8.71), one study, involving 589 participants (Analysis 5.1).

We judged the quality of evidence for ACR50 with 200 and 400 mg certolizumab pegol at 52 weeks to be **high.**

The NNTB was close to 4 for all the sub analyses (Table 4).

Health-related quality of life

We found an improvement in physical function and quality of life measured with the HAQ and SF-36 (in the mental and physical components) at all follow-ups (see 'Health-related quality of life' tables, (Table 5)) with certolizumab pegol compared to placebo.

HAQ at 24 weeks, 200 mg: mean difference (MD) -0.35 (95% CI -0.43 to -0.26), four studies, involving 1268 participants (Analysis 7.1).

We judged the quality of evidence for HAQ at 24 weeks, 200 mg to be **moderate**. We downgraded the quality of evidence by one level, due to a high risk of attrition bias (per protocol analysis).

HAQ disability index (HAQ-DI) at 24 weeks, 400 mg: MD -0.38 (95% CI -0.48 to -0.28), four studies, involving 1425 participants (Analysis 7.2).

We judged the quality of evidence for HAQ-DI, 24 weeks, 400 mg to be **moderate**. We downgraded the quality of evidence by one level, due to a high risk of attrition bias (per protocol analysis).

HAQ-DI at 24 weeks, any dose: MD -0.36 (95% CI -0.43 to -0.29), five studies, involving 2246 participants (Analysis 8.1).

We judged the quality of evidence for HAQ-DI, 24 weeks any dose 200 mg to be **moderate**. We downgraded the quality of evidence by one level, due to a high risk of attrition bias (per protocol analysis).

HAQ-Di, 52 weeks, any dose: MD -0.32 (95% CI -0.39 to -0.26), two studies, involving 1837 participants (Analysis 9.1).

We judged the quality of evidence for HAQ-DI at 24 weeks, 200 mg to be **moderate**. We downgraded the quality of evidence by one level, due to a high risk of attrition bias (per protocol analysis).

We judged the quality of evidence for HAQ-DI at 52 weeks, any dose to be to be **moderate**. We downgraded the quality of evidence by one level, due to a high risk of attrition bias (per protocol analysis). This analysis reported a High value of I^2. We explained this due to that the results of RAPID1 showed a very high values MD -0.42 whereas the remaining trial showed lowest values around MD of -0.18. Moreover the CI of RAPID1 did not overlap the remaining trial.

SF-36 physical component summary (PCS) at 24 weeks, any dose: MD 5.29 (95% CI 4.37 to 6.21), three studies, involving 1765 participants (Analysis 14.1).

SF-36 mental component summary (MCS) at 24 weeks, any dose: MD 4.01 (95% CI 2.94 to 5.08), four studies, involving 2012 participants (Analysis 15.1);

We judged the quality of evidence for SF-36 PCS and SF-36 MCS at 24 weeks, any dose, to be **moderate**. We downgraded the quality of evidence by one level due to a high risk of attrition bias (per protocol analysis).

SF-36 PCS at 52 weeks, any dose: MD 6.47 (95% CI 5.13 to 7.81), one study, involving 982 participants (Analysis 16.1).

SF-36 MCS at 52 weeks, any dose: MD 4.30 (95% CI 2.57 to 6.03), one study, involving 982 participants (Analysis 17.1).

We judged the quality of evidence for SF-36 PCS and SF-36 MCS at 52 weeks, any dose, to be **moderate**. We downgraded the quality of evidence by one level, due to a high risk of attrition bias (per protocol analysis).

DAS-28

We observed significant improvements for all doses and at any given time point compared to placebo.

At 24 weeks the proportion of participants achieving remission (DAS < 2.6) was higher in the 200 mg certolizumab pegol group than in the placebo group (RR 2.94, 95% CI 1.64 to 5.28), six studies, involving 2420 participants (Analysis 19.1.1); and RR of 1.71 (95% CI 1.43 to 2.04) at 52 weeks, three studies, involving 1689 participants (Analysis 20.1.1.).

We judged the quality of evidence for DAS < 2.6, 200 mg at 24 and 52 weeks to be **high**.

The RR for participants achieving remission (DAS < 2.6) with 200 mg certolizumab pegol at 12 weeks was 1.99 (95% CI 1.44 to 2.76), two studies, involving 1942 participants (Analysis 21.1).

We judged the quality of evidence for DAS < 2.6 at 12 weeks, 200 mg to be **high**.

The RR for participants achieving remission (DAS < 2.6) with 400 mg certolizumab pegol was 7.18 (95% CI 3.12 to 16.50) at 24 weeks, three studies, involving 1201 participants (Analysis 21.3); and at 52

weeks the RR was 12.49 (95% CI 3.99 to 39.12), one study, involving 583 patients (Analysis 21.5).

We judged the quality of evidence for DAS < 2.6, 400 mg at 24 and 52 weeks to be **high**.

Radiological changes

Radiological changes were expressed as modified Total Sharp Scores (mTSS), the erosion score (ES) and joint space narrowing (JSN). All certolizumab pegol groups showed improvements compared to placebo in the mean changes from baseline. There was a clear radiological benefit, regardless of the dose, associated with drug exposure time (see 'Radiological changes', Table 6).

ES at 200 mg, 24 weeks: MD -0.35 (95% CI -0.50 to -0.21), two studies, involving 859 participants (Analysis 29.1).

We judged the quality of evidence for ES at 200 mg, 24 weeks to be **moderate**. We downgraded the quality of evidence by one level, due to a high risk of attrition bias (per protocol analysis).

ES at 200 mg, 52 weeks: MD -1.14 (95% CI -1.54 to -0.74), two studies, involving 1235 participants (Analysis 29.3).

We judged the quality of evidence for ES at 200 mg, 52 weeks to be **moderate**. We downgraded the quality of evidence by one level, due to a high risk of attrition bias (per protocol analysis).

ES at any dose, 24 weeks: MD -0.70 (95% CI -0.98 to -0.42), two studies, involving 1437 participants (Analysis 30.1).

We judged the quality of evidence for ES at any dose, 24 weeks to be **moderate**. We downgraded the quality of evidence by one level, due to a high risk of attrition bias (per protocol analysis).

ES at any dose, 52 weeks: MD -1.16 (95% CI -1.56 to -0.77), two studies, involving 1599 participants (Analysis 31.1).

We judged the quality of evidence for ES at any dose, 52 weeks to be **moderate**. We downgraded the quality of evidence by one level, due to a high risk of attrition bias (per protocol analysis).

Joint space narrowing (JSN) at 200 mg, 24 weeks: MD -0.45 (95% CI -0.77 to -0.13), two studies, involving 861 participants (Analysis 32.1).

We judged the quality of evidence for JSN at 200 mg, 24 weeks to be **moderate**. We downgraded the quality of evidence by one level, due to a high risk of attrition bias (per protocol analysis).

JSN at 200 mg, 52 weeks: MD -0.67 (95% CI -1.02 to -0.32), two studies, involving 1239 participants (Analysis 32.3).

We judged the quality of evidence for JSN at 200 mg, 52 weeks to be **moderate**. We downgraded the quality of evidence by one level, due to a high risk of attrition bias (per protocol analysis).

JSN at any dose, 24 weeks: MD -0.50 (95% CI -0.79 to -0.21), two studies, involving 1439 participants (Analysis 33.1).

We judged the quality of evidence for JSN at any dose, 24 weeks to be **moderate**. We downgraded the quality of evidence by one level, due to a high risk of attrition bias (per protocol analysis).

JSN at any dose, 52 weeks: MD -0.70 (95% CI -1.04 to -0.36), two studies, involving 1602 participants (Analysis 34.1).

We judged the quality of evidence for JSN at any dose, 52 weeks to be **moderate**. We downgraded the quality of evidence by one level, due to a high risk of attrition bias (per protocol analysis).

MTSS at any dose, 24 weeks: MD -0.86 (95% CI -1.19 to -0.53), three studies, involving 1753 participants (Analysis 35.1).

We judged the quality of evidence for mTSS at any dose, 24 weeks to be **moderate**. We downgraded the quality of evidence by one level, due to a high risk of attrition bias (per protocol analysis).

Modified Total Sharp Scores (mTSS) at 200 mg, 24 weeks: MD -0.74 (95% CI -1.11 to -0.37), three studies, involving 1029 participants (Analysis 35.1.1).

We judged the quality of evidence for mTSS at 200 mg, 24 weeks to be **moderate**. We downgraded the quality of evidence by one level, due to a high risk of attrition bias (per protocol analysis).

MTSS at any dose, 52 weeks: MD -1.63 (95% CI -2.13 to -1.13), three studies, involving 1915 participants (Analysis 36.1).

We judged the quality of evidence for mTSS at any dose, 52 weeks to be **moderate**. We downgraded the quality of evidence by one level, due to a high risk of attrition bias (per protocol analysis).

MTSS at 200 mg, 52 weeks: MD -1.54 (95% CI -2.06 to -1.01), three studies, involving 1462 participants (Analysis 36.1.1).

We judged the quality of evidence for mTSS 200 mg, 52 weeks to be **moderate**. We downgraded the quality of evidence by one level, due to a high risk of attrition bias (per protocol analysis).

Serious adverse events (SAEs) as defined in the studies

The clinical study summary of CDP870-004 2001 did not define SAEs. All the new trials that were added in this update reported on SAEs.

We reported adverse events grouped by the dosages:

SAEs for certolizumab pegol 200 mg and any follow-up time point: Peto OR 1.47 (95% CI 1.13 to 1.91), nine studies, involving 3927 participants (Analysis 41.1);

We judged the quality of evidence for SAEs for certolizumab pegol 200 mg and any follow-up to be **high**.

SAEs for certolizumab pegol 400 mg and any follow-up time point: RR 1.98 (95% CI 1.36 to 2.90), six studies, involving 1624 participants (Analysis 42.1); 95 events were reported in the certolizumab pegol groups versus 31 events in the control groups.

We judged the quality of evidence for SAEs for certolizumab pegol 400 mg at any follow-up time point to be **high**.

We decided to use Peto OR due to the low number of events in both 200 and 400 mg of certolizumab pegol.

All withdrawals

There were more withdrawals "at any dose and at any follow-up" in placebo groups (53%) versus the certolizumab pegol groups (23%):

RR 0.47 (95% CI 0.39 to 0.56), 13 studies, involving 5200 participants (Analysis 43.1).

We judged the quality of evidence for all withdrawals "at any dose and at any follow-up" to be **moderate**. We downgraded the quality of evidence by one level for inconsistency due to heterogeneity (not all of the confidence intervals overlap, and I^2 is 79%).

Withdrawals due to adverse events

There were more withdrawals "at any dose and at any follow-up due to adverse events" in the certolizumab pegol groups (5%) versus placebo groups (4%).

Withdrawals at any dose and at any follow-up due to adverse events: Peto OR 1.45 (95% CI 1.09 to 1.94), 12 studies, involving 5236 participants (Analysis 43.2).

We judged the quality of evidence for withdrawals at any dose and at any follow-up due to adverse events for certolizumab pegol to be **high**.

We have included all results in Summary of findings for the main comparison.

Minor outcomes

ACR20 and ACR70

We saw an improvement in ACR20 and ACR70 compared to placebo for all doses and at any time point.

ACR20 for any dose at 24 weeks: RR 2.76 (95% CI 2.29 to 3.33), eight studies, involving 2935 participants (Analysis 44.1).

ACR70 for any dose at 24 weeks: RR 4.15 (95% CI 2.68 to 6.42), seven studies, involving 2705 participants (Analysis 44.3).

We judged the quality of evidence for ACR20 and ACR70 for any dose at 24 weeks for certolizumab pegol to be **high.**

ACR20 for any dose at 52 weeks: RR 1.46 (95% CI 1.11 to 1.93), three studies, involving 2180 participants (Analysis 45.1).

We judged the quality of evidence for ACR20 for any dose at 52 weeks for certolizumab pegol to be **moderate.** We downgraded the quality of evidence one level for inconsistency due to heterogeneity (not all the confidence intervals overlap and I^2 is 88%).

ACR70 for any dose at 52 weeks: RR 1.89 (95% CI 1.44 to 2.48), three studies, involving 2180 participants (Analysis 45.3).

We judged the quality of evidence for ACR70 for any dose at 52 weeks for certolizumab pegol to be **high.**

Adverse events

We reported all adverse events in Data and analyses but we have not commented on all of them in this section, but only those that we thought were noteworthy (see Table 7).

Any adverse event

We pooled the data for any adverse event from nine trials: 200 mg certolizumab pegol: RR 1.16 (95% CI 1.03 to 1.31), nine studies, involving 3927 participants (Analysis 50.1).

We judged the quality evidence for any adverse event for 200 mg certolizumab pegol to be**moderate**. We downgraded the quality of evidence one level for inconsistency due to heterogeneity (not all the confidence intervals overlap and I^2 is 74%).

Safety, any adverse event at 400 mg certolizumab pegol: RR 1.19 (95% CI 1.05 to 1.34), six studies, involving 1624 participants (Analysis 50.2).

We judged the quality of evidence for any adverse event for 400 mg certolizumab pegol to be **high.**

We excluded Choy 2002 because it showed more events than participants in the certolizumab pegol group (62 events in 24 participants) as well as in the placebo group (19 events in 12 participants). We therefore could not calculate the RR.

Adverse events: severe intensity as defined in the studies

There were no differences in the number of SAEs between participants treated with 200 mg: Peto OR 1.14 (95% CI 0.78 to 1.65), four studies, involving 2249 participants Analysis 50.7).

We judged the quality of evidence for adverse events with severe intensity for 200 mg certolizumab pegol to be **moderate**. We downgraded the quality of evidence one level for imprecision due to the 95% confidence interval around the pooled effect including both harm and no harm.

Participants treated with 400 mg of certolizumab pegol: Peto OR 1.23 (95% CI 0.83 to 1.81), five studies involving 1462 participants (Analysis 50.8).

We judged the quality of evidence for adverse events with severe intensity for 400 mg certolizumab pegol to be **moderate**. We downgraded the quality of evidence one level for imprecision, due to the 95% confidence interval around the pooled effect including both harm and no harm.

Serious adverse infections (SAIs)

This composite outcome included any severe events of infections, infestations and tuberculous (disseminated tuberculosis, peritoneal tuberculosis, pulmonary tuberculosis, lymph node tuberculosis, tuberculosis), lower respiratory tract infection, and obstructive chronic bronchitis with acute exacerbation. More SAIs were reported in the 200 mg certolizumab pegol-treated group (Peto OR 1.94, 95% CI 0.99 to 3.80), three studies, involving 1283 participants; and in the 400 mg certolizumab pegol-treated group (Peto OR 3.25, 95% CI 1.65 to 6.39), four studies, involving 1422 participants; 63 events were reported in the certolizumab pegol groups versus 13 events in the control groups. There were no differences between the rates of SAIs in the 200 mg and 400 mg certolizumab pegol groups. See more details in (Analysis 50.11; Analysis 50.12)

We judged the quality of evidence for SAIs for 200 mg certolizumab pegol to be **moderate**. We downgraded the quality of evidence one level for imprecision due to the 95% confidence interval around the pooled effect including both harm and no harm.

We judged the quality of evidence for SAIs for 400 mg certolizumab pegol to be **high.**

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 the placebo and certolizumab pegol-treated groups. Eleven deaths due to adverse events in the certolizumab pegol groups were reported, versus one death in the control groups:

200 mg certolizumab pegol: Peto OR 1.63 (95% CI 0.41 to 6.47), six studies involving 3322 participants (Analysis 50.13).

We judged the quality of evidence for adverse events leading to death for 200 mg certolizumab pegol to be **moderate**. We downgraded the quality of evidence one level for imprecision due to the 95% confidence interval around the pooled effect including both harm and no harm.

400 mg certolizumab pegol: Peto OR 2.16 (95% CI 0.40 to 11.79), three studies, involving 1179 participants (Analysis 50.14).

We judged the quality of evidence for adverse events leading to death for 400 mg certolizumab pegol to be **moderate**. We downgraded the quality of evidence one level for imprecision due to the 95% confidence interval around the pooled effect including both harm and no harm.

Death

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

In Smolen 2009, in the 200 mg certolizumab pegol-treated group one participant died of myocardial infarction; one died during the study in the 400 mg certolizumab pegol-treated group (fracture, shock), which was assessed as unlikely to be related to the study medication.

In Choy 2002, in the open phase one participant in the certolizumab pegol-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.

In Weinblatt 2012, one participant died of sigmoid diverticulitis and one of necrotising pneumonia; both deaths were ruled out as possibly related to certolizumab pegol.

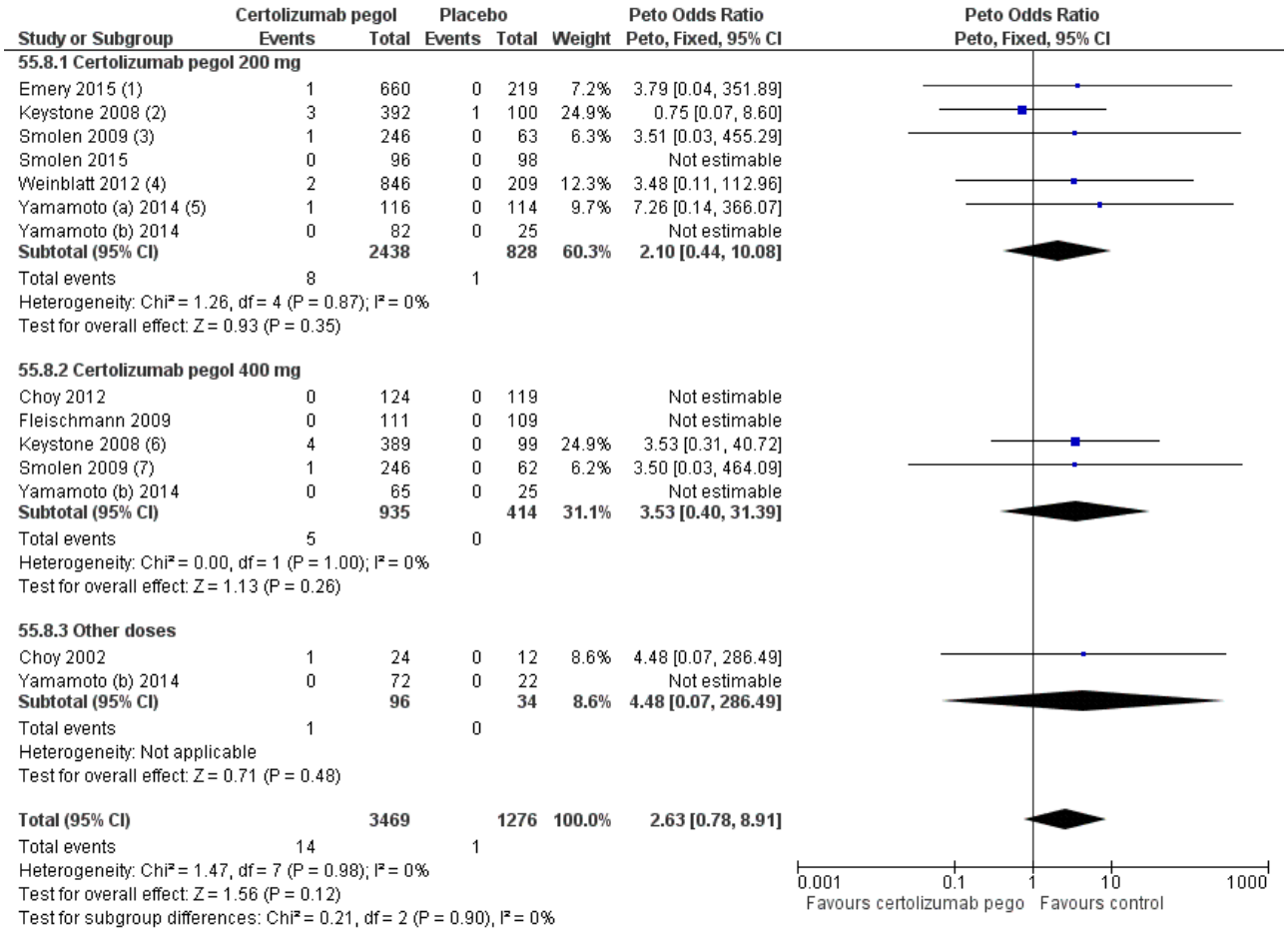
In Yamamoto (a) 2014, one participant died of a rupture of a dissecting aortic aneurysm in the thoracic region, but UCB considered this unlikely to have been related to the study medication.

In Emery 2015 "The single CZP-related death in this study occurred in a 65-year-old patient of Indian origin, with hypertension and diabetes mellitus. The patient died of cardiorespiratory failure and acute respiratory distress syndrome, secondary to septic shock caused by bowel perforations. Acid-fast bacillus stains of the gut and saliva were positive. This, in conjunction with the gut pathology, led to a diagnosis of disseminated, non-characterised, mycobacterium infection; the QuantiFERON test was negative and there was no PCR confirmation of TB".

Choy 2012; Smolen 2015; Fleischmann 2009; Yamamoto (b) 2014; Østergaard 2015; Atsumi 2016 did not report any deaths.

Overall certolizumab pegol deaths: Peto OR 2.63 (95% CI 0.78 to 8.91), 10 studies, involving 4745 participants (Analysis 50.19) and Figure 4.

Figure 4. Forest plot of comparison 49: Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX), outcome: 49.8 Deaths.



Footnotes

(1) Calculations of events were done according to the percentages of FAS (Full Analysis Set) 213 patients in placebo group and 655 in CZP group. We did...
(2) Two deaths: one participant of hepatic neoplasm, and the other of cardiac arrest. One more died of peritonitis, cirrhosis, and general deterioration of...
(3) 1 participant died of myocardial infarction
(4) Two deaths in the CZP group: one case of sigmoid diverticulitis in a 73-year-old man with pancreatitis, and one of necrotising pneumonia, both deaths...
(5) 1 participant died of a rupture of a dissecting aortic aneurysm in the thoracic region, but UCB considered that in unlikely to have beeen related to study...
(6) Four deaths: 1 cerebral stroke, 1 myocardial necrosis, 1 cardiac arrest and 1 atrial fibrillation)
(7) 1 participant died by fracture and shock

We judged the quality of evidence for deaths at any dose of certolizumab pegol to be **moderate**. We downgraded the quality of evidence one level for imprecision due to the 95% confidence interval around the pooled effect including both harm and no harm.

Tuberculosis

We noted a significant increase in the number of cases of tuberculosis in both certolizumab pegol-treated groups: 10 participants (0.4%) in the certolizumab pegol 200 mg group and five (0.7%) in the certolizumab pegol 400 mg group, versus two and no cases in their respective placebo groups: 200 mg certolizumab pegol Peto OR 1.90 (95% CI 0.55 to 6.58),seven studies, involving 3538 participants (Analysis 50.20;); 400 mg certolizumab pegol Peto OR 4.55 (95% CI 0.71 to 29.11), three studies, involving 1179 participants (Analysis 50.21). The overall analysis with both doses (200 and 400 mg) did not reach statistical significance: Peto OR 1.91 (95% CI 0.61 to 5.96), seven studies, involving 4074 participants (Analysis 50.22). In Smolen 2009, five participants in the certolizumab pegol arms (three in certolizumab pegol 200 mg and two in 400 mg) developed tuberculosis (three from Russia, one each from Poland and Latvia). In NCT00993317 (200 mg certolizumab pegol) two participants developed tuberculosis. For this update, only five participants developed tuberculosis in the Emery 2015 study, three in the certolizumab pegol group and two in the placebo group.

We judged the quality of evidence for tuberculosis for 200 mg and 400 mg of certolizumab pegol to be to be **moderate**. We downgraded the quality of evidence one level for imprecision, due to the 95% confidence interval around the pooled effect including both harm and no harm.

Other infections

The types of different infections reported (pneumonitis, bacterial arthritis, mastitis, urinary tract infection, herpes viral, bacterial

peritonitis, and opportunistic infection) are presented in Data and analyses.

Upper respiratory tract infection was more frequent with 200 mg certolizumab pegol than in the placebo group (Peto OR 1.68, 95% CI 1.28 to 2.20), eight studies, involving 3608 participants (Analysis 50.34); and 400 mg certolizumab pegol (Peto OR 1.42, 95% CI 0.77 to 2.61), four studies, involving 1364 participants (Analysis 50.35).

We judged the quality of evidence for upper respiratory tract infection for 200 mg certolizumab pegol to be **high.**

We judged the quality of evidence for upper respiratory tract infection for 400 mg certolizumab pegol to be **moderate**. We downgraded the quality of evidence one level for imprecision, due to the 95% confidence interval around the pooled effect including both harm and no harm.

Nasopharyngitis was more frequent with both doses of certolizumab pegol than in the placebo group: 200 mg certolizumab pegol Peto OR 1.37 (95% CI 1.01 to 1.84) seven studies, involving 2553 participants (Analysis 50.44)); and 400 mg certolizumab pegol Peto OR 1.98 (95% CI 1.26 to 3.11), four studies, involving 1364 participants (Analysis 9.41). (Analysis 50.45)

We judged the quality of evidence for nasopharyngitis for 200 mg and 400 mg of certolizumab pegol to be **moderate**. We downgraded the quality of evidence one level for imprecision, due to the 95% confidence interval around the pooled effect including both harm and no harm.

Pain at the site of injection

Pain at the site of injection was not statistically significant compared with placebo: in the 200 mg certolizumab pegol-treated group (Peto OR 1.85, 95% CI 0.49 to 6.92), three studies, involving 1091 participants (Analysis 50.46); This analysis reported a High value of I^2. We explained this due to that the results of RAPID1 showed a very high values RR 4.60 whereas the remaining trial showed lowest values around RR of 0.05. Moreover the CI of RAPID1 did not overlap the remaining trials.

When we studied 400 mg certolizumab pegol-treated group we found (Peto OR 1.74, 95% CI 0.41 to 7.42), three studies, involving 1179 participants (Analysis 50.47). The wide CIs were due to the fact that, surprisingly, pain was not observed in any placebo group. Similar data were observed for local reactions at the injection site. We judged the quality of evidence pain for 200 mg and 400 mg of certolizumab pegol to be **high.**

Other adverse events

Hypertension was more frequent with both doses of certolizumab pegol than with placebo: 200 mg certolizumab pegol Peto OR 3.09 (95% CI 1.64 to 5.84), four studies, involving 1353 participants (Analysis 50.48); 400 mg certolizumab pegol: Peto OR 3.35 (95% CI 1.80 to 6.20), three studies, involving 1121 participants (Analysis 50.49).

We judged the quality of evidence for other adverse events for 200 mg and 400 mg of certolizumab pegol to be **high.**

The secondary events for headache, blood disorders, laboratory disorders, back pain, nausea/vomiting, urinary tract infections, pruritus and cough and others are described in detail in Data and analyses.

Despite the report from the EMA (www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001037/WC500069735.pdf), we could not extract more data on adverse events, because the information was disclosed as combined data without the number of events in each trial. Moreover, the adverse events were grouped by 'primary system organ class': cardiac disorders, endocrine disorders, neoplasms benign, malignant and unspecified (excluding cysts and polyps).

Pain (VAS assessment)

Participants' assessment of arthritis pain with a visual analogue scale (VAS) score (0 to 100 mm) improved at all doses and at all time points. At week 24, the overall mean difference (MD) was -21.07 (95% CI -23.59 to -18.55), four studies, involving 2064 participants (Analysis 52.1); and at week 52 the MD was -23.48 (95% CI -27.09 to -19.88), one study, involving 982 participants (Analysis 53.1).

We judged the quality of evidence for patients' assessment of arthritis pain with a VAS for 200 mg and 400 mg of certolizumab pegol to be **high.** .

Withdrawals due to lack of efficacy

There were more withdrawals "due to lack of efficacy" in placebo groups (39%) versus the certolizumab pegol groups (13%)

Withdrawals at any dose and at any follow-up due to lack of efficacy: RR 0.31 (95% CI 0.26 to 0.37), eight studies, involving 3433 participants(Analysis 54.1).

We judged the quality of evidence for withdrawals due to lack of efficacy at any dose and at any follow-up for certolizumab pegol to be **high.**

Assessment of heterogeneity

When we analysed the ACR50 at 24 weeks (Analysis 44.2) we found a low probability of statistical heterogeneity (I^2 = 0%). When we reviewed the demographics of Phase III studies (Table 2) we found similar proportions of men and women, similar mean ages, and similar baseline HAQ-Di. We only found differences in the mean disease duration in Fleischmann 2009 and Choy 2012, around 9.4 years compared with around six years in most arms of the other studies where data were available (with low heterogeneity, I^2 = 13%). Disease duration was not available for Smolen 2015; Yamamoto (a) 2014; Yamamoto (b) 2014 (I^2 = 6%, and an overall I^2 = 7%) (Analysis 56.5). Rheumatoid factor (RF) positivity varied from around 74% in the certolizumab pegol-treated participants in Weinblatt 2012 up to 100% in Fleischmann 2009. Similarly disease activity measures such as CRP and swollen joint counts, but not DAS-28 and HAQ-D1, were generally lower in Weinblatt 2012.

When we analysed the ACR50 at 52 weeks (Analysis 45.2) we found a high probability of statistical heterogeneity (I^2 = 84%). When we compared the new trials Atsumi 2016 and Emery 2015 with the previous trial Keystone 2008, we observed that the average period of persistent disease in the new trials is around four months, whereas for Keystone 2008 it is 6.1 years. Baseline HAQ-Di in Keystone 2008 and Emery 2015 is around 1.6 whereas in Atsumi 2016 it is around 1.1. Participants in Atsumi 2016 are MTX-naïve,

participants in Emery 2015 are DMARDS-naïve, whereas in Keystone 2008 participants were treated on average with 1.3 DMARDS.

However, despite these differences there were no compelling reasons for not combining the trial data for the most important variables.

Although we include 14 trials in this update, no more than seven trials were analysed in each forest plot, so we did not produce a funnel plot.

Subgroup analysis

We had planned subgroup analyses for the duration of the illness (approximately three years evolution), participants' sex, drug dose, administration and methodological quality, but only subgroup analysis of the dose of certolizumab pegol was performed. All Phase III trials were conducted in participants with a high mean duration of RA (from 6.1 to 9.5 years) and we could not obtain any data categorised by sex. All Phase III trials allowed previous DMARD treatment (mean from 1.2 to two years). All Phase III trials included in the meta-analysis were rated as high quality, and so we did not perform more subgroup analysis.

Sensitivity analysis

We have done a sensitivity analysis with the major outcome ACR50. In the previous version of this review we re-analysed quality (adequate sequence generation, good allocation concealment, adequate blinding, etc.) and did not show any changes. For this update we have more information about the quality of the trials from UCB, and we rated most trials as high quality, so we did not perform a sensitivity analysis based on quality. However, we sought heterogeneity by analysing for doses of certolizumab pegol, size, use of concomitant MTX, different populations (Japanese and Korean trials versus other populations) and by published versus unpublished trials, but found no statistical heterogeneity (Analysis 56.1; Analysis 56.2; Analysis 56.3; Analysis 56.4; Analysis 56.6). These analysis were performed for 24 weeks in our previous review and remain unchanged because the new trials included in this update were conducted to 52 weeks. When we analysed for the same categories we did find heterogeneity from the Keystone 2008 in all the issues that were tested (Analysis 57.1; Analysis 57.2; Analysis 57.3; Analysis 57.4; Analysis 57.5).

Finnally we analysed imputing missing values in the same proportion as reported ACR50% , imputing the 50 % of ACR50 % and the results are robust for ACR50 200 mg to 24 weeks RR 3.34 (95% CI 2.68 to 4.17) and RR 1.17 (95% CI 1.04 to 1.32). Only when we checked the worst case (all the missing values did not reach ACR50 in certolizumab pegol) and did ACR50 in placebo the results were favouring to placebo RR 0.47 (95% CI 0.43 to 0.52). Analysis 56.7; Analysis 56.8; Analysis 56.9.

DISCUSSION

Summary of main results

This review evaluates the benefits and harms of certolizumab pegol for the treatment of people with RA when compared to placebo, using RCTs with at least three months of follow-up.

The results and conclusions did not change from the previous version of the review. There is low-level evidence from randomised controlled trials that certolizumab pegol, alone or combined with methotrexate, is beneficial in the treatment of RA: it improved the American College of Rheumatology ACR50 (pain, function and other symptoms of RA), health-related quality of life, and the chance of remission of RA, reduced joint damage as seen on the x-ray, and increased serious adverse events. Fewer people stopped taking their treatment, but most of them stopped due to serious adverse events. Adverse events were more frequent with active treatment. We found a potential risk of serious adverse events.

We found 14 studies, three more than in the previous version of the review. The duration of follow-up was from 12 to 52 weeks and the range of doses of certolizumab pegol varied from 50 to 400 mg given subcutaneously.

Certolizumab pegol at the standard dose (200 mg) was shown to be clinically effective at 12, 24 and 52 weeks. However the data from 52 weeks should be interpreted with caution, because a large number of participants deemed not to be achieving a sufficient response were withdrawn at week 24.

Important clinical differences between placebo and certolizumab pegol were observed for measures of disease activity, in favour of certolizumab pegol. The differences were both statistically significant and clinically important for the participant-reported outcomes ACR50, HAQ, and SF-36 (physical (PCS) and mental (MCS) component summary scores), and for structural damage measures. Changes in HAQ at 24 weeks with 200 mg certolizumab pegol were -0.35 (mean changes in HAQ greater than -0.22 are clinically meaningful). In addition, the results with SF-36 (physical and mental components) can be considered relevant because in people with RA improvements in the SF-36 PCS and HAQ-DI are associated with improved work productivity and reduced long-term disability, healthcare use, costs and mortality (Hazes 2010).

All certolizumab pegol groups showed improvements in radiological outcomes compared to placebo, measured as the mean changes from baseline. There was a clear radiological benefit, although it should be borne in mind that radiographic changes occur in a relatively small proportion of people with RA over the duration of research studies, and the changes did not represent a clinically meaningful benefit for participants.

Serious adverse events were more frequent in the certolizumab pegol groups.

We observed more withdrawals in participants treated with certolizumab pegol. Participants in the placebo group were more likely to discontinue treatment, due to lack of beneficial effect, but more participants withdrew from the certolizumab pegol group, due to adverse reactions. The most frequent side effects were infections and nasopharyngitis. Unfortunately, the newer clinical trials do not provide data on hypertension. However, as reported in the previous version, hypertension is increased in the certolizumab pegol group.

In the previous version we stated we would compare our data with data from the EMA documents. We requested access to the drug company submissions to the EMA for marketing authorisation of certolizumab pegol. Our request was denied, despite an appeal. The EMA stated that "...in the course of emerging legal proceedings before the General Court of the European Union, the Agency has been ordered to suspend the implementation of the certain

decisions granting access to documents submitted by marketing authorisation holders of medicinal products".

Mortality was increased with certolizumab pegol. These differences did not achieve statistical significance but it should be noted that there was only one death in the placebo group compared with 14 in the certolizumab pegol group. Death was primarily related to cardiovascular events, as reported by Bykerk 2013. However, treatment with anti-TNF has been shown to reduce cardiovascular events in people with RA (Roubille 2015).

We found an increased risk of serious infections with certolizumab pegol. This risk is recognised with anti-TNFs, both in randomised trials and in observational studies (FDA 2013).

Contrary to the findings of Lopez-Olivo 2012, we did not find an increased risk of malignancies or lymphoma, for 200 mg or for 400 mg of certolizumab pegol.

We have found discordance between the number of cases of tuberculosis reported in ClinicalTrials.org and the one instance reported in Emery 2015. Despite the difference, the frequency of tuberculosis has decreased in recent clinical trials. This could be due to several reasons. In 2007 the WHO introduced stricter tuberculosis screening guidelines, considering a positive purified protein derivative (PPD) test 5 mm or more (previously between 10 and 20 mm according to each national guideline), and tuberculosis prophylaxis was recommended if active tuberculosis was ruled out. Furthermore, fewer participants from areas of high tuberculosis prevalence have been recruited, and latent tuberculosis is generally an exclusion criterion.

The results and conclusions did not change from the previous review.

Overall completeness and applicability of evidence

We have included all available RCTs for certolizumab pegol in people with RA, with a September 2016 search date. This updated review provides confirmatory evidence of the benefit of certolizumab pegol for people with RA.

It is important to state that three studies had a follow-up of 52 weeks, and in two of them non-responders were withdrawn at week 24. Thus there are important uncertainties about sustained effects in a disease with a lifelong course and the need for therapy over many years. An additional note of caution relates to the population selection in terms of significant co morbidities and exclusion of people with previous malignancy, for example.

In all trials except the Smolen 2015 trial (without a clear definition of its inclusion and exclusion criteria in ClinicalTrials.org), people with previous neoplasia, any risk of infectious disease, previous tuberculosis, or prior treatment with any TNFα inhibitor were excluded. In the Yamamoto (a) 2014, Yamamoto (b) 2014 and NCT00993317) trials, people with New York Heart Association (NYHA) class III or IV heart failure were also excluded. Moreover, in the Keystone 2008 trial “Patients who, in the investigator’s opinion, were at a high risk of infection" were excluded, as were those who had a history of malignancy, demyelinating disease, blood dyscrasias, or severe, progressive, and/or uncontrolled renal, hepatic, haematologic, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, or cerebral disease”. Thus, whilst it is clear that certolizumab pegol is beneficial and has an acceptable safety profile in people selected for clinical trials, careful clinical judgement is needed to ensure benefits in routine care, particularly in people susceptible to infections such as those with chronic respiratory diseases.

We only have information about the comparison between certolizumab pegol and placebo. There is no head-to-head comparison between certolizumab pegol and other anti-TNFs. For this reason current evidence does not support the use of certolizumab pegol over another anti-TNF.

Quality of the evidence

The quality of the evidence found in the trials included in this review was high to moderate. Studies had high standards for treatment allocation, concealment, blinding, and attrition bias. Other GRADE considerations for downgrading are: imprecision, indirectness and inconsistency or other bias.

Despite differences in the importance of the outcomes (higher for ACR50, HAQ and DAS remission, and lower for radiological changes), we rated the quality of the evidence as high for all the outcomes except for the HAQ, radiological changes and all withdrawals, which we rated as moderate quality.

Outcome measures in favour of certolizumab pegol were statistically significant in both random-effects and fixed-effect models. We chose to apply a random-effects model, although statistical heterogeneity was low. Clinical heterogeneity, however, was substantial (for example, with varying follow-up times, doses, use of methotrexate) and, as expected, pooling resulted in wide confidence intervals.

Major outcomes

Summary of findings for the main comparison for certolizumab pegol 200 mg, structured according to the GRADE system (GRADE Handbook), showed:

1) We judged the quality of evidence for the primary outcome **ACR 50% improvement at** 24 weeks to be **high.**

2) We judged the quality of evidence for the primary outcome **HAQ** at 24 weeks to be **moderate**. We downgraded the quality of evidence by one level, due to a high risk of attrition bias (per protocol analysis).

3) We judged the quality of evidence for the primary outcome **Proportion of participants achieving DAS < 2.6 (remission)** at 24 weeks to be **high**.

4) We judged the quality of evidence for the primary outcome **Erosion score** (ES), at 24 weeks to be **moderate**. We downgraded the quality of evidence by one level, due to a high risk of attrition bias (per protocol analysis).

5) We judged the quality of evidence for the primary outcome **Serious adverse events** at 24 weeks to be **high**.

6) We judged the quality of evidence for the primary outcome **Withdrawals**, at 24 weeks to be **moderate.** We downgraded the quality of evidence
one level for inconsistency, due to heterogeneity (not all the confidence intervals overlap and I^2 is 79%).

7) We judged the quality of evidence for the primary outcome **Withdrawals due to adverse events** at 24 weeks to be **high**.

Minor outcomes

8) We judged the quality of evidence for the secondary outcome **ACR20** at 24 weeks to be **high**.

9) We judged the quality of evidence for the secondary outcome **ACR70** at 24 weeks to be **high**.

10) We judged the quality of evidence for **Tuberculosis** for 200 mg and 400 of certolizumab pegol to be to be **moderate**. We downgraded the quality of evidence one level for imprecision, due to the 95% confidence interval around the pooled effect including both harm and no harm.

11) We judged the quality of evidence for **Death** for any dose of certolizumab pegol to be **moderate**. We downgraded the quality of evidence one level for imprecision, due to the 95% confidence interval around the pooled effect including both harm and no harm.

12) We judged the quality of evidence for the secondary outcome **Withdrawals due to lack of efficacy** to be **high**.

Potential biases in the review process

This updated review has fewer limitations than the earlier version, primarily because key data from a greater number of studies, including key study quality data, were available either as published reports or directly from the pharmaceutical company. From 14 included trials, 12 with over 5400 participants reported benefits and 14 trials reported safety, providing a substantial evidence base. We lacked detail that may have been available in submissions to the EMA as part of this drug's marketing authorisation and we also did not have access to study protocols, so we were not able to judge whether there was a concern about selective reporting. Lack of availability of detailed study reports with individual patient data denied us the opportunity of presenting a richer description of adverse events, particularly serious adverse reactions.

Agreements and disagreements with other studies or reviews

The NICE 2009 and EMA 2009 reports, performed as systematic reviews, have shown results quite similar to those in our review.

The meta-analysis by Singh 2011 described the adverse effects of nine biologics and included RCTs, controlled clinical trials (CCTs) and open-label extensions (OLEs), showing similar overall results. Moreover, Singh 2011 found similar results with certolizumab pegol for serious adverse events and serious infections, but failed to find an increased rate of withdrawals due to adverse events. In this study the risk of serious infections was about four times higher for certolizumab pegol and the authors performed sensitivity analyses using different models to explain the results. However, the significant differences between certolizumab pegol and five other biologics as determined in the standard dose model (main model) persisted in the unadjusted and dose-adjusted models for each comparison, with the minor exception of certolizumab pegol versus golimumab.

Zhou 2014 did not find differences in adverse events in a meta-analysis of nine RCTs of certolizumab pegol in RA. Only six trials for adverse events were included in this systematic review. The reason for the difference from our results is that Zhou 2014 only include adverse events until week 24. However, there was agreement in ACR response rate at 24 weeks.

AUTHORS' CONCLUSIONS

Implications for practice

This review confirms that certolizumab pegol compared with placebo is clinically beneficial, improving ACR50, quality of life and increasing the chance of remission. In addition certolizumab pegol compared with placebo reduces the risk of radiographic damage. There is a potential risk of serious adverse events, including hypertension and tuberculosis in susceptible individuals, which should be borne in mind when considering certolizumab pegol. There was no direct evidence comparing certolizumab with other TNF inhibitors.

There is a moderate to high certainty of evidence, obtained from randomised controlled trials, that certolizumab pegol, alone or combined with methotrexate, is beneficial in the treatment of RA. It improved ACR50 (pain, function and other symptoms of RA), health-related quality of life, and the chance of remission of RA, reduced joint damage as seen on the x-ray, but increased serious adverse events. Fewer people stopped taking their treatment, but most of those who did stopped because of serious adverse events. Adverse events were more frequent with active treatment. We found a clinically but not statistically significant risk of serious adverse events.

Implications for research

Treatment options for RA have expanded considerably in recent years and include biologic agents targeting a variety of elements of the inflammatory process. It is important that we undertake studies to compare the new drugs that have been shown to be effective in clinically-relevant populations.

We must emphasize that complete remission is the major target in clinical practice, and it should be considered as an outcome for future clinical trials using ACR/EULAR remission criteria (Felson 2011).

New agents continue to target people who have failed to respond to methotrexate. Given that there are a number of biologics that have been found to be effective in this patient group, ethics review boards need to consider whether it is justifiable to undertake studies of new agents for this population that compare the effectiveness to placebo or to background methotrexate.

Longer-term studies and observational data are important for the assessment of longer-term drug toxicity and rarer adverse events.

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REFERENCES

References to studies included in this review

Atsumi 2016 *{published data only}*

Atsumi T, Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Tanaka Y, et al. Baseline parameters identified in early, methotrexate-naive rheumatoid arthritis patients with better outcomes with certolizumab pegol+methotrexate compared to placebo+methotrexate: Post-hoc analyses of c-opera, a randomized, controlled, phase 3 study. Annals of the Rheumatic Diseases.Conference: Annual European Congress of Rheumatology of the European League Against Rheumatism, EULAR 2015 Rome Italy. 10 - 13 June 2015. 2015; Vol. 74:716-7.

Atsumi T, Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Tanaka Y, et al. Clinical benefit of 1-year certolizumab pegol treatment in MTX-naïve, early rheumatoid arthritis patients is maintained after discontinuation up to 1 year. Arthritis and Rheumatology.Conference: American College of Rheumatology/ Association of Rheumatology Health Professionals Annual Scientific Meeting, ACR/ARHP 2015 San Francisco, CA United States. 6 - 11 November 2015. 2015; Vol. 67.

* Atsumi T, Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Tanaka Y, et al. The first double-blind, randomised, parallel-group certolizumab pegol study in methotrexate-naive early rheumatoid arthritis patients with poor prognostic factors, C-OPERA, shows inhibition of radiographic progression. *Annals of the Rheumatic Diseases* 2016;**75**(1):75-83.

Atsumi T, Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Tanaka Y, et al. The first early rheumatoid arthritis, certolizumab pegol, multicenter, double-blind, randomized, parallel-group study: C-Opera, in patients fulfilling the 2010 ACR/EULAR classification criteria, demonstrates inhibition of joint damage progression. Annals of the Rheumatic Diseases.Conference: Annual European Congress of Rheumatology of the European League Against Rheumatism, EULAR 2014 Paris France. 11 - 14 June 2014. 2014; Vol. 73.

Atsumi T, Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Tanaka Y, et al. The first, multicenter, double-blind, randomized, parallel-group study of certolizumab pegol in early rheumatoid arthritis demonstrates inhibition of joint damage progression. Arthritis and Rheumatology.Conference: 2014 ACR/ARHP Annual Meeting Boston, MA United States. 14 - 19 November 2014. 2014; Vol. 66:S1078-9.

CDP870-004 2001 *{published and unpublished data}*

Emery P, Smolen J, Choy E, et al. CDP870 a novel, humanised tumour necrosis factor alpha inhibitor improves HRQOL. Late breaking abstract. European League Against Rheumatism Annual Conference. 2002.

* European Medicines Agency. Assesment report for Cimzia. Procedure No EMEA/H/C/001037. www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001037/WC500069735.pdf. London, 2009 (accessed 3rd July 2017):1-47. [Procedure No.EMEA/H/C/001037]

Keystone E, Choy E, Kalden J, Klareskog, Sany J, Smolen J, et al. CDP870, A novel pegylated, humanized TNF-alpha inhibitor, is effective in treating the signs and symptoms of rheumatoid arthritis (RA). Abstract to Rheumatology annual scientific meeting [abstract # LB-3]. 2001.

Choy 2002 *{published data only}*

* Choy EH, Hazleman B, Smith M, Moss K, Lisi L, Scott DG, et al. Efficacy of a novel pegylated humanized anti-TNF fragment (CDP870) in patients with rheumatoid arthritis: a phase II double-blinded, randomized, dose-escalating trial. *Rheumatology (Oxford)* 2002;**41**(10):1133-7.

Choy 2012 *{published data only}*

* Choy E, McKenna F, Vencovsky J, Valente R, Goel N, Vanlunen B, et al. Certolizumab pegol plus MTX administered every 4 weeks is effective in patients with RA who are partial responders to MTX. *Rheumatology (Oxford)* 2012;**51**(7):1226-34.

UCB. Clinical Study Summary Study No.: CDP870-014. www.ucb.com/_up/ucb_com_patients/documents/C87032_CSS_20080608.pdf 2008 (accessed 3rd July 2017).

Emery 2015 *{published data only}*

Emery P, Bingham C, Burmester GR, Bykerk VP, Furst D, Mariette X, et al. Improvements in workplace and household productivity following 52 weeks of treatment with certolizumab pegol in combination with methotrexate in DMARD-naive patients with severe, active and progressive rheumatoid arthritis: Results from the c-early randomized, double-blind, controlled phase 3 study. Value in Health.Conference: ISPOR 18th Annual European Congress Milan, Italy.Conference. 7 - 11 November 2015. 2015; Vol. 18:7.

Emery P, Bingham CO, Burmester G-R, Bykerk VP, Furst DE, Mariette X, et al. Improvements in patient-reported outcomes and workplace and household productivity following 52 weeks of treatment with certolizumab pegol in combination with methotrexate in DMARD-naive early rheumatoid arthritis patients: Results from the C-early randomized, double-blind, controlled phase 3 study. Annals of the Rheumatic Diseases.Conference: Annual European Congress of Rheumatology of the European League Against Rheumatism, EULAR 2015 Rome Italy. 10 - 13 June 2015. 2015; Vol. 74:712-3.

Emery P, Bingham CO, Burmester G-R, Bykerk VP, Furst DE, Mariette X, et al. SAT0165 Improvements in patient-reported outcomes and workplace and household productivity following 52 weeks of treatment with certolizumab pegol in combination with methotrexate in dmard-naïve early rheumatoid arthritis patients: results from the C-Early randomized, double-blind, controlled phase 3 study. *Annals of the Rheumatic Diseases* 2015;**74**(Suppl 2):712-3.

* Emery P, Bingham CO, Burmester G-R, Bykerk VP, Furst DE, Mariette X, et al. sSAT0164 The first study of certolizumab pegol in combination with methotrexate in dmard-naïve early rheumatoid arthritis patients led to Sustained clinical response and inhibition of radiographic progression at 52 weeks: The C-Early randomized, double-blind, controlled phase 3 study. *Annals of the Rheumatic Diseases* 2015;**74**(Suppl 2):712.

Weinblatt M, Bingham C, Burmester G, Bykerk V, Furst DE, Mariette X, et al. Early response as a predictor of long-term remission in DMARD-naive patients with severe, active and progressive rheumatoid arthritis treated with certolizumab pegol in combination with methotrexate. Arthritis and Rheumatology.Conference: American College of Rheumatology/ Association of Rheumatology Health Professionals Annual Scientific Meeting, ACR/ARHP 2015 San Francisco, CA United States. 6 - 11 November 2015. 2015; Vol. 67.

Weinblatt M, Bingham C, Burmester G, Bykerk VP, Furst DE, Mariette X, et al. Certolizumab pegol in combination with methotrexate in DMARD-naive patients with active, severe, progressive rheumatoid arthritis: Results from a randomized, double-blind, controlled phase 3 study. Arthritis and Rheumatology.Conference: American College of Rheumatology/ Association of Rheumatology Health Professionals Annual Scientific Meeting, ACR/ARHP 2015 San Francisco, CA United States. 6 - 11 November 2015. 2015; Vol. 67.

Fleischmann 2009 *{published data only}*

Fleischmann D, Mason D, Cohen S. Efficacy and safety of certolizumab pegol monotherapy in patients with rheumatoid arthritis failing previous DMARD therapy. *Annals of the Rheumatic Diseases* 2007;**66 Suppl II**:169.

Fleischmann R, Keininger DL, Tahiri-Fitzgerald E, Mease P. Certolizumab pegol monotherapy 400mg every 4 weeks improves physical functioning and reduces pain in patients with rheumatoid arthritis Who have previously failed DMARD therapy. Program and abstracts of the European League Against Rheumatism (EULAR) Annual Meeting; Barcelona, Spain 13-16 June [Abstract #0148]. 2007.

* Fleischmann R, Vencovsky J, Van Vollenhoven RF, Borenstein D, Box J, Coteur G, et al. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease modifying antirheumatic therapy: the FAST4WARD study. *Annals of the Rheumatic Diseases* 2009;**68**(6):805-11.

Keystone E, Mason D, Fleischmann R. Certolizumab pegol 400 mg every 4 weeks as monotherapy rapidly reduces disease activity in active rheumatoid arthritis. Program and abstracts of the American College of Rheumatology (ACR) 71st Annual Meeting; November 6 - 11; Boston, Massachusetts. [Abstract #277]. 2007.

Strand V, Brown M, Purcaru O, Richard L. Certolizumab pegol monotherapy improves productivity in patients with active rheumatoid arthritis: results from a phase III randomized controlled trial. Program and abstracts of the European League Against Rheumatism (EULAR) Annual Meeting; Barcelona, Spain 13 - 16 June [Abstract #0478]. 2007.

Strand V, Keininger D, Tahiri-Fitzgerald E, Fleischmann R. Certolizumab pegol monotherapy 400mg every 4 weeks improves health-related quality of life and relieves fatigue in patients with rheumatoid arthritis who have previously failed DMARD therapy. Program and abstracts of the European League Against Rheumatism (EULAR) Annual Meeting; Barcelona, Spain 13 - 16 June [Abstract #0205]. 2007.

Keystone 2008 *{published data only}*

Curtis JR, Chen L, Luijtens K, Navarro-Millan I, Goel N, Gervitz L, et al. Dose escalation of certolizumab pegol from 200 mg to 400 mg every other week provides no additional efficacy in rheumatoid arthritis: an analysis of individual patient-level data. *Arthritis and Rheumatism* 2011;**63**(8):2203-8.

Curtis JR, Luijtens K, Kavanaugh A. Predicting future response to certolizumab pegol in rheumatoid arthritis patients: features at 12 weeks associated with low disease activity at 1 year. *Arthritis Care Research (Hoboken)* 2012;**64**(5):658-67.

Haraoui B, Bykerk VP, Van Vollenhoven R, De Longueville M, Luijtens K, Ralston P, et al. Analysis of pooled data from two randomized controlled trials and their open-label extensions: Long-term safety in rheumatoid arthritis before and after certolizumab pegol dose increase/decrease. Arthritis and Rheumatology.Conference: 2014 ACR/ARHP Annual Meeting Boston, MA United States 14 - 19 N0vember 2014. 2014; Vol. 66:S199.

* Keystone E, Heijde D, Mason D Jr, Landewé R, Vollenhoven RV, Combe B, et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis and Rheumatism* 2008;**58**(11):3319-29.

Keystone E, Landewé R, Van Vollenhoven R, Combe B, Strand V, Mease P, et al. 5-Year results from the RAPID 1 trial and open-label extension: long-term safety and efficacy of certolizumab pegol in combination with methotrexate in the treatment of rheumatoid arthritis. *Annals of the Rheumatic Diseases* 2013;**72**(12):A228-9. [10.1136/annrheumdis-2013-203695. [Epub ahead of print]]

Keystone E, Landewé R, Van Vollenhoven R, Combe B, Strand V, Mease P, et al. Long-term safety and efficacy of certolizumab pegol in combination with methotrexate in the treatment of rheumatoid arthritis: 5-year results from a 52-week randomized controlled trial and open-label extension study. Journal of Rheumatology Conference: 69th Annual Meeting of the Canadian Rheumatology Association, CRA 2014 Whistler, BC Canada. 24 February - 1 March 2014. 2014; Vol. 41:7.

Keystone E, Landewé R, Van Vollenhoven R, Combe B, Strand V, Mease P, et al. Long-term safety and efficacy of certolizumab pegol in combination with methotrexate in the treatment of rheumatoid arthritis: 5-year results from the RAPID 1 trial and open-label extension. *Annals of the Rheumatic Diseases* 2013;**65**:S988-9. [PUBMED: 23918037]

Keystone E, Mason D, Combe B. The anti-TNF certolizumab pegol in combination with methotrexate is significantly more effective than methotrexate alone in the treatment of patients with active rheumatoid arthritis: 1-year results from the RAPID 1 study. Program and abstracts of the American College of Rheumatology (ACR) 71st Annual Meeting; 6 - 11 November 2007; Boston, Massachusetts [Abstract #700]. 2007.

Keystone EC, Combe B, Smolen J, Strand V, Goel N, van Vollenhoven R, et al. Sustained efficacy of certolizumab

pegol added to methotrexate in the treatment of rheumatoid arthritis: 2-year results from the RAPID 1 trial. *Rheumatology (Oxford)* 2012;**51**:1628-38.

NCT00175877. 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. clinicaltrials.gov/ct2/show/NCT00175877 (first received 9th September 2005).

Strand V, Keininger DL, Tahiri-Fizgerald E. Certolizumab pegol results in clinically meaningful improvements in physical function and health-related quality of life in patients with active rheumatoid arthritis despite treatment with methotrexate. Program and abstracts of the American College of Rheumatology (ACR) 71st Annual Meeting; 6 - 11 November 2007; Boston, Massachusetts. [Abstract #946]. 2007.

Strand V, Mease P, Burmester G, Nikaï E, Coteur G, Vollenhoven R, et al. Rapid and sustained improvements in health-related quality of life, fatigue, and other patient-reported outcomes in rheumatoid arthritis patients treated with certolizumab pegol plus methotrexate over 1 year: results from the RAPID 1 randomized controlled trial. Arthritis Research & Therapy 2009; Vol. 11, issue 6:R170.

UCB. Preliminary results suggest certolizumab pegol plus methotrexate is effective in reducing signs and symptoms of rheumatoid arthritis in patients refractory to methotrexate. Results from the RAPID 1 Study. Abstract number: OPO016. EULAR 2007. 2007.

Van der Heijde D, Keystone EC, Curtis JR, Landewé RB, Schiff MH, Khanna D, et al. Timing and magnitude of initial change in disease activity score 28 predicts the likelihood of achieving low disease activity at 1 year in rheumatoid arthritis patients treated with certolizumab pegol: a post-hoc analysis of the RAPID 1 trial. *Journal of Rheumatology* 2012;**39**(7):1326-33.

Van der Heijde D, Strand V, Keystone E, Landewé R. Inhibition of radiographic progression by lyophilized certolizumab pegol added to methotrexate in comparison with methotrexate alone in patients with rheumatoid arthritis: the RAPID 1 trial. Program and abstracts of the American College of Rheumatology (ACR) 71st Annual Meeting; November 6-11; Boston, Massachusetts. [Abstract #940]. 2007.

Van der Heijde D, Weinblatt M, Landewé R, Goel N, Wells A, Fleischmann R. Inhibition of progression of structural damage by week 16 with certolizumab pegol: Results from the RAPID trials. *Arthritis and Rheumatism* 2008;**58**(9 Suppl):529-30 .

NCT00993317 *{published data only}*

* NCT00993317. A study of CDP870 as add-on medication to methotrexate (MTX) in patients with rheumatoid arthritis. clinicaltrials.gov/ct2/show/study/NCT00993317 (firs treceived 9th October 2009).

Smolen 2009 *{published data only}*

Haraoui B, Bykerk VP, Van Vollenhoven R, De Longueville M, Luijtens K, Ralston P, et al. Analysis of pooled data from two randomized controlled trials and their open-label extensions: Long-term safety in rheumatoid arthritis before and after certolizumab pegol dose increase/decrease. Arthritis and Rheumatology.Conference: 2014 ACR/ARHP Annual Meeting Boston, MA United States 14 - 19 N0vember 2014. 2014; Vol. 66:S199.

Kavanaugh A, Smolen JS, Emery P, Purcaru O, Keystone E, Richard L, et al. Effect of certolizumab pegol with methotrexate on home and work place productivity and social activities in patients with active rheumatoid arthritis. *Arthritis and Rheumatism* 2009;**61**(11):1592-600.

Landewé R, Strand V, Smolen J, Van der Heijde D. Liquid formulation certolizumab pegol with methotrexate decreases progression of structural joint damage in rheumatoid arthritis patients: the RAPID 2 study. Program and abstracts of the American College of Rheumatology (ACR) 71st Annual Meeting; 6 - 11 November 2007; Boston, Massachusetts. [Abstract #696]. 2007.

Mease P, Mason D, Kavanaugh A, Smolen J. Efficacy and rapid response of certolizumab pegol liquid formulation in combination with methotrexate (MTX) in patients with active rheumatoid arthritis despite MTX therapy: results from the RAPID 2 study. Program and abstracts of the American College of Rheumatology (ACR) 71st Annual Meeting; 6 - 11 November 2007; Boston, Massachusetts. [Abstract #941]. 2007.

Schiff M, Keininger DL, Tahiri-Fitzgerald E. Certolizumab pegol added onto methotrexate improves physical functioning and reduces pain in patients with rheumatoid arthritis who have an incomplete response to methotrexate: data from rapid 2. Program and abstracts of the European League Against Rheumatism (EULAR) Annual Meeting; Barcelona, Spain 13 - 16 June [Abstract #0200]. 2007.

Smolen J, Brzezicki J, Mason D, Kavanaugh A. Efficacy and safety of certolizumab pegol in combination with methotrexate (mtx) in patients with active rheumatoid arthritis despite MTX therapy: results from the Rapid 2 study. Program and abstracts of the European League Against Rheumatism (EULAR) Annual Meeting; Barcelona, Spain 13 - 16 June [Abstract #0202]. 2007.

* Smolen JS, Landewe RB, Mease PJ, BrzezickiJ, Mason D, Luijtens K, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. *Annals of the Rheumatic Diseases* 2009;**68**:797-804.

Smolen JS, Van Vollenhoven R, Kavanaugh A, Strand V, Vencovsky J, Schiff M, et al. Certolizumab pegol plus methotrexate 5-year results from the rheumatoid arthritis prevention of structural damage (RAPID) 2 randomized controlled trial and long-term extension in rheumatoid arthritis patients. *Arthritis Research & Therapy* 2015;**17**:245.

Strand V, Keininger DL, Tahiri-Fizgerald E. Certolizumab pegol results in clinically meaningful improvements in physical function and health-related quality of life in patients with active rheumatoid arthritis despite treatment with methotrexate. Program and abstracts of the European League Against Rheumatism (EULAR) Annual Meeting; Barcelona, Spain 13 - 16 June 2007 [Abstract #0335]. 2007.

Strand V, Smolen JS, Van Vollenhoven RF, Mease P, Burmester GR, Hiepe F, et al. Certolizumab pegol plus methotrexate provides broad relief from the burden of rheumatoid arthritis: analysis of patient-reported outcomes from the RAPID 2 trial. *Annals of the Rheumatic Diseases* 2011;**70**(6):996-1002.

Smolen 2015 *{published data only}*

NCT00674362. Rheumatoid arthritis (RA) moderate to low disease activity study (CERTAIN). clinicaltrials.gov/ct2/show/NCT00674362 (first received 5th May 2008).

Smolen JS, Emery P, Ferraccioli G, Samborski W, Berenbaum F, Davies O, et al. Maintenance of remission in rheumatoid arthritis patients with low-moderate disease activity following withdrawal of certolizumab PEGOL treatment: Week 52 results from the certain study. *Annals of the Rheumatic Disease* 2013;**71 Suppl 3**:361.

* Smolen JS, Emery P, Ferraccioli GF, Samborski W, Berenbaum F, Davies OR, et al. Certolizumab pegol in rheumatoid arthritis patients with low to moderate activity: the CERTAIN double-blind, randomised, placebo-controlled trial. Annals of the Rheumatic Diseases 2015; Vol. 74, issue 5:843-50. [DOI: 10.1136/annrheumdis-2013-204632]

Smolen JS, Van Vollenhoven R, Kavanaugh A, Strand V, Vencovsky J, Schiff M, et al. Certolizumab pegol plus methotrexate 5-year results from the rheumatoid arthritis prevention of structural damage (RAPID) 2 randomized controlled trial and long-term extension in rheumatoid arthritis patients. *Arthritis Research & Therapy* 2015;**17**:245.

Weinblatt 2012 *{published data only}*

Pope J, Bingham CO 3rd, Fleischmann RM, Dougados M, Massarotti EM, Wollenhaupt J, et al. Impact of certolizumab pegol on patient-reported outcomes in rheumatoid arthritis and correlation with clinical measures of disease activity. *Arthritis Research & Therapy* 2015;**17**:343.

* Weinblatt ME, Fleischmann R, Huizinga TW, Emery P, Pope J, Massarotti EM, et al. Efficacy and safety of certolizumab pegol in a broad population of patients with active rheumatoid arthritis: results from the REALISTIC phase IIIb study. *Rheumatology (Oxford)* 2012;**51**:2204-14.

Weinblatt ME, Fleischmann R, Van Vollenhoven RF, Emery P, Huizinga TW, Cutolo M, et al. Twenty-eight-week results from the REALISTIC phase IIIb randomized trial: efficacy, safety and predictability of response to certolizumab pegol in a diverse rheumatoid arthritis population. *Arthritis Research & Therapy* 2015;**17**:325. [DOI: 10.1186/s13075-015-0841-9]

Yamamoto (a) 2014 *{unpublished data only}*

NCT00791921. Efficacy confirmation trial of CDP870 without coadministration of methotrexate (MTX) in Japanese rheumatoid arthritis (RA). clinicaltrials.gov/show/NCT00791921 (first received 14 November 2008).

NCT00850343. Long-term treatment study of certolizumab pegol without coadministration of methotrexate in Japanese rheumatoid arthritis (RA) patients. clinicaltrials.gov/ct2/show/NCT00850343?term=NCT00850343&rank=1 (first received 23rd February 2009).

Takeuchi T, Yamamoto K, Yamanaka H, Ishiguro N, Tanaka Y, Eguchi K, et al. Better clinical responses seen early with the loading dose of certolizumab pegol are maintained until one year. Annals of the Rheumatic Diseases.Conference: Annual European Congress of Rheumatology of the European League Against Rheumatism, EULAR 2014 Paris France. 11 - 14 June 2014. 2014; Vol. 73.

Tanaka Y, Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Eguchi K, et al. Long-term efficacy and safety of certolizumab pegol in Japanese rheumatoid arthritis patients who could not receive methotrexate: 52-week results from an open-label extension of the HIKARI study. Modern Rheumatology 2013; Vol. 24, issue 5:725-33. [DOI: 10.3109/14397595.2013.865822]

* Yamamoto, Kazuhiko, Takeuchi, Tsutomu, Yamanaka, Hisashi, et al. Efficacy and safety of certolizumab pegol without methotrexate co-administration in Japanese patients with active rheumatoid arthritis: The HIKARI randomized, placebo-controlled trial. *Modern Rheumatology* 2014;**24**:552-560.

Yamanaka H, Yamamoto K, Takeuchi T, Ishiguro N, Tanaka Y, Eguchi K, et al. AB0469. Improved physical function, pain, and health related quality of life with certolizumab pegol in Japanese rheumatoid arthritis patients without methotrexate co-administration:results from the Hikari study. *Annals of the Rheumaic Diseases* 2013;**71 Suppl 3**:664.

Yamanaka H, Yamamoto K, Takeuchi T, Ishiguro N, Tanaka Y, Eguchi K, et al. Certolizumab pegol improved physical function and heath related quality of life in patients with active rheumatoid arthritis who could not be treated with methotrexate: results form HIKARI study. *Modern Rheumatology* 2012;**22 Suppl ll**:S83.

Yamamoto (b) 2014 *{published data only}*

NCT00791999. Efficacy confirmation trial of CDP870 as add-on medication to methotrexate (MTX) in Japanese rheumatoid arthritis (RA). clinicaltrials.gov/ct2/show/study/NCT00791999?term=NCT00791999&rank=1 (first received 14th November 2008).

Takeuchi T, Yamamoto K, Yamanaka H, Ishiguro N, Tanaka Y, Eguchi K, et al. Better clinical responses seen early with the loading dose of certolizumab pegol are maintained until one year. Annals of the Rheumatic Diseases.Conference: Annual European Congress of Rheumatology of the European League Against Rheumatism, EULAR 2014 Paris France. 11 - 14 June 2014. 2014; Vol. 73.

Tanaka Y, Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Eguchi K, et al. Long-term efficacy and safety of certolizumab pegol in Japanese rheumatoid arthritis patients with an inadequate response to methotrexate: 52-week results from an open-label extension of the J-RAPID study. *Modern Rheumatology* 2014;**24**(5):734-43.

* Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Tanaka Y, Eguchi K, et al. Efficacy and safety of certolizumab pegol plus methotrexate in Japanese rheumatoid arthritis patients

with an inadequate response to methotrexate: the J-RAPID randomized, placebo-controlled trial. *Modern Rheumatology* 2014;**24**(5):715-24. [DOI: 10.3109/14397595.2013.864224]

Yamanaka H, Yamamoto K, Takeuchi T, Ishiguro N, Tanaka Y, Eguchi K, et al. AB0468 Improved physical function, pain, and health related quality of life with certolizumab pegol in Japanese rheumatoid arthritis patients with an inadequate response to methotrexate: Results from the JRapid study. *Annals of the Rheumatic Diseases* 2013;**71 Suppl 3**:664. [DOI: 10.1136/annrheumdis-2012-eular.468]

Yamanaka H, Yamamoto K, Takeuchi T, Ishiguro N, Tanaka Y, Eguchi K, et al. Certolizumab pegol improved physical function and heath related quality of life in patients with active Rheumatoid Arthritis despite treatment with methotrexate: results form the JRAPID study. *Modern Rheumatology* 2012;**22 Suppl ll**:S83.

Østergaard 2015 *{published data only}*

Østergaard M, Axelsen MB, Jacobsson LTH, Schaufelberger C, Hansen MS, Bijlsma JWJ, et al. Dynamic magnetic resonance imaging in the assessment of the response to certolizumab pegol in rheumatoid arthritis patients: Results from a phase IIIB randomized study. *Arthritis and Rheumatology.Conference: 2014 ACR/ARHP Annual Meeting Boston, MA United States.Conference Start: 20141114 Conference End: 20141119.Conference Publication: (var.pagings)* 2014;**66**(pp S518-S519):October.

* Østergaard M, Jacobsson LTH, Schaufelberger C, Hansen MS, Bijlsma JWJ, Dudek A, et al. MRI assessment of early response to certolizumab pegol in rheumatoid arthritis: a randomised, double-blind, placebo-controlled phase IIIb study applying MRI at weeks 0, 1, 2, 4, 8 and 16. *Annals of the Rheumatic Diseases* 2015;**74**(6):1156-63.

References to studies excluded from this review

Alten 2013 *{published and unpublished data}*

Alten R, Fleischmann R, van Vollenhoven R, Vencovsky J, Davies O, Stach C, et al. Long term tolerability and efficacy of a 4-week-administration of certolizumab pegol as monotherapy and combination therapy in rheumatoid arthritis; 5-year-data of an open extension study. *Zeitschrift Für Rheumatologie* 2013;**72**:111.

Bykerk 2015 *{published data only}*

Bykerk VP, Bingham C, Burmester G, Furst DE, Mariette X, Purcaru O, et al. Reduction of disease burden on workplace and household productivity following 52 weeks of treatment with certolizumab pegol in combination with methotrexate in DMARD-naive patients with active, severe, progressive rheumatoid arthritis. *Arthritis and Rheumatology.Conference: American College of Rheumatology/Association of Rheumatology Health Professionals Annual Scientific Meeting, ACR/ARHP 2015 San Francisco, CA United States.Conference Start: 20151106 Conference End: 20151111.Confer* 2015;**67**(no pagination):October.

Curtis 2014 *{published data only}*

Curtis JR, Churchill M, Kivitz A, Samad A, Gauer L, Coteur G, et al. Randomization to patient-reported RAPID3 versus physician-based CDAI tools for prediction of treatment response and assessment of patient-reported outcomes in rheumatoid arthritis patients receiving certolizumab pegol: Results from the predict study. Annals of the Rheumatic Diseases.Conference: Annual European Congress of Rheumatology of the European League Against Rheumatism, EULAR 2014 Paris France. 11 -14 June 2014. 2014; Vol. 73.

Curtis 2015a *{published data only}*

Curtis JR, Churchill M, Kivitz A, Samad A, Gauer L, Gervitz L, et al. A randomized trial comparing disease activity measures for the assessment and prediction of response in rheumatoid arthritis patients initiating certolizumab pegol. *Arthritis & Rheumatology* 2015;**67**(12):3104-12.

Curtis 2015b *{published data only}*

Curtis JR, De Longueville M, O'Brien C, Haraoui B. Improvement in disease activity and the long-term risk of serious infectious events in rheumatoid arthritis patients treated with certolizumab pegol. Arthritis and Rheumatology.Conference: American College of Rheumatology/Association of Rheumatology Health Professionals Annual Scientific Meeting, ACR/ARHP 2015 San Francisco, CA United States. 6 - 11 November 2015. 2015; Vol. 67.

Dose Flex 2007 *{published data only}*

* Furst DE, Shaikh SA, Greenwald M, Bennett B, Davies O, Luijtens K, et al. Two dosing regimens of certolizumab pegol in patients with active rheumatoid arthritis. *Arthritis Care & Research* 2015;**67**(2):151-60.

NCT00580840. Dosing flexibility study in patients with rheumatoid arthritis (DoseFlex). clinicaltrials.gov/ct2/show/results/NCT00580840 (first received 21st December 2007).

Fleischmann 2013 *{published data only}*

Fleischmann R, Van Vollenhoven R, Vencovsky J, Alten R, Davies O, Stach C, et al. Long-term safety and efficacy of 4-weekly certolizumab pegol monotherapy and combination therapy in rheumatoid arthritis: 5-year results from an open-label extension study. *Annals of the Rheumatic Diseases* 2013;**72**:435.

Kavanaugh 2013 *{published data only}*

Kavanaugh A, Smolen JS, Emery P, Keystone E, Strand V, Purcaru O, et al. Long-term benefits over more than 4 years of certolizumab pegol combination therapy on workplace and household productivity, and participation in social activities in rheumatoid arthritis: Results from the open-label extension study. *Value in Health* 2013;**16**:A570.

Kavanaugh 2014 *{published data only}*

Kavanaugh A, Mease PJ, Strand V, Purcaru O, Curtis JR. PMS66 - Effect of certolizumab pegol on workplace And household productivity In United States patients with rheumatoid arthritis with or without prior anti-Tnf exposure: results from the Predict study. *Value in Health* 2014;**17**(3):A53.

Kivitz 2014 *{published data only}*

Kivitz AJ, Schechtman J, Texter M, Fichtner A, De Longueville M, Chartash EK. Vaccine responses in patients with rheumatoid

arthritis treated with certolizumab pegol: results from a single-blind randomized phase IV trial. *Journal of Rheumatology* 2014;**41**(4):648-57.

NCT00160641 *{published data only}*

NCT00160641. A study of the safety and effectiveness of liquid certolizumab pegol in the treatment of signs and symptoms of rheumatoid arthritis and in prevention of joint damage in patients with active rheumatoid arthritis. clinicaltrials.gov/ct2/show/NCT00160641?term=NCT00160641&rank=1 (first received 8th September 2005).

NCT00160693 *{published data only}*

NCT00160693. Open label long-term safety study of certolizumab pegol (CZP) for patients with rheumatoid arthritis. clinicaltrials.gov/ct2/show/NCT00160693 (first received 6th September 2005).

NCT00753454 *{published data only}*

NCT00753454. Open label extension for patients coming from the dosing flexibility study in patients with rheumatoid arthritis (RA) (Dose Flex II). clinicaltrials.gov/ct2/show/NCT00753454?term=NCT00753454&rank=1 (first received 5th June 2008).

NCT00843778 *{published data only}*

NCT00843778. Follow-up of rheumatoid arthritis (RA) moderate to low disease activity study (CERTAIN 2). clinicaltrials.gov/ct2/show/NCT00843778?term=NCT00843778&rank=1 (first received 5th January 2009).

NCT00851318 *{published data only}*

NCT00851318. Long-term treatment study of certolizumab pegol (CDP870) as add-on medication to methotrexate in Japanese rheumatoid arthritis (RA) Patients. clinicaltrials.gov/ct2/show/NCT00851318?term=certolizumab+and+arthritis&lup_s=01%2F01%2F2013&lup_e=03%2F01%2F2016&rank=11 (first received 23rd February 2009).

NCT00993668 *{unpublished data only}*

NCT00993668. Assessing the use of certolizumab pegol in adult subjects with rheumatoid arthritis on the antibody response when receiving influenza virus and pneumococcal vaccines. clinicaltrials.gov/ct2/show/results/NCT00993668?term=NCT00993668&rank=1 (first received 9th October 2009).

NCT01197066 *{published data only}*

NCT01197066. Open-label, extension study of CDP870 in patients with rheumatoid arthritis. clinicaltrials.gov/ct2/show/NCT01197066? (first received 17th March 2010).

NCT01255761 PREDICT *{published data only}*

NCT01255761. A comparison of two assessment tools in predicting treatment success of cimzia in rheumatoid arthritis subjects (PREDICT). clinicaltrials.gov/ct2/show/NCT01255761?term=NCT01255761&rank=1 (first received 6th December 2010).

NCT01292265 *{published data only}*

NCT01292265. A 12 week study to assess changes in joint inflammation using ultrasonography in patients with rheumatoid arthritis (RA). clinicaltrials.gov/ct2/show/NCT01292265?term=certolizumab+and+arthritis&lup_s=01%2F01%2F0201&lup_e=03%2F01%2F2016&rank=25 (first received 7th February 2011).

NCT01374971 *{published data only}*

NCT01374971. Rheumatoid arthritis treatment and biopsy study assessing certolizumab pegol (Cimzia). clinicaltrials.gov/ct2/show/results/NCT01374971?term=NCT01374971&rank=1 (first received 14th June 2011).

NCT01443364 *{published data only}*

NCT01443364. Open label study to assess the predictability of early response to certolizumab pegol in patients with rheumatoid arthritis (SPEED). clinicaltrials.gov/ct2/show/NCT01443364?term=certolizumab+and+arthritis&lup_s=01%2F01%2F2013&lup_e=03%2F01%2F2016&rank=13 (first received 27th September 2011).

NCT01526434 *{published data only}*

NCT01526434. Health-related quality of life and patient-reported outcomes in rheumatoid arthritis patients treated with certolizumab pegol. clinicaltrials.gov/ct2/show/NCT01526434?term=certolizumab+and+arthritis&lup_s=01%2F01%2F0201&lup_e=03%2F01%2F2016&rank=28 (first received 1st February 2012).

NCT02319642 *{published data only}*

NCT02319642. An open-label extension study of certolizumab pegol in Chinese patients with rheumatoid arthritis who enrolled in RA0044 (RAPID-C OLE). clinicaltrials.gov/ct2/show/NCT02319642?term=certolizumab+and+arthritis&lup_s=01%2F01%2F2013&lup_e=03%2F01%2F2016&rank=4 (first received 15th December 2014).

NCT02586246 *{published data only}*

NCT02586246. Long-term treatment study of CDP870 self-injection in patients with active rheumatoid arthritis who are participating in the long-term treatment studies (Study 275-08-002 or Study 275-08-004) of CDP870. clinicaltrials.gov/ct2/show/NCT02586246?term=certolizumab+and+arthritis&lup_s=01%2F01%2F0201&lup_e=03%2F01%2F2016&rank=24 (first received 23rd October 2015).

References to ongoing studies

NCT01295151 *{published data only}*

NCT01295151. SWITCH clinical trial for patients with rheumatoid arthritis who have failed an initial TNF-blocking drug (SWITCH). clinicaltrials.gov/ct2/show/NCT01295151 (first received 11th February 2011).

* Navarro C, Nuria C, Brown S, Bosworth A, et al. The 'Switch' study protocol: a randomised-controlled trial of switching to an alternative tumour-necrosis factor (TNF)-inhibitor drug or abatacept or rituximab in patients with rheumatoid arthritis who have failed an initial TNF-inhibitor drug. BMC Musculoskeletal Disorders 2014; Vol. 15:452. [DOI: 10.1186/1471-2474-15-452]

NCT01489384 *{published data only}*

NCT01489384. Cimzia treatment in rheumatoid arthritis: randomizing to stop versus continue disease-

modifying anti-rheumatic drug(s). clinicaltrials.gov/ct2/show/NCT01489384?term=certolizumab+and+arthritis&lup_s=01%2F01%2F0201&lup_e=03%2F01%2F2016&rank=45 (first received 7th December 2011).

NCT01491815 *{published data only}*

NCT01491815. Active conventional therapy compared to three different biologic treatments in early rheumatoid arthritis with subsequent dose reduction. clinicaltrials.gov/ct2/show/NCT01491815?term=certolizumab+and+arthritis&lup_s=01%2F01%2F0201&lup_e=03%2F01%2F2016&rank=51 (first received 8th December 2011).

NCT01500278 *{published data only}*

NCT01500278. Study to assess the short- and long-term efficacy of certolizumab pegol plus methotrexate compared to adalimumab plus methotrexate in subjects with moderate to severe rheumatoid arthritis (RA) inadequately responding to methotrexate. clinicaltrials.gov/ct2/show/NCT01500278?term=certolizumab+and+arthritis&lup_s=01%2F01%2F2013&lup_e=03%2F01%2F2016&rank=11 (first received 22nd December 2011).

NCT01602302 *{published data only}*

NCT01602302. Ultrasound and withdrawal of biological DMARDs in rheumatoid arthritis. clinicaltrials.gov/ct2/show/NCT01602302?term=certolizumab+and+arthritis&lup_s=01%2F01%2F0201&lup_e=03%2F01%2F2016&rank=48 (first received 16th May 2012).

NCT02151851 *{published data only}*

NCT02151851. A study of certolizumab pegol as additional therapy in Chinese patients with active rheumatoid arthritis (RAPID-C). clinicaltrials.gov/ct2/show/NCT02151851?term=certolizumab+and+arthritis&lup_s=01%2F01%2F2013&lup_e=03%2F01%2F2016&rank=18 (first received 28th May 2014).

NCT02293590 *{published data only}*

NCT02293590. RICE: Remission by Intra-articular Injection Plus Certolizumab. clinicaltrials.gov/ct2/show/NCT02293590?term=certolizumab+and+arthritis&lup_s=01%2F01%2F0201&lup_e=03%2F01%2F2016&rank=50 (first received 30th October 2014).

NCT02430909 *{published data only}*

NCT02430909. Multiple dose study of UCB4940 as add-on to certolizumab pegol in subjects with rheumatoid arthritis. clinicaltrials.gov/ct2/show/NCT02430909?term=certolizumab+and+arthritis&lup_s=01%2F01%2F0201&lup_e=03%2F01%2F2016&rank=34 (first received 27th April 2015).

NCT02466581 *{published data only}*

NCT02466581. Dose reduction for early rheumatoid arthritis patients with low disease activity. clinicaltrials.gov/ct2/show/NCT02466581?term=certolizumab+and+arthritis&lup_s=01%2F01%2F0201&lup_e=03%2F01%2F2016&rank=42 (first received 29th May 2015).

Additional references

Abasolo 2016

Abasolo L, Ivorra-Cortes J, Leon L, Jover JA, Fernandez-Gutierrez B, Rodriguez-Rodriguez L. Influence of demographic and clinical factors on the mortality rate of a rheumatoid arthritis cohort: A 20-year survival study. *Seminars in Arthritis and Rheumatism* 2016;**45**(5):533-8.

Arnett 1988

Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis and Rheumatism* 1988;**31**(3):315-24.

Bhandari 2004

Bhandari M, Busse JW, Jackowski D, Montori VM, Schünemann H, Sprague S, et al. Association between industry funding and statistically significant pro-industry findings in medical and surgical randomized trials. *Canadian Medical Association Journal* 2004;**170**(4):477-80.

Blumenauer 2002

Blumenauer BT, Judd M, Wells GA, Burls A, Cranney A, Hochberg MC, et al. Infliximab for the treatment of rheumatoid arthritis. *Cochrane Database of Systematic Reviews* 2002, Issue 3. [DOI: 10.1002/14651858.CD003785]

Bongartz 2006

Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA* 2006;**295**(19):2275-85.

Brennan 2008

Brennan FM, McInnes IB. Evidence that cytokines play a role in rheumatoid arthritis. *The Journal of Clinical Investigation* 2008;**118**(11):3537-45.

Bykerk 2013

Bykerk VP, Cush J, Winthrop K, Calabrese L, Lortholary O, de Longueville M, et al. Update on the safety profile of certolizumab pegol in rheumatoid arthritis: an integrated analysis from clinical trials. *Annals of the Rheumatic Diseases* 2015;**74**(1):96-103. [DOI: 10.1136/annrheumdis-2013-203660]

Chen 2006

Chen YF, Jobanputra P, Barton P, Jowett S, Bryan S, Clark W, et al. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness. Health Technology Assessment 2006; Vol. 10, issue 42:1-235.

Cross 2014

Cross M, Smith E, Hoy D, Carmona L, Wolfe F, Vos T, et al. The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. *Annals of the Rheumatic Diseases* 2014;**73**(7):1316-22.

Doran 2002

Doran MF, Pond GR, Crowson CS, O'Fallon WM, Gabriel SE. Trends in incidence and mortality in rheumatoid arthritis in Rochester, Minnesota, over a forty-year period. *Arthritis and Rheumatism* 2002;**46**:625-31.

Dörner 2016

Dörner T, Strand V, Cornes P, Gonçalves J, Gulácsi L, Kay J, et al. The changing landscape of biosimilars in rheumatology. *Annals of the Rheumatic Diseases* 2016;**75**(6):974-82.

EMA 2009

European Medical Agency. Assesment report for Cimzia. Procedure No EMEA/H/C/001037. www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001037/WC500069735.pdf. London, 2009 (accessed 4th July 2017):1-47. [Procedure No.EMEA/H/C/001037]

Emparanza 2015

Emparanza JI, Cabello JB, Burls AJE. Does evidence-based practice improve patient outcomes? An analysis of a natural experiment in a Spanish hospital. *Journal of Evaluation in Clinical Practice* 2015;**21**(6):1059-65.

FDA 2013

Center for Drug Evaluation and Research. Postmarket Drug Safety Information for Patients and Providers - Information for Healthcare Professionals: Cimzia (certolizumab pegol), Enbrel (etanercept), Humira (adalimumab), and Remicade (infliximab). www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm124185.htm (accessed 7 Jul 2014).

Felson 2011

Felson DT, Smolen JS, Wells G, Zhang B, Van Tuyl LHD, Funovits J, et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Arthritis and Rheumatism* 2011;**63**(3):573-86.

Glanville 2006

Glanville JM, Lefebvre C, Miles JN, Camosso-Stefinovic J. How to identify randomized controlled trials in MEDLINE: ten years on. *Journal of the Medical Library Association* 2006;**94**(2):130-6.

Hazes 2010

Hazes JM, Taylor P, Strand V, Purcaru O, Coteur G, Mease P. Physical function improvements and relief from fatigue and pain are associated with increased productivity at work and at home in rheumatoid arthritis patients treated with certolizumab pegol. *Rheumatology (Oxford)* 2010;**49**(10):1900-10.

Higgins 2011

Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org.

Jobanputra 2012

Jobanputra P, Maggs F, Deeming A, Carruthers D, Rankin E, Jordan AC, et al. A randomised efficacy and discontinuation study of etanercept versus adalimumab (RED SEA) for rheumatoid arthritis: a pragmatic, unblinded, non inferiority study of first TNF inhibitor use: outcomes over 2 years. *BMJ Open* 2012;**2**(6):e001395.

Keystone 2012

Keystone EC, Combe B, Smolen J, Strand V, Goel N, van Vollenhoven R, et al. Sustained efficacy of certolizumab pegol added to methotrexate in the treatment of rheumatoid arthritis: 2-year results from the RAPID 1 trial. *Rheumatology (Oxford)* 2012;**51**(9):1628-38.

Kharlamova 2016

Kharlamova N, Jiang X, Sherina N, Potempa B, Israelsson L, Quirke AM, et al. Antibodies to Porphyromonas gingivalis Indicate Interaction Between Oral Infection, Smoking, and Risk Genes in Rheumatoid Arthritis Etiology. *Arthritis & Rheumatology* 2016;**68**(3):604-13.

Laird 1990

Laird NM, Wang F. Estimating rates of change in randomized clinical trials. *Controlled Clinical Trials* 1990;**11**(6):405-19.

Laupacis 1988

Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. *New England Journal of Medicine* 1988;**318**(26):1728-33.

Lethaby 2013

Lethaby A, Lopez-Olivo MA, Maxwell L, Burls A, Tugwell P, Wells GA. Etanercept for the treatment of rheumatoid arthritis. *Cochrane Database of Systematic Reviews* 2013, Issue 5. [DOI: 10.1002/14651858.CD004525.pub2]

Lopez-Olivo 2014

Lopez-Olivo MA, Siddhanamatha HR, Shea B, Tugwell P, Wells GA, Suarez-Almazor ME. Methotrexate for treating rheumatoid arthritis. *Cochrane Database of Systematic Reviews* 2014, Issue 6. [DOI: 10.1002/14651858.CD000957.pub2]

Lundberg 2013

Lundberg K, Bengtsson C, Kharlamova N, Reed E, Jiang X, Kallberg H, et al. Genetic and environmental determinants for disease risk in subsets of rheumatoid arthritis defined by the anticitrullinated protein/peptide antibody fine specificity profile. *Annals of the Rheumatic Diseases* 2013;**72**(5):652-8.

MacGregor 2000

MacGregor AJ, Snieder H, Rigby AS, Koskenvuo M, Kaprio J, Aho K, et al. Characterizing the quantitative genetic contribution to rheumatoid arthritis using data from twins. *Arthritis and Rheumatism* 2000;**43**(1):30-7.

Meune 2009

Meune C, Touze E, Trinquart L, Allanmore Y. Trends in cardiovascular mortality in patients with rheumatoid arthritis over 50 years: a systematic review and meta-analysis of cohort studies. *Rheumatology* 2009;**48**:1309-13.

Navarro-Millán 2013

Navarro-Millán I, Curtis JR. Newest clinical trial results with antitumor necrosis factor and non antitumor necrosis factor biologics for rheumatoid arthritis. *Current Opinion in Rheumatology* 2013;**25**(3):384–90.

Navarro-Sarabia 2005

Navarro-Sarabia F, Ariza-Ariza R, Hernandez-Cruz B, Villanueva I. Adalimumab for treating rheumatoid arthritis. *Cochrane Database of Systematic Reviews* 2005, Issue 3. [DOI: 10.1002/14651858.CD005113.pub2]

NICE 2009

UCB. Certolizumab pegol (CIMZIA©) for the treatment of rheumatoid arthritis. Single technology appraisal (STA) manufacturer submission to NICE. NICE 2009:1-180.

Okada 2014

Okada Y, Wu D, Trynka G, Raj T, Terao C, Ikari K, et al. Genetics of rheumatoid arthritis contributes to biology and drug discovery. *Nature* 2014;**506**(7488):376-81.

Puolakka 2005

Puolakka K, Kautiainen H, Möttönen T, Hannonen P, Korpela M, Hakala M, et al. FIN-RACo Trial Group. Early suppression of disease activity is essential for maintenance of work capacity in patients with recent-onset rheumatoid arthritis: five-year experience from the FIN-RACo trial. *Arthritis and Rheumatology* 2005;**52**(1):36-4.

Roubille 2015

Roubille C, Richer V, Starnino T, McCourt C, McFarlane A, Fleming P, et al. The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: a systematic review and meta-analysis. *Annals of the Rheumatic Diseases* 2015;**74**(3):480-9.

Singh 2009

Singh JA, Christensen R, Wells GA, Suarez-Almazor ME, Buchbinder R, Lopez-Olivo MA, et al. Biologics for rheumatoid arthritis: an overview of Cochrane reviews. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD007848.pub2]

Singh 2010

Singh JA, Noorbaloochi S, Singh G. Golimumab for rheumatoid arthritis. *Cochrane Database of Systematic Reviews* 2010, Issue 1. [DOI: 10.1002/14651858.CD008341]

Singh 2011

Singh JA, Wells GA, Christensen R, Tanjong Ghogomu E, Maxwell L, MacDonald JK, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. *Cochrane Database of Systematic Reviews* 2011, Issue 2. [DOI: 10.1002/14651858.CD008794.pub2]

Singh 2012

Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care and Research* 2012;**64**:625-39.

Singh 2015

Singh JA, Cameron C, Noorbaloochi S, Cullis T, Tucker M, Christensen R, et al. Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis. *Lancet* 2015;**386**(9990):258-65.

Singh 2016

Singh A, Saag KG, Bridges SL, Akl A, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Care & Research* 2016;**68**(1):1-25.

Smolen 2014

Smolen JS, Landewé R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Annals of the Rheumatic Diseases* 2014;**73**(3):492-509.

Sokka 2003

Sokka T, Krishnan E, Hakkinen A, Hannonen P. Functional disability in rheumatoid arthritis patients compared with a community population in Finland. *Arthritis and Rheumatism* 2003;**48**(1):59-63. [PUBMED: 12528104]

Thompson 1999

Thompson SG, Sharp SJ. Explaining heterogeneity in meta-analysis: a comparison of methods. *Statistics in Medicine* 1999;**18**(20):2693-708.

Tureson 2013

Turesson C. Extra-articular rheumatoid arthritis. *Current Opinion in Rheumatology* 2013;**23**(3):360–6.

Wong 2006a

Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. *Journal of the Medical Library Association* 2006;**94**(1):41-7.

Wong 2006b

Wong SS, Wilczynski NL, Haynes RB. Optimal CINAHL search strategies for identifying therapy studies and review articles. *Journal of Nursing Scholarship* 2006;**38**(2):194-9.

Yee 2003

Yee CS, Filer A, Pace A, Douglas K, Situnayake D, Rowe IF. West Midlands Rheumatology Services and Training Committee. The prevalence of patients with rheumatoid arthritis in the West Midlands fulfilling the BSR criteria for anti-tumour necrosis factor therapy: an out-patient study. *Rheumatology (Oxford)* 2003;**42**:856-9.

Young 2000

Young A, Dixey J, Cox N, Davies P, Devlin J, Emery P, et al. How does functional disability in early rheumatoid arthritis affect

patients and their lives? Results of 5 years of follow-up in 732 patients from the early RA study (ERAS). *Rheumatology* 2000;**39**(6):603-11.

Yusuf 1991

Yusuf S, Wittes J, Probstfield J, Tyroler HA. Analysis and interpretation of treatment effects in subgroups of patients in randomized clinical trials. *JAMA* 1991;**266**(1):93-8.

Zhou 2014

Zhou Q, Zhou Y, Chen H, Wang Z, Tang Z, Liu J. The efficacy and safety of certolizumab pegol (CZP) in the treatment of active rheumatoid arthritis (RA): a meta-analysis from nine randomized controlled trials. *International Journal of Clinical and Experimental Medicine* 2014;**7**(11):3870-80.

References to other published versions of this review

Ruiz Garcia 2009

Ruiz Garcia V, Burls A, Cabello López JCL, Fry-Smith AFS, Galvez-Muñoz JG, Jobanputra P, et al. Certolizumab pegol (CDP870) for rheumatoid arthritis in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 1. [DOI: 10.1002/14651858.CD007649]

Ruiz Garcia 2011

Ruiz Garcia V, Jobanputra P, Burls A, Cabello JB, Gálvez Muñoz JG, Saiz Cuenca ESC, Fry-Smith A. Certolizumab pegol (CDP870) for rheumatoid arthritis in adults. *Cochrane Database of Systematic Reviews* 2011, Issue 2. [DOI: 10.1002/14651858.CD007649.pub2]

Ruiz Garcia 2014

Ruiz Garcia V, Jobanputra P, Burls A, Cabello JB, Vela Casasempere P, Bort-Marti S, et al. Certolizumab pegol (CDP870) for rheumatoid arthritis in adults. *Cochrane Database of Systematic Reviews* 2014, Issue 9. [DOI: 10.1002/14651858.CD007649.pub3]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Atsumi 2016

Methods	Randomised clinical trial, double-blind
Participants	Eligible patients were 20–64 years old with RA fulfilling the 2010 ACR/EULAR classification criteria.
Interventions	1. 400 mg of CDP870 plus MTX given at week 0, 2. 4, and thereafter 200 mg CDP870 given every 2 weeks (n=159) 2. Placebo plus MTX given every 2 weeks (n=157)
Outcomes	Primary outcome measures: Inhibition of radiographic progression at week 52 Secondary outcomes measures: Inhibition of radiographic progression at week 24; Clinical remission rate at week 24 and week 52
Notes	**C-OPERA Trial** **Countries/Cities**: 73 sites in Japan **Dates conducted:** from October 2011 to August 2013 **Eligibility criteria**: Eligible patients were 20–64 years old with RA fulfilling the 2010 ACR/EULAR classification criteria. Patients had ≤12 months of persistent arthritic symptoms, at least moderate disease activity (Disease Activity Score 28-joint assessment (DAS28) with erythrocyte sedimentation rate (ESR) ≥3.2) and were MTX-naive. In addition, patients had poor prognostic factors: high anti-cyclic citrullinated peptide (anti-CCP) anti- body (≥3× upper limit of normal (ULN)) and either positive rheumatoid factor (RF) and/or presence of bone erosions (based on radiographs of hands/feet, assessed by the investigator at each study site). **Adverse events as a specified outcome**: adverse events and serious adverse events were reported **Funding sources:** Astellas Pharma Inc

Atsumi 2016 *(Continued)*

Conflict of interest: Principal Investigators are **NOT** employed by the organization sponsoring the study.

Restriction Description: Institute and/or Principal Investigator may publish trial data generated at their specific study site after Sponsor publication of the multi-center data. Sponsor must receive a site's manuscript prior to publication to ensure that no confidential information of Sponsor is included in the document. Sponsor may delay the publication for to seek patent protection.

TA has taken part in speakers' bureaus for Astellas, Bristol-Myers, Chugai and Mitsubishi-Tanabe; KY has received consultancy fees from Abbott, BMS, Chugai, Eisai, Mitsubishi-Tanabe, Pfizer, Roche and UCB Pharma, and has received research grants from Abbott, Eisai, Mitsubishi-Tanabe, Pfizer, Santen and UCB Pharma;

TT has received consultancy fees from AstraZeneca, Asahi Kasei, Eli Lilly, Mitsubishi-Tanabe and Novartis, research grants from Abbott, Astellas, BMS, Chugai, Daiichi-Sankyo, Eisai, Janssen, Mitsubishi-Tanabe, Nippon Shinyaku, Otsuka, Pfizer, Sanofi-Aventis, Santen, Takeda and Teijin, and has taken part in speakers' bureaus for Abbott, BMS, Chugai, Eisai, Janssen, Mitsubishi-Tanabe, Pfizer and Takeda and UCB Pharma; HY has received consultancy fees from Abbott, Astellas, BMS, Chugai, Eisai, Janssen, Mitsubishi-Tanabe, Pfizer, Takeda and UCB Pharma, and has received research grants from Abbott, Astellas, BMS, Chugai, Eisai, Janssen, Mitsubishi-Tanabe, Pfizer, Takeda and UCB Pharma; NI has received research grants from Abbott, Astellas, BMS, Takeda, Chugai, Eisai, Janssen, Kaken Mitsubishi-Tanabe and Pfizer, and has taken part in speakers' bureaus for Abbott, Astellas, BMS, Chugai, Eisai, Janssen, Kaken, Mitsubishi-Tanabe, Otsuka, Pfizer, Taisho-Toyama and Takeda;

YT has received research grants from Astellas, AbbVie, BMS, Chugai, Daiichi-Sankyo, Mitsubishi-Tanabe, MSD, has received consultancy fees from Abbott, AbbVie, Asahi Kasei, Astellas, AstraZeneca, Chugai, Daiichi-Sankyo, Eisai, Eli Lilly, GSK, Janssen, Mitsubishi-Tanabe, MSD, Pfizer, Quintiles, Takeda and UCB Pharma, and has taken part in speakers' bureaus for Abbott, AbbVie, Asahi Kasei, Astellas, AstraZeneca, Chugai, Daiichi-Sankyo, Eisai, Eli Lilly, GSK, Janssen, Mitsubishi-Tanabe, MSD, Pfizer, Quintiles, Takeda and UCB Pharma; KE has received consultancy fees from UCB Pharma; AW has received research grants from Daiichi-Sankyo, Dainippon-Sumitomo, Kyorin, Meiji Seika; Shionogi, Taiho, Taisho and Toyama Chemical, and has taken part in speakers' bureaus for Daiichi-Sankyo, Dainippon-Sumitomo, GSK, Mitsubishi-Tanabe, MSD, Pfizer, Shionogi and Taisho-Toyama;

HO has received consultancy fees from Astellas and UCB Pharma; SY has received research grant from BMS and taken part in speakers' bureaus for AbbVie, Astellas, Chugai, Eizai, Pfizer, Mitsubishi-Tanabe and Takeda; YY has no competing interests to disclose; YK has received speakers' bureau from Astellas, Chugai, and Ono; TM has received speaker honoraria from Pfizer Japan, Janssen Pharmaceutical Co. and Astellas Pharma; and research grants form Quintiles Transnational Japan K.K, Janssen Pharmaceutical Co., Takeda Chemical Industries, Daiichi Sankyo Co., Astellas Pharma, Eli Lilly Japan K.K., MSD Co., Nippon Kayaku Co., Parexel International Corp., Pfizer Japan and Bristol-Myers Squibb; MI has received payment for lectures from Astellas, Chugai, Ono and Tanabe-Mitsubishi, has received research grants from Pfizer and a royalty fee from Chugai; TS is an employee of UCB Pharma;

TO is an employee of Astellas;

DvdH has received consultancy fees from AbbVie, Amgen, AstraZeneca, Augurex, BMS, Celgene, Centocor, Chugai, Covagen, Daiichi, Eli-Lilly, Galapagos, GSK, Janssen Biologics, Merck, Novartis, Novo-Nordisk, Otsuka, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, UCB Pharma and Vertex; and is the Director of Imaging Rheumatology bv;

NM has received research grants from Abbott, Astellas, Chugai, Eisai, Mitsubishi-Tanabe, Pfizer and Takeda;

TK has received consultancy fees from AbbVie, Astellas, BMS, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi-Tanabe, Pfizer, Santen, Taisho-Toyama, Takeda, Teijin and UCB Pharma, and has taken part in speakers' bureaus for Abbott, Astellas, BMS, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi-Tanabe, Pfizer, Santen, Taisho-Toyama, Takeda, Teijin and UCB Pharma.

Risk of bias

Bias	Authors' judgement	Support for judgement

Atsumi 2016 *(Continued)*

Random sequence generation (selection bias)	Low risk	"Patients were randomised 1:1"
Allocation concealment (selection bias)	Low risk	"via an interactive web-response system"
Blinding (performance bias and detection bias) ACR50	Low risk	ACR50 is a clinical outcome determined by healthcare professionals who were blinded to study medications.
Blinding (performance bias and detection bias) All outcomes	Low risk	As above
Incomplete outcome data (attrition bias) ACR50	Low risk	Participants who did not achieve an improvement of symptoms at or after week 24, i.e. if moderate or higher disease activity (DAS28 (ESR) ≥3.2) persisted ≥ 4 weeks in either treatment arm, were eligible to receive rescue treatment with open-label certolizumab pegol after discontinuing D-B period. As a consequence, the withdrawal rate in CTZ arm was 22.6%; withdrawal rate in Placebo arm was 44.6%
Incomplete outcome data (attrition bias) All outcomes	Low risk	As above
Selective reporting (reporting bias)	Low risk	Data from all radiological (except for JSN outcome), clinical and safety outcomes were provided
Other bias	Low risk	The study appears to be free of other sources of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study did not report blinding of participants. Drug administration was performed by dedicated non-blinded persons, because obvious differences between certolizumab pegol and Placebo; however, these personnel were not permitted to engage in other study activities, to maintain blinding. All investigators and healthcare professionals involved in safety/efficacy assessments were blind to study medications
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All investigators and healthcare professionals involved in safety/efficacy assessments were blind to study medications. mTSS as main outcome assessed by radiologist (namely, healthcare professionals)

CDP870-004 2001

Methods	Double-blind, multiple dose, 12-week, placebo-controlled dose-ranging study
Participants	326 participants with a history of inadequate response or intolerance to at least 1 DMARD and active RA at screening
Interventions	1. Placebo 2. 50, 100, 200, 400, 600 and 800 mg sc Given every 4 weeks in 2 dose groups, panel 1 and panel 2 "Placebo: 40; active: 40-41/arm); Panel 2: 122 (Placebo 44, active: 39/arm). PP: 186, and 113 pts."
Outcomes	ACR20, ACR50, ACR70, subset of the ACR criterion, DAS responder rates at week 12

CDP870-004 2001 *(Continued)*

	Follow-up 12 weeks
Notes	**Countries/Cities:** Not stated **Dates conducted** ("not stated") **Eligibility criteria:** RA with a history of inadequate response or intolerance to at least 1 DMARD and active RA at screening **Adverse events as a specified outcome:** 'not reported'. We only have data from ACR20 at week 12 Funding sources: no data Conflict of interest: no data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	UCB reported: "Randomized code generated by Pharmaceutical Packaging Service and based on instruction of the randomisation procedure prepared by Celltech R&D statistic"
Allocation concealment (selection bias)	Unclear risk	UCB reported: "Patients were randomly assigned to treatment groups during the DB phase (week 0_12) and received either placebo or CDP-870 SC"
Blinding (performance bias and detection bias) ACR50	High risk	UCB reported as blinded but stated: "CPD-870 and the placebo utilized in this study (saline) did not have the same viscosity therefore full blinding was not possible. Study drug was to be prepared by a pharmacist having no other involvement in the study; injections of study medications were given by a nurse or physician who had no other involvement in the study..."
Blinding (performance bias and detection bias) All outcomes	High risk	See above
Incomplete outcome data (attrition bias) ACR50	High risk	Data were not available
Incomplete outcome data (attrition bias) All outcomes	High risk	Data were not available
Selective reporting (reporting bias)	Low risk	Efficacy was defined as ACR improvement in disease activity at week 12 and was described
Other bias	Unclear risk	There were so few data that was impossible to judge
Blinding of participants and personnel (performance bias) All outcomes	High risk	See above
Blinding of outcome assessment (detection bias) All outcomes	High risk	See above

Choy 2002

Methods	Randomised double-blind placebo-controlled trial
Participants	36 people with RA defined by ACR classification criteria. People with active diseased defined as having 3 or the following 4 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. Participants had to have failed treatment with at least 1 DMARD and have been off treatment for at least 4 weeks
Interventions	1. Single intravenous infusion of placebo (n = 12) 2. 1, 5 or 20 mg/kg of certolizumab pegol (each n = 8) for 8 weeks
Outcomes	ACR20, ACR50, ACR70, pain score (0 - 10 cm), DAS, TJC, SJC, Health Assessment Questionnaire (HAQ), C-reactive protein (CRP) Follow-up 8 weeks
Notes	This study was only considered to assess safety because follow-up was less than 12 weeks In the open-label phase, 1 participant 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. **Countries/Cities:** patients recruited from out-patient rheumatology clinics in London, Cambridge, Norfolk and Norwich (UK). **Dates conducted:** not reported **Eligibility criteria**: Patients aged 18–75 yr who satisfied the 1987 revised American College of Rheumatology (ACR) diagnostic criteria for RA **Adverse events:** were reported **Funding sources:** not stated, but UCB had all the data and sent us details of how was done **Conflict of interest:** DA Isenberg, worked for Celltech Research and Development, Slough, UK

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were divided into 4 groups. In each group of 12 patients 8 received active treatment and 4 received placebo. UCB explain to us: "Methods for sequence generation was randomised, DB, sequential ascending dose"
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding (performance bias and detection bias) ACR50	Low risk	The study was blinded and UCB stated: "all data were entered and Database locked after completion of the clinical phase for the first study period and before ESR and CRP were entered into the database. ESR and CRP data were withheld from investigator and sponsor study personal during the course of the study because knowledge of patient's profile could potentially unblind the study..., auto AB, anti certolizumab pegol level, TNFalpha, IL6 and IL1b were transferred into the database after DB lock"
Blinding (performance bias and detection bias) All outcomes	Low risk	See above

Choy 2002 *(Continued)*

Incomplete outcome data (attrition bias) ACR50	Low risk	Reasons for withdrawals were disclosed 92% of certolizumab pegol group and 50% of placebo completed 8 weeks of treatment. We imputed missing data for analysis
Incomplete outcome data (attrition bias) All outcomes	Low risk	Safety analysis also imputed missing data
Selective reporting (reporting bias)	Low risk	All the outcomes were available in the clinical study report as figures
Other bias	Low risk	The study appears to be free of other sources of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	UCB stated: " the study pharmacist prepared for infusion the study medication and diluent, the pharmacy covered the solution with an opaque material and labelled it with “130mL CDP870 Engineered Fab’ Conjugated to PEG or sodium acetate placebo diluent” “For IV use only”, administration details, the patient number, patient initials, date and time to use the medication by and name of investigator."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above

Choy 2012

Methods	Phase III, randomised double-blind placebo-controlled multicentre trial 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.
Participants	People with RA who are partial responders to MTX. 250 participants with RA, aged 18+ years, were randomised to 1 of 2 regimens of sc 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.Participants 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). Inclusion and exclusion criteria were identical to Keystone 2008, but discontinued all DMARDs at least 28 days or 5 half-lives prior to first dose of study drug
Interventions	1. Certolizumab pegol 400 mg plus MTX (n=125) 2. Placebo sc plus MTX (n=125) Every 4 weeks for a total of 6 injections
Outcomes	Primary: ACR20 and safety at 24 weeks Secondary endpoints: Participant’s assessment of pain (VAS), participant’s global assessment of arthritis, physician’s global assessment of arthritis, participant’s assessment of physical function by HAQ-DI, acute phase reactant value (only CRP for this study) Follow-up 24 weeks
Notes	**NCT00544154.** Clinical study summary provided by UCB

Choy 2012 *(Continued)*

Countries/Cities: 7 countries (Austria, Belgium, Czech Republic, Germany, Ireland, USA and the UK)

Dates conducted: between October 2002 and January 2004.

Eligibility criteria: patients were aged 18–75 years, with adult-onset RA of at least 6 months' duration as defined by the 1987 ACR criteria and active disease defined as nine or more tender joints, nine or more swollen joints and at least one of the three following criteria: ≥45 min of morning stiffness, ESR ≥28 mm/h (Westergren) or CRP >10 mg/l. Patients were required to have been receiving MTX for at least 6 months and on a stable dosage of 15–25 mg/week for at least 8 weeks before the first dose of study medication (10–15 mg/week was deemed acceptable in cases where a dosage reduction had been necessary because of toxicity). All other DMARDs were to have been discontinued at least 28 days before the first study medication dose

Adverse events as a specified outcome: AEs were reported at each study visit. Treatment-emergent AEs were those reported after the first dose of study medication, including worsening of pre-existing conditions. Serious AEs (SAEs) were those that resulted in death or were life-threatening, caused or prolonged hospitalizations, required parenteral antibiotics, and/or that resulted in persistent or significant disability, incapacity or congenital abnormality/birth defect.

Funding sources: UCB

Conflict of interest: J.V. was a speaker at the meeting organized by UCB and is a member of a UCB advisory board. E.C. has received grants/research support from Abbott Laboratories, Allergan, Boehringer Ingelheim, Chelsea Therapeutics, GSK, Jazz Pharmaceuticals, Merrimack Pharmaceutical, MSD, Pfizer, Pierre Fabre Medicament, Roche, Chugai and Wyeth and UCB Pharma.

E.C. has also received consultancy fees from Abbott Laboratories, Allergan, Boehringer Ingelheim, Chelsea Therapeutics, Eli Lilly, GSK, Jazz Pharmaceuticals, Merrimack Pharmaceutical, MSD, Pfizer, Pierre Fabre Medicament, Roche, Schering Plough, Synovate, Chugai, MedImmune and Wyeth and UCB Pharma. E.C. is a member of a Speaker's Bureau for Abbott Laboratories, Allergan, Boehringer Ingelheim, Chelsea Therapeutics, Eli Lilly, GSK, Jazz Pharmaceuticals, Merrimack Pharmaceutical, MSD, Pfizer, Pierre Fabre Medicament, Roche, Schering Plough, Chugai and Wyeth and UCB Pharma.

B.V. is a UCB Pharma employee and has been granted UCB Pharma stock appreciation rights.

N.G. is a former employee of UCB Pharma, and is currently an employee of Array Biopharma, Inc. N.G. owns UCB Pharma stock.

O.D. is an employee of UCB Pharma and holds stock options.

R.A. has received research grants from Abbott, BMS, Merck Pharma GmbH, Novartis, Pfizer, Roche and UCB Pharma. R.A. is a member of a speaker's bureau for Abbott Laboratories, BMS, Horizon Pharma, Merck Pharma GmbH, Novartis, Roche, and has received consulting fees from Abbott Laboratories, Horizon Pharma, Merck Pharma GmbH, Novartis and Roche. R.A. has held non-remunerative positions of influence for Abbott Laboratories, BMS, Novartis Pharmaceuticals Corporation and Roche. All other authors have declared no conflicts of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	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 Phase III trial)
Allocation concealment (selection bias)	Low risk	Via IVRS
Blinding (performance bias and detection bias) ACR50	Low risk	UCB: "All the study staff with the exception of the unblinded dispenser, was blind to the treatment". "Each study center was required to have a written blinding plan in place signed by the principal investigator, which detailed the

Choy 2012 *(Continued)*

		study center's steps for ensuring that the double blind nature of the study was maintained"
Blinding (performance bias and detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias) ACR50	Low risk	Full account of all withdrawals and reasons for withdrawals 77.8% of certolizumab pegol group and 53.7% of placebo completed 6 months of treatment. We imputed missing data for analysis
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysis per protocol for HAQ and safety “Of the 247 patients randomised, 124 patients in the certolizumab pegol plus MTX group (98%) and 119 in the placebo plus MTX group (98%) received at least one injection (243 total)"
Selective reporting (reporting bias)	Low risk	All the prespecified outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	See above "To preserve the blind to clinical research staff, the study site pharmacist labelled clinical supplies (study medication syringes), and a sorbitol placebo was used to match the viscosity of certolizumab pegol"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above

Emery 2015

Methods	Randomised clinical trial, double-blind
Participants	880 participants were randomised. 3 were randomised in error, were not dosed, and were withdrawn shortly afterwards as screen failures. 2 were included in the randomised Set 1 (RS1) only, and 1 of the 3 was conservatively excluded from any output. Therefore, 879 subjects are in RS1.
Interventions	1. Placebo + MTX (n= 219) 2. MTX + certolizumab pegol 400 mg at 0, 2, 4 weeks, followed by a maintenance dose of certolizumab pegol 200 mg until week 50 (n=660)
Outcomes	Primary: Percentage of participants in sustained remission at week 52 Secondary: Radiographic changes (mTTs, JNS, JE), ACR20, ACR50 and ACR70 at 52 weeks; Percentage of participants with clinical remission (ACR/EULAR) at week 52 DAS 28 < 2.6 at week 52 Change in CDAI SDAI at week 52 HAQ-DI week 52 Work product survey at week 52. Serious adverse events; other adverse events
Notes	**C-EARLY trial** **Countries/Cities**: Europe, Australia, North America and Latin America at 181 sites **Dates conducted:** from January 2012 to September 2015 **Eligibility criteria**: Eligible patients were DMARD-naïve, diagnosed with RA ≤1 year prior to randomisation, fulfilled the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism

Emery 2015 *(Continued)*

(EULAR) classification criteria and had poor prognostic factors for severe disease progression (positive for rheumatoid factor (RF) or anticitrullinated peptide antibody (ACPA) at screening).

Adverse events as a specified outcome: adverse events and serious adverse events were reported

Funding sources: UCB Pharma SA

Conflict of interest: Principal Investigators are **NOT**employed by the organization sponsoring the study.The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **more than 60 days but less than or equal to 180 days**. The sponsor cannot require changes to the communication and cannot extend the embargo.

PE received consultancy and speaker's fee from Pfizer, MSD, AbbVie, UCB Pharma, Roche, Bristol-Myers Squibb, Schering-Plough, Novartis and Samsung. COBIII received consultancy fees from UCB Pharma. GRB received consultancy fees from AbbVie, MSD, Pfizer, Roche and UCB Pharma. DEF received research grants from Abbott, Actelion, Amgen, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, NIH, Novartis, Pfizer, Roche/Genentech and UCB Pharma; consultancy fees from Abbott, Actelion, Amgen, Bristol-Myers Squibb, Biogen IDEC, Janssen, Gilead, GlaxoSmithKline, NIH, Novartis, Pfizer, Roche/Genentech and UCB Pharma and other fees from Abbott, Actelion, Amgen, Bristol-Myers Squibb, Biogen, IDEC, Janssen, Gilead, NIH, Roche/Genentech, Abbott, Actelion and UCB Pharma.

XM received research grants from Pfizer, GlaxoSmithKline and Roche and consultancy fees from Bristol-Myers Squibb, GlaxoSmithKline, Pfizer, Roche, UCB Pharma and Sanofi-Aventis. DvdH received consultancy fees from AbbVie, Amgen, AstraZeneca, Augurex, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Centocor, Chugai, Covagen, Daiichi, Eli-Lilly, Galapagos, GlaxoSmithKline, Janssen, Merck, Novo-Nordisk, Otsuka, Pfizer, Roche, Sanofi-Aventis, UCB Pharma and Vertex; research grants from AbbVie, Amgen, AstraZeneca, Augurex, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Centocor, Chugai, Covagen, Daiichi, Eli-Lilly, Galapagos, GlaxoSmithKline, Janssen, Merck, Novo-Nordisk, Otsuka, Pfizer, Roche, Sanofi-Aventis, UCB Pharma and Vertex and is Director of Imaging at Rheumatology BV.

RvV received research support from AbbVie, Bristol-Myers Squibb, GlaxoSmithKline, Pfizer, Roche and UCB Pharma and consultancy fees from AbbVie, Biotest, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, Eli-Lilly, Merck, Pfizer, Roche, UCB Pharma and Vertex.

CA is an employee of UCB Pharma.

IM is an employee of UCB Pharma. OP is an employee of UCB Pharma.

DT is an employee of UCB Pharma.

BV is an employee of UCB Pharma.

MEW received research grants from Amgen, Bristol-Myers Squibb, Crescendo Bioscience and UCB Pharma and consultancy fees from AbbVie, Amgen, AstraZeneca, Bristol-Myers Squibb, Crescendo Bioscience, Eli-Lilly, MedImmune, Merck, Novartis, Pfizer, Roche and UCB Pharma.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	UCB Pharma explained to us that was a external central of randomisation
Allocation concealment (selection bias)	Low risk	UCB private files: "An IXRS (interactive voice/web response system) is used for subject registration as well as randomisation and treatment allocation". The system stratified by disease duration of more or less than 4 months
Blinding (performance bias and detection bias) ACR50	Low risk	UCB private files; "Sponsor, investigator site and vendor staff involved will be blinded to the testaments assignment with the following exceptions: sponsor clinical study supplies coordinator and qualifier person unblinded site personnel involved in ESR determination"

Emery 2015 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	UCB private files: "Sponsor, investigator site and vendor staff involved will be blinded to the testaments assignment with the following exceptions: sponsor clinical study supplies coordinator and qualifier person unblinded site personnel involved in ESR determination"
Incomplete outcome data (attrition bias) ACR50	Low risk	Participants not achieving sufficient improvement (defined as DAS (ESR) < 3.2 and/or > 1.2 point improvement in DAS 28 (ESR)) from baseline at weeks 20 and 24 were withdrawn to allow them to switch to a complementary medication. There were 34% of withdrawals in placebo group and 24% in certolizumab pegol group at week 52
Incomplete outcome data (attrition bias) All outcomes	Low risk	See above
Selective reporting (reporting bias)	Low risk	All the outcomes in the protocol in www.clinicaltrials.gov were available
Other bias	Low risk	The study appears to be free of other sources of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	UCB private files: "Sponsor, investigator site and vendor staff involved will be blinded to the testaments assignment with the following exceptions: sponsor clinical study supplies coordinator and qualifier person unblinded site personnel involved in ESR determination"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	UCB private files: "Sponsor, investigator site and vendor staff involved will be blinded to the testaments assignment with the following exceptions: sponsor clinical study supplies coordinator and qualifier person unblinded site personnel involved in ESR determination"

Fleischmann 2009

Methods	Randomised double-blind trial
Participants	220 people aged 18 - 75 years
Interventions	1. Certolizumab pegol 400 mg sc every 4 weeks (n = 111) 2. Placebo (n = 109) for 24 weeks
Outcomes	ACR20, 50, 70, HAQ-DI, pain (VAS and mBPI), DAS-28, fatigue, and SF-36 Follow-up 24 weeks
Notes	CPD870-011 **FAST4WARD** **Countries/Cities**: conducted at 36 sites in Austria, Czech Republic and the USA. **Dates conducted:** June 2003 to July 2004 **Eligibility criteria**: with RA defined by the ACR classification criteria who had previously failed at least 1 DMARD were included. Those previously treated with a TNF inhibitor were excluded. Participants had to have a TJC of ≥ 9 (out of 68), SJC of ≥ 9 (out of 66) and 1 of the following: morning stiffness of ≥ 45 minutes; ESR ≥ 28 mm/H; or CRP > 10 mg/L. People with a previous history of a serious or life-threatening infection were excluded. People with a history of TB, or evidence of TB on a chest radiograph, or those with a positive reaction to PPD reaction were also excluded. Patients on concurrent corticos-

Fleischmann 2009 *(Continued)*

teroids were allowed entry provided the dose was the equivalent of 10 mg or less of prednisolone. Parenteral corticosteroids were not permitted

Adverse events as a specified outcome:safety were assessed at baseline and weeks 1, 2, 4, 8, 12, 16, 20 and 24, with additional safety assessments at 4 and 12 weeks post final dose. Additional plasma samples were taken at weeks 21 and 22.

Funding sources: UCB

Conflict of interest: JV has received a fee from UCB for speaking at a National Congress; RFvV has received consulting fees from UCB; DB has received reimbursement from UCB for attending a symposium and funds for research; JB has received reimbursement from UCB for attending a symposium and funds for research; GC is a full time employee of and holds stocks in UCB; AI is a full time employee at UCB and has shares in the company; NG is a full time employee of UCB and has shares and stock options in the company; VS has worked as an independent biopharmaceutical consultant in clinical development and regulatory affairs since September 1991 and is currently a consultant to various companies, but has not and does not now hold stock in any company. RF has received consulting fees and funds for clinical research from UCB.

JV has received a fee from UCB for speaking at a National Congress;

RFvV has received consulting fees from UCB; DB has received reimbursement from UCB for attending a symposium and funds for research; JB has received reimbursement from UCB for attending a symposium and funds for research;

GC is a full time employee of and holds stocks in UCB; AI is a full time employee at UCB and has shares in the company;

NG is a full time employee of UCB and has shares and stock options in the company;

VS has worked as an independent biopharmaceutical consultant in clinical development and regulatory affairs since September 1991 and is currently a consultant to various companies, but has not and does not now hold stock in any company.

RF has received consulting fees and funds for clinical research from UCB.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Code list prepared by independent group
Allocation concealment (selection bias)	Low risk	Via IVRS
Blinding (performance bias and detection bias) ACR50	Low risk	UCB stated: "All the study staff with the exception of the unblinded dispenser, was blind to the treatment". "Each study center was required to have a written blinding plan in place signed by the principal investigator, which detailed the study center's steps for ensuring that the double blind nature of the study was maintained"
Blinding (performance bias and detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias) ACR50	Low risk	68.5% of certolizumab pegol group and 25.7% of placebo completed 6 months of treatment. We imputed missing data for analysis
Incomplete outcome data (attrition bias)	Low risk	Full account of all withdrawals and reasons for withdrawals

Fleischmann 2009 *(Continued)*

All outcomes		Quote: "All efficacy analyses were performed on the modified intent to treat (mITT) population (all randomised patients who had taken >1 dose of study medication). The actual number of subjects in the summaries varies slightly from the mITT numbers due to non-imputable missing data for each parameter. For the primary analysis, patients were considered ''responders'' if they achieved an ACR20 response vs baseline at week 24. Patients who withdrew for any reason were considered non responders." The safety analysis was based on the 'last observation carried forward' approach
Selective reporting (reporting bias)	Low risk	All the outcomes were available
Other bias	Low risk	The study appears to be free of other sources of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	See above
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above

Keystone 2008

Methods	Randomised double-blind trial
Participants	982 participants aged > 18 years Participants were randomised 2:2:1
Interventions	1. Certolizumab pegol sc at an initial dosage of 400 mg given at weeks 0, 2, and 4, with a subsequent dosage of 200 mg (n= 393)or 400 mg given every 2 weeks, plus MTX (n=390) 2. Placebo plus MTX, same regimen (n=199)
Outcomes	Co-primary endpoints: ACR20 at week 24 and the mean change from baseline in the mTSS at week 52 Major secondary end points: Change from baseline in mTSS at week 24 Change from baseline in the HAQ-DI at weeks 24 and 52 ACR20 responder rate at week 52 ACR50 and ACR70 responder rates at weeks 24 and 52 Follow-up 24 - 52 weeks
Notes	**RAPID1 Trial** **Countries/Cities**:79 sites from EEUU, Argentina, Australia, Belgium, Bulgaria, Canada, Chile, Croatia, Czech Republic, Israel, Latvia, Russian Federation,Ukraine **Dates conducted:** from February 2005 to October 2006 **Eligibility criteria**: patients were aged 18 years or older with active RA (according to the 1987 ACR RA classification criteria with an inadequate response to MTX therapy (≥ 10 mg weekly for ≥ 6 months with stable doses for ≥ 2 months prior to baseline). Patients were ineligible if they had previously failed to respond to treatment with a TNF inhibitor. People with a history of TB or a chest radiograph showing active or latent TB or those with a positive reaction to PPD were also excluded

Keystone 2008 *(Continued)*

Adverse events as a specified outcome: adverse events and serious adverse events were reported

Funding sources: UCB Pharma

Conflict of interest: Dr. Keystone has received consulting fees, speaking fees, and/or honoraria from Abbott, Amgen, Wyeth, Centocor, UCB, Roche, Genentech, Schering-Plough, and Bristol-Myers Squibb (less than USD 10,000 each).

Dr. van der Heijde has received consulting fees, speaking fees, and/or honoraria from Abbott, Amgen, Centocor, UCB, Roche, Schering-Plough, and Bristol-Myers Squibb (less than USD 10,000 each). Dr. Landewe´ has received consulting fees, speaking fees, and/or honoraria from Abbott, Amgen, Bristol-Myers Squibb, Centocor, Schering-Plough, UCB, and Wyeth (less than USD 10,000 each).

Dr. van Vollenhoven has received consulting fees, speaking fees, and/or honoraria from UCB (more than USD 10,000).

Dr. Combe has received consulting fees, speaking fees, and/or honoraria from Abbott, Bristol-Myers Squibb, Merck, Sharp, & Dohme, Roche, Schering, UCB, and Wyeth (less than USD 10,000 each).

Dr. Emery has received consulting fees from UCB (less than USD 10,000). Dr. Strand receives consulting fees (her primary source of income) from Abbott Immunology, Allergan, Almirall, AlPharma, Amgen, AstraZeneca, Bayhill, Bexel, Biogen Idec, Can-Fite, Centocor, Chelsea, Cypress Bioscience, Dianippon Sumitomo, Euro-Diagnostica, FibroGen, Forest, Genelabs, Genentech, Human Genome Sciences, Idera, Incyte, Jazz, Lexicon Genetics Lux Biosciences, Merck Serono, Novartis, Novo Nordisk, Noxxon Pharma, Nuon, Ono Pharmaceutical, Pfizer, Procter & Gamble, Rigel, RiGEN, Roche, Sanofi-Aventis, Savient, Schering-Plough, Scios, SKK, UCB, VLST, Wyeth, XDx, and Zelos Therapeutics (less than USD 10,000 each) and receives fees as a member of the advisory board for Abbott, Amgen, Biogen Idec, Bioseek, Bristol-Myers Squibb, Can-Fite, Centocor, Chelsea, Cypress, Euro-Diagnostica, Forest, Idera, Incyte, Jazz, Novartis, Pfizer, Rigel, RiGEN, Roche, Savient, Schering-Plough, UCB, XDx, and Wyeth (less than USD 10,000 each).

Dr. Mease has received consulting fees, speaking fees, and/or honoraria from UCB (less than USD 10,000).

Mr. Desai owns stock or stock options in UCB

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Code list prepared by independent group
Allocation concealment (selection bias)	Low risk	IVRS used to allocate participant to treatment group (2:2:1 ratio)
Blinding (performance bias and detection bias) ACR50	Low risk	UCB stated: "All the study staff with the exception of the unblinded dispenser, was blind to the treatment. Each study center was required to have a written blinding plan in place signed by the principal investigator, which detailed the study center's steps for ensuring that the double blind nature of the study was maintained"
Blinding (performance bias and detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias) ACR50	Low risk	65% of certolizumab 200 mg and 70.3% certolizumab 400 mg of group and 22% of placebo completed 12 months of treatment. We imputed missing data for analysis

Keystone 2008 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Full account of all withdrawals and reasons for withdrawals HAQ, quote: "Analyses were performed using the last observation carried forward (LOCF) method for imputation of missing scores in the total ITT population and the actual scores (observed) in those who withdrew at week 16" Safety: ITT analysis
Selective reporting (reporting bias)	Low risk	All the outcomes that are of interest to this review have been reported in the prespecified way
Other bias	Low risk	The study appears to be free of other sources of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	See above
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above

NCT00993317

Methods	Randomised, double-blind (participant, investigator, outcomes assessor), placebo-controlled, parallel-assignment, safety/efficacy study
Participants	Adult-onset RA (18 Years to 75 Years) of at least 6 months but not longer than 15 years, as defined by the 1987 ARA's criteria, with active disease
Interventions	1. CDP870 200 mg, 400 mg CDP870 given at weeks 0, 2, 4, and thereafter 200 mg CDP870 given every 2 weeks until week 22 (sc) plus MTX (n= 85) 2. Placebo plus MTX, same regimen (n= 42)
Outcomes	ACR20, ACR50, ACR70 responder rate; changes in HAQ-Di Follow-up 24 weeks
Notes	See clinicaltrials.gov/ct2/show/study/NCT00993317 **Countries/Cities**: 15 hospital in Korea **Dates conducted: f**rom October 2009 to August 2011 **Eligibility criteria**: • Adult-onset RA of at least 6 months but not longer than 15 years in duration as defined by the 1987 American College of Rheumatology classification criteria • Active RA disease as defined by at least 9 tender joints and 9 swollen joints, ESR of 30 mm/hour or CRP of 1.5 mg/dL • MTX (with or without folic acid) for at least 24 weeks prior to the Baseline visit, The dose of MTX and route of administration must have been stable for at least 8 weeks prior to the baseline visit. The minimum stable dose of MTX allowed is 10 mg weekly. **Adverse events as a specified outcome**: adverse events and serious adverse events were reported **Funding sources:** Korea Otsuka Pharmaceutical Co Ltd

NCT00993317 *(Continued)*

	Conflict of interest: "Principal Investigators are **NOT** employed by the organization sponsoring the study". "There is **NOT** an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	External central randomisation
Allocation concealment (selection bias)	Low risk	The allocation sequence was generate using uniform random numbers from SAS RANUNI function
Blinding (performance bias and detection bias) ACR50	Low risk	"All study staff with the exception of the unblinded dispenser were blind to the treatment, ... These unblinded personnel were not allowed to engage in any other study activities"
Blinding (performance bias and detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias) ACR50	Low risk	70% of certolizumab pegol group and 50% of placebo completed 6 months of treatment. We imputed missing data for analysis
Incomplete outcome data (attrition bias) All outcomes	Low risk	Full account of all withdrawals and reasons for withdrawals Raw data Per protocol analysis in change in HAQ-DI; 95% of certolizumab pegol group and 95% of placebo were imputed for analysis Safety: ITT Judged at high risk of bias due to > 20% dropout rate at 24 months in the treatment group
Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way
Other bias	Low risk	The study appears to be free of other sources of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	See above
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above

Smolen 2009

Methods	Randomised double-blind trial

Smolen 2009 *(Continued)*

Participants	619 participants aged > 18 years Participants were randomised 2:2:1
Interventions	1. Certolizumab pegol sc, 400 mg at weeks 0, 2 and 4, followed by 200 (n= 246)or 400 mg every 2 weeks, plus MTX (n= 246) 2. Placebo (saline) plus MTX (n= 127)
Outcomes	Primary endpoints: ACR20 response at week 24, and physician's global assessment of disease activity, participant's assessment of pain, HAQ-DI and serum CRP or ESR Secondary endpoints: ACR50, ACR70, mean change from baseline in van der Heijde mTSS, SF-36 Health Survey,and individual ACR core set variables. Disease activity was assessed using the DAS-28 (ESR) Follow-up 24 weeks
Notes	**RAPID2 Trial** **Countries/Cities**: 121 sites from EEUU, Argentina, Australia, Belgium, Bulgaria, Canada, Chile, Croatia, Czech Republic, Estonia, Finland, France, Hungary, Israel, Latvia, Lithuania, Mexico, New Zealand, Russian Federation, Serbia, Slovakia, Ukraine **Dates conducted:** from June 2005 to February 2012 **Eligibility criteria**: RA of at least 6 months and defined by the ACR classification criteria who had received MTX for ≥ 6 months at a stable dose of ≥ 10 mg/week for at least 2 months before baseline were included. At inclusion, participants had to have active disease as defined by: TJC and SJC of ≥ 9, ESR ≥ 30 mm/H, and a CRP of ≥15 mg/L. People with a disease duration of > 15 years were excluded. People previously treated with a TNF inhibitor were also excluded if they had previously failed to respond to treatment. Participants with history of, or positive chest x-ray findings for TB, or a PPD skin test (defined as positive indurations by 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 TB, the person could be enrolled at the discretion of the investigator. In total, 101 participants (16%) were enrolled with a PPD test > 5 mm at baseline. Participants 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. **Adverse events as a specified outcome**: adverse events and serious adverse events were reported **Funding sources:** UCB Pharma **Conflict of interest:** J Smolen, R B Landewé, P Mease, RF van Vollenhoven, A Kavanaugh, M Schiff, GR Burmester, V Strand and D van der Heijde serve as consultants to UCB, Inc. RB Landewé, A Kavanaugh, M Schiff and D van der Heijde receive research funding from UCB, Inc and GR Burmester J Vencovsky have received honorarium from UCB, Inc for speaking. D Mason and K Luijtens are employees of UCB, Inc. J Brzezicki has nothing to disclose

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Code list prepared by independent group

Smolen 2009 *(Continued)*

Allocation concealment (selection bias)	Low risk	IVRS used to allocate participant to treatment group (2:2:1 ratio)
Blinding (performance bias and detection bias) ACR50	Low risk	UCB stated: "All the study staff with the exception of the unblinded dispenser, was blind to the treatment. Each study center was required to have a written blinding plan in place signed by the principal investigator, which detailed the study center's steps for ensuring that the double blind nature of the study was maintained"
Blinding (performance bias and detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias) ACR50	Low risk	71% of certolizumab pegol 200 mg and 74% of certolizumab pegol 400 mg respectively and 13% of placebo groups completed 6 months of treatment. We imputed missing data for analysis
Incomplete outcome data (attrition bias) All outcomes	Low risk	Full account of all withdrawals and reasons for withdrawals Safety: ITT analysis. Quote: "two patients in the placebo group received certolizumab pegol 200 mg and were included in the certolizumab pegol 200 mg group for safety evaluations"
Selective reporting (reporting bias)	Low risk	All the outcomes that are of interest in the review have been reported in the prespecified way
Other bias	Low risk	The study appears to be free of other sources of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	See above
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Radiographs were read centrally and blinded (for treatment, visit and participant identification) and checked independently by 2 experienced readers

Smolen 2015

Methods	A Phase IIIB, multicentre, double-blind, placebo-controlled, parallel-group study to evaluate the safety and efficacy of certolizumab pegol, administered with DMARD
Participants	People with low to moderate disease activity RA on DMARDs therapy for at least 6 months.
Interventions	1. 2 x 200 mg certolizumab pegol sc injections at week 0, week 2, (96 patients)and week 4, followed by 200 mg injections every 2 weeks until the last drug administration (Week 22) 2. Placebo (98 patients) , same regimen
Outcomes	Efficacy evaluations were performed every 4 weeks from weeks 0 to 52. Adverse events (AEs) were assessed every two weeks. Primary efficacy endpoint was the proportion of patients in stable CDAI remission (CDAI≤2.8) at both weeks 20 and 24. Secondary outcomes included: DAS remission, ACR20, ACR50, ACR70, SDAI, HAQ-DI, SF-36, Change From Baseline in Patient's Global Assessment of Disease Activity - Visual Analog Scale (PtGADA-VAS) and Change From Baseline in Fatigue Assessment Scale at Week 24 Follow-up 24 weeks
Notes	**CERTAIN Trial**

Smolen 2015 *(Continued)*

http://clinicaltrials.gov/ct2/show/NCT00674362?term=NCT00674362&rank=1

Countries/Cities: All patients, recruited from centres in Austria, France, Germany, Italy and Poland

Dates conducted: conducted between June 2008 and December 2010.

Eligibility criteria: Eligible patients (≥18 years of age) had a diagnosis of RA23 (6 months–10 years), LDA/MDA at screening and baseline (defined by CDAI >6 and ≤16, ≥2 tender joints (28-joint count, TJC), ≥2 swollen joints (28-joint count, SJC) and either erythrocyte sedimentation rate (Westergren-ESR) ≥28 mm/h or C-reactive protein (CRP) >10 mg/L). Patients must have received mono or combination DMARD therapy (MTX, leflunomide, sulfasalazine and/or hydroxychloroquine) for ≥6 months (dose stable ≥2 months) prior to baseline, with corticosteroid dose stable >1 month (for exclusion criteria, see online supplementary material).

Adverse events as a specified outcome: Safety analysis was performed up to week 52 plus 12-week safety follow-up

Funding sources: UCB

Conflict of interest: This study is not published. Despite this, the following statement was on the trials registry, "Principal Investigators are **NOT** employed by the organization sponsoring the study"

JS has received grants from and provided expert advice to UCB Pharma. PE has received grants and consultancy fees from UCB Pharma, Pfizer, Merck, Abbott, Roche and BMS. GF has received speaking fees from UCB Pharma.

WS has acted as a consultant for UCB Pharma.

FB has received consultancy fees for UCB Pharma.

HB is a consultant for UCB Pharma.

OD is an employee and a shareholder for UCB Pharma.

WK and OP are employees of UCB Pharma.

BB is a former employee of UCB Pharma and also holds stock options with UCB Pharma

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomised in a 1:1 ratio; Randomisation was performed centrally using an interactive voice-response system.
Allocation concealment (selection bias)	Low risk	Allocation by IVRS; so done remotely and therefore concealment satisfactory
Blinding (performance bias and detection bias) ACR50	Low risk	UCB stated: "All the study staff with the exception of the unblinded dispenser, was blind to the treatment. Each study center was required to have a written blinding plan in place signed by the principal investigator, which detailed the study center's steps for ensuring that the double blind nature of the study was maintained"
Blinding (performance bias and detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias) ACR50	Low risk	Full account of all withdrawals and reasons for withdrawals 87.5% of certolizumab pegol group and 81% of placebo completed 6 months of treatment. We imputed missing data for analysis

Smolen 2015 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	85% in SF-36, 84% in Pain VAS, and 94% in HAQ of certolizumab pegol group completed 24 months of treatment. We imputed missing data for analysis. ITT in safety analysis
Selective reporting (reporting bias)	Low risk	All the prespecified outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Subject, caregiver, investigator and outcome assessor"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Subject, caregiver, investigator and outcome assessor"

Weinblatt 2012

Methods	Randomised, double-blind (subject, outcomes assessor), parallel-assignment, safety/efficacy study
Participants	Adults with established moderate-to-severe rheumatoid arthritis
Interventions	1. 400 mg certolizumab pegol given as 2 x 200 mg sc injections at weeks 0, 2, and 4, followed by 200 mg certolizumab pegol given as 1 sc injection at weeks 6, 8, and 10. At Week 12 participants enter the open-label phase and receive 200 mg of certolizumab pegol every other week for a minimum 16 additional weeks until certolizumab pegol is commercially available (n=851) 2. Placebo (0.9% saline) given as 2 sc injections at weeks 0, 2, and 4, followed by placebo given as 1 sc injection at weeks 6, 8, and 10. At week 12 participants enter the open-label phase and receive 200 mg of certolizumab pegol every other week for a minimum 16 additional weeks until certolizumab pegol is commercially available (n=212)
Outcomes	Primary outcome: ACR20 response rate at week 12. Other outcomes: responder rate, disease activity, fatigue, physical functioning. Time frame: week 12 and every 8 weeks thereafter, until study completion Follow-up 12 weeks
Notes	clinicaltrials.gov/ct2/show/results/NCT00717236?term=NCT00717236&rank=1 **REALISTIC Trial** **Countries/Cities**: 181 sites in EEUU, Canada, Frannce, Italy, Netherlands and Spain **Dates conducted:** from July 2008 to March 2011 **Eligibility criteria**: Eligible patients were ≥18 years of age, had adult-onset RA as defined by the 1987 ACR criteria for at least 3 months and showed an unsatisfactory response or intolerance to at least one DMARD (MTX, LEF, SSZ, chloroquine or HCQ, AZA and/or gold). Subjects had active disease as defined by at least five tender and at least four swollen joints (28-joint count) and either ≥10 mg/l CRP or ≥28 mm/h ESR (Westergren method) at screening. **Adverse events as a specified outcome**: adverse events and serious adverse events were reported **Funding sources:** UCB Pharma

Weinblatt 2012 *(Continued)*

Conflict of interest: "Principal Investigators are **NOT** employed by the organization sponsoring the study.". " There **IS** an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed." " Restriction Description: UCB has > 60 but <= 180 days to review results communications prior to public release and may delete information that is confidential and compromises ongoing studies or is considered proprietary. This restriction is not intended to compromise the objective scientific integrity of the manuscript, it being understood that the results shall be published regardless of outcome"

M.D. has received research grants and consulting fees from Abbott Laboratories, Bristol-Myers Squibb, Pfizer, Roche and UCB Pharma.

T.W.J.H. has received consulting fees from UCB Pharma.

R.F.v.V. has received research grants and consulting fees from UCB Pharma. C.O.B. has served as an investigator and received consulting fees from UCB Pharma. J.P. has received research grants and consulting fees from UCB Pharma, Abbott Laboratories, Actelion, Amgen, AstraZeneca, Bristol-Myers Squibb, Genentech, GlaxoSmithKline, Johnson & Johnson, MedImmune, Merck, Novartis, Pfizer, Roche, Sanofi, Sorono, Teva and United Therapeutics.

N.G. is a former employee of UCB Pharma and is currently an employee of Quintiles. N.G. owns UCB Pharma stock.

R.F. has received research grants and consulting fees from UCB Pharma.

M.E.W. has received research grants from Abbott, Bristol-Myers Squibb, Roche, Biogen/Idec, Medimmune, Cresendo Bioscience and UCB Pharma, and consulting fees from UCB Pharma, Abbott Laboratories, Amgen, Bristol-Myers Squibb, Roche, Biogen/Idec, Medimmune, Cresendo Bioscience Pfizer and Centocor.

J.W. has received consultancy fees from, and participated in a speakers bureau for, UCB Pharma. O.D. is a UCB Pharma employee and has stocks, stock options or bond holdings in UCB Pharma.

P.E. has received research grants and consulting fees from Pfizer, Merck, Abbott Laboratories, Roche, Bristol-Myers Squibb and UCB Pharma. B.D. is a UCB Pharma employee and owns UCB Pharma stock.

E.M. has received consulting fees from UCB Pharma, Amplimmune, Constellation Pharmaceuticals and Wachovia; has worked as an investigator for Bristol-Myers Squibb and Roche; and has received honorarium from the ACR and Up to Date.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomised 4:1 via an interactive voice response system"
Allocation concealment (selection bias)	Low risk	"Patients were randomised 4:1 via an interactive voice response system"
Blinding (performance bias and detection bias) ACR50	Low risk	Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken. UCB stated: "All the study staff with the exception of the unblinded dispenser, was blind to the treatment". "Each study center was required to have a written blinding plan in place signed by the principal investigator, which detailed the study center's steps for ensuring that the double blind nature of the study was maintained"
Blinding (performance bias and detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias)	Low risk	90% of certolizumab pegol group and 86% of placebo completed 12 weeks of treatment

Weinblatt 2012 *(Continued)*
ACR50

Incomplete outcome data (attrition bias) All outcomes	Low risk	Full account of all withdrawals and reasons for withdrawals ITT analysis for efficacy outcomes but per protocol analysis for safety: 9 participants fewer in certolizumab pegol arm and 3 fewer in placebo group
Selective reporting (reporting bias)	Low risk	All the outcomes that are of interest to this review have been reported in the prespecified way
Other bias	Low risk	The study appears to be free of other sources of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Although blinding is not described, blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken

Yamamoto (a) 2014

Methods	Randomised, double-blind trial
Participants	Eligible patients were aged 20–74 years, Certoluzimab pegol (n= 116) Placebo (n= 114)
Interventions	1. Induction dose of 400 mg in weeks 0, 2 and 4, and thereafter 200 mg CDP870 given sc every 2 weeks until week 22 2. Placebo, same regimen
Outcomes	Primary outcome: ACR20 at week 12 Secondary outcome: ACR20 at week 24 Follow-up 24 weeks
Notes	clinicaltrials.gov/ct2/show/NCT00791921?term=00791921&rank=1 **HIKARI Trial** **Countries/Cities**: 66 centers across Japan **Dates conducted:** between 19 November 2008 and 16 September 2010 **Eligibility criteria**: patients with active RA who could not receive MTX due to insufficient efficacy, safety concerns or previous discontinuation for safety reasons. inclusion criteria: • Must have a diagnosis of adult-onset RA of at least 6 months but not longer than 15 years as defined by the 1987 ACR classification criteria • Must have active RA disease as defined by: at least 6 tender joints and 6 swollen joints; ESR of 28 mm/hour or CRP of 2.0 mg/dL • Have failed to respond or have been resistant to at least 1 DMARD (including MTX) • MTX cannot be administered for any of the reasons: incomplete response/safety concerns Exclusion criteria:

Yamamoto (a) 2014 *(Continued)*

- A diagnosis of any other inflammatory arthritis
- Have a secondary, non-inflammatory type of arthritis (e.g. osteoarthritis, fibromyalgia)
- Currently have, or who have a history of, a demyelinating or convulsive disease of the central nervous system (e.g. multiple sclerosis, epilepsy)
- Have NYHA Class III or IV congestive heart failure
- Have, or who have a history of, tuberculosis
- Have a high risk of infection (with a current infectious disease, a chronic infectious disease, a history of serious infectious disease)
- Currently have, or who have a history of, malignancy
- Women who are breastfeeding or pregnant, who are of childbearing potential
- Previously received treatment with 2 or more anti-TNFα drugs or who previously failed to respond to treatment with 1 or more anti-TNFα drugs

Fewer than 10% of the participants were exposed to a previous TNF with a wash-out period minimum of 3 months for etanercept or 6 months for other biologics

Adverse events as a specified outcome: Treatment-emergent AEs (TEAEs) included all events from after administration of study drug until the last evaluation visit (not including the safety follow-up visit). TEAEs were coded by system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA)

Funding sources: Otsuka Pharmaceutical Co., Ltd. and UCB Japan

Conflict of interest: This study is already not published. This statement was in the trials registry: "Principal Investigators are **NOT** employed by the organization sponsoring the study. There is **NOT** an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed".

KY has served as a consultant for UCB Pharma, Pfizer, Abbott, BMS, Roche, Chugai, Mitsubishi-Tanabe and Eisai and has received research funding from UCB Pharma, Pfizer, Abbott, Santen, Mitsubishi-Tanabe and Eisai.

TT has served as a consultant for AstraZeneca, Eli Lilly, Novartis, Mitsubishi-Tanabe and Asahi Kasei, has received research support from Abott, Astellas, BMS, Chugai, Daiichi-Sankyo, Eisai, Janssen, Mitsubishi-Tanabe, Nippon Shinyaku, Otsuka, Pfizer, Sanofi-Aventis, Santen, Takeda and Teijin, and has served on speaker bureaus for Abbott, BMS, Chugai, Eisai, Janssen, Mitsubishi-Tanabe, Pfizer and Takeda.

HY has served as a consultant for, and received research funding from, UCB Pharma, Abbott, Astellas, BMS, Chugai, Eisai, Janssen, Mitsubishi-Tanabe, Pfizer and Takeda.

NI has received research funding from Takeda, Mitsubishi- Tanabe, Astellas, Chugai, Abbott, BMS, Eisai, Janssen, Kaken and Pfizer and has served on speaker bureaus for Takeda, Mitsubishi-Tanabe, Astellas, Chugai, Abbott, BMS, Eisai, Janssen, Kaken, Pfizer, Taisho-Toyama and Otsuka.

YT has received research funding from BMS, MSD, Chugai, Mitsubishi-Tanabe, Astellas, Abbott, Eisai and Janssen and has served on speaker bureaus for UCB Pharma, Mitsubishi- Tanabe, Abbott, Eisai, Chugai, Janssen, Santen, Pfizer, Astellas, Daiichi-Sankyo, GSK, AstraZeneca, Otsuka, Actelion, Eli Lilly, Nippon Kayaku, Quintiles Transnational and Ono.

KE has served as a consultant for UCB Pharma

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	External central of randomisation. Randomization by blocks

Yamamoto (a) 2014 *(Continued)*

Allocation concealment (selection bias)	Low risk	The allocation sequence was generate using uniform random numbers from SAS RANUNI function
Blinding (performance bias and detection bias) ACR50	Low risk	"All study staff with the exception of the unblinded dispenser were blind to the treatment, ... These unblinded personnel were not allowed to engage in any other study activities"
Blinding (performance bias and detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias) ACR50	Low risk	71% of certolizumab pegol group and 15% of placebo completed 6 months of treatment. We imputed missing data for analysis
Incomplete outcome data (attrition bias) All outcomes	Low risk	Full account of all withdrawals and reasons for withdrawals ITT analysis. Quote: "Of the 230 subjects in the Full Analysis Set (FAS), 230 are included in the adverse event reporting based upon the Safety Set (SS) population. The Safety Set includes all subjects randomised who received at least 1 dosing"
Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest to this review have been reported in the prespecified way
Other bias	Low risk	The study appears to be free of other sources of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Without any details
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above

Yamamoto (b) 2014

Methods	Treatment, randomised, double-blind (participant, caregiver, investigator, outcomes assessor), dose-comparison, parallel-assignment, safety/efficacy study
Participants	Eligible patients were aged from 20–74 years and had a diagnosis of RA defined by ACR (1987) criteria for 0.5–15 years.
Interventions	Patients were randomised 1:1:1:1 to subcutaneous CZP 100, 200, or 400 mg plus MTX, or saline placebo plus MTX, every 2 weeks (Q2W). 1. Drug: CDP870 400 mg (n= 85) 2. Drug: CDP870 200 mg (n= 82) 3. Drug: CDP870 100 mg (n= 72) 4. Drug: placebo of CDP870 (n=77)
Outcomes	Primary outcome measures:ACR20 responder rate: week 12, 24 Secondary outcome measures:ACR20/50/70 responder rate: weeks 1, 2, 4, 6, 8, 12, 14, 16, 20, 24DAS-28 (ESR): weeks 1, 2, 4, 6, 8, 12, 14, 16, 20, 24 Modified Total Sharp Score: week 24

Yamamoto (b) 2014 *(Continued)*

Follow-up 24 weeks

Notes

clinicaltrials.gov/ct2/show/NCT00791999?term=NCT00791999&rank=1

JRAPID Trial

Countries/Cities: 67 centers across Japan

Dates conducted: conducted between 19 November 2008 and 18 August 2010

Eligibility criteria: patients with active RA and an inadequate response to MTX received CZP or placebo while continuing to take their previous dosage of MTX. The MTX regimen could not be changed after initiation of the study treatment.

Adverse events as a specified outcome: Treatment-emergent AEs (TEAEs) included all events from after the administration of the study drug until the last evaluation visit (not including the safety follow-up visit). TEAEs were coded by system organ class and preferred term using MedDRA terminology (v11.1)

Funding sources: Otsuka Pharmaceutical Co., Ltd; UCB Japan Co. Ltd

Conflict of interest: "Principal Investigators are **NOT** employed by the organization sponsoring the study". "There is **NOT** an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed".

The competing interests of all authors are provided below.

KY has served as a consultant for UCB Pharma, Pfizer, Abbott, BMS, Roche, Chugai, Mitsubishi-Tanabe and Eisai, and has received research funding from UCB Pharma, Pfizer, Abbott, Santen Mitsubishi-Tanabe, and Eisai.

TT has served as a consultant for AstraZeneca, Eli Lilly, Novartis, Mitsubishi-Tanabe and Asahi Kasei, and has received research support from Abott, Astellas, BMS, Chugai, Daiichi-Sankyo, Eisai, Janssen, Mitsubishi-Tanabe, Nippon Shinyaku, Otsuka, Pfizer, Sanofi-Aventis, Santen, Takeda and Teijin, and has served on speaker bureaus for Abbott, BMS, Chugai, Eisai, Janssen, Mitsubishi-Tanabe, Pfizer and Takeda.

HY has served as a consultant for, and received research funding from, UCB Pharma, Abbott, Astellas, BMS, Chugai, Eisai, Janssen, Mitsubishi-Tanabe, Pfizer and Takeda.

NI has received research funding from Takeda, Mitsubishi-Tanabe, Astellas, Chugai, Abbott, BMS, Eisai, Janssen, Kaken and Pfizer, and has served on speaker bureaus for Takeda, Mitsubishi-Tanabe, Astellas, Chugai, Abbott, BMS, Eisai, Janssen, Kaken, Pfizer, Taisho-Toyama and Otsuka.

YT has received research funding from BMS, MSD, Chugai, Mitsubishi-Tanabe, Astellas, Abbott, Eisai and Janssen, and has served on speaker bureaus for UCB Pharma, Mitsubishi-Tanabe, Abbott, Eisai, Chugai, Janssen, Santen, Pfizer, Astellas, Daiichi-Sankyo, GSK, AstraZeneca, Otsuka, Actelion, Eli Lilly, Nippon Kayaku, Quintiles Transnational and Ono.

KE has served as a consultant for UCB Pharma.

AW has received research support from Astellas, Daiichi- Sankyo, Kyorin, Shionogi, Taisho, Dainippon-Sumitomo, Taiho, Toyama Chemical and Meiji Seika, and has served on speaker bureaus for Abott, MSD, Otsuka, GSK, Shionogi, Daiichi-Sankyo, Taisho-Toyama, Dainippon-Sumitomo, Mitsubishi-Tanabe, Toyama Chemical, Bayer and Pfizer.

HO has served as a consultant for UCB Pharma and Astellas.

TS is an employee of Otsuka.

YS is an employee of UCB Pharma.

DvH has served as a consultant for, and received research support from, AbbVie, Amgen, AstraZeneca, BMS, Centocor, Chugai, Daiichi, Eli Lilly, GSK, Janssen, Merck, Novartis, Novo-Nordisk, Otsuka, Pfizer, Roche, Sanofi-Aventis, Schering-Plough, UCB Pharma and Vertex. DvH is also director of Imaging Rheumatology bv.

Yamamoto (b) 2014 *(Continued)*

NM has received research support from Pfizer, Takeda, Mitsubishi-Tanabe, Chugai, Abbott, Eisai and Astellas.

TK has served on speaker bureaus for UCB Pharma, Pfizer, Chugai, Abbott, Mitsubishi-Tanabe, Takeda, Eisai, Santen, Astellas, Taisho-Toyama, BMS, Teijin and Daiichi-Sankyo.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	External central of randomisation. Randomization by blocks
Allocation concealment (selection bias)	Low risk	The allocation sequence was generate using uniform random numbers from SAS RANUNI function
Blinding (performance bias and detection bias) ACR50	Low risk	"All study staff with the exception of the unblinded dispenser were blind to the treatment, ... These unblinded personnel were not allowed to engage in any other study activities"
Blinding (performance bias and detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias) ACR50	Low risk	66% of certolizumab pegol 100 mg, 80% of certolizumab pegol 200 mg, and 76% of certolizumab pegol 400 mg group (overall 74% in certolizumab pegol groups) and 32% of placebo completed 6 months of treatment. We imputed missing data for analysis.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Safety, quote: "Of the 316 subjects in the Full Analysis Set (FAS), 316 are included in the adverse event reporting based upon the Safety Set (SS) population. The Safety Set includes all subjects randomised who received at least 1 dosing"
Selective reporting (reporting bias)	High risk	Participants were recruited in Japan between 2008 and 2010. In 2008, DAS28 (ESR) and Modified Total Sharp Score were secondary outcomes. In 2012 these outcomes were deleted from clinicaltrials.gov/ct2/show/record/NCT00791999?term=NCT00791999&rank=1&sect=X0125
Other bias	Low risk	The study appears to be free of other sources of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No details available
Blinding of outcome assessment (detection bias) All outcomes	Low risk	See above

Østergaard 2015

Methods	Randomised, double-blind, placebo-controlled
Participants	41 participants with active RA despite DMARD. Participants were randomised 2:1

Østergaard 2015 *(Continued)*

Interventions	1. certolizumab pegol (loading dose 400 mg every 2 weeks at weeks 0 – 4; certolizumab pegol 200 mg every 2 weeks at weeks 6 – 16) (n= 27) 2. Placebo, then certolizumab pegol (placebo at weeks 0 – 2; certolizumab pegol loading dose at weeks 2 – 6; certolizumab pegol 200 mg every 2 weeks at weeks 8 – 16) (n= 13)
Outcomes	Primary: Change in synovitis measured by Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT), Rheumatoid Arthritis Magnetic Resonance Image Scoring System (RAMRIS) score at weeks 1, 2, 4, 8 and 16 Secondary: Change From Baseline to Week 16 in the Dynamic Magnetic Resonance Image (MRI) Parameter, Initiation Rate of Enhancement (IRE); Change from baseline to week 16 in the dynamic MRI parameter, Maximal Enhancement (ME); Change from baseline to week 16 in the dynamic MRI parameter, number of voxels (Nvox) with plateau and washout pattern; Percentage of participants achieving a good European League Against Rheumatism (EULAR) response at week 16; Percentage of participants meeting the ACR 20% criteria at week 16
Notes	**MARVELOUS Trial** Only the data obtained at week 2 were useful. After week 2 both arms were treated with certolizumab pegol. Out of all the primary and secondary outcomes studied, only DAS and ACR20 measured at week 2 were reported. However since they are shown as a figure we are unable to use them. Only adverse event data were reported at week 2 **Countries/Cities**: Denmark, Polland, Netherlands, Sweden **Dates conducted: From NOvember 2010 to September 2013** **Eligibility criteria**: The study population was ≥18 years of age with adult-onset RA of between 3 months and 15 years duration, as defined by the 1987 American College of Rheumatology (ACR) classification criteria **Adverse events as a specified outcome**: adverse events and serious adverse events were reported **Funding sources:** UCB **Conflict of interest:** Principal Investigators are **NOT**employed by the organization sponsoring the study.The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **more than 60 days but less than or equal to 180 days.** The sponsor cannot require changes to the communication and cannot extend the embargo. Competing interests MØ has received grant/research support from Abbott, Pfizer and Centocor, has acted as a consultant for Abbott, Pfizer, Merck, Roche, and UCB Pharma and has taken part in speakers bureaus for Abbott, Pfizer, Merck, BMS, UCB Pharma, and Mundipharma; LTHJ has received grant/research support from Pfizer and has acted as a paid instructor for Abbvie, BMS, MSD, Pfizer and UCB Pharma; MSH has acted as sponsored investigator for UCB Pharma and participated as an advisory board member for Roche; JWJB has received grant/research support from Roche, UCB, Pfizer, MSD and BMS and has received consultancy fees from Roche, UCB, Pfizer, MSD, BMS and Jansen; FS, RH and BS-E are employees of UCB Pharma; HB has received consulting fees, honoraria, research or institutional support, educational grants, equipment, services or expenses from Abbott, Amgen, AstraZeneca, Aventis, Bristol Myers Squibb, Cambridge Nutritional Foods, Dansk Droge, Eurovita, Ferrosan, GlaxoSmithKline, Hoechst, LEO, Lundbeck, MSD, Mundipharma, Norpharma, NutriCare, Nycomed, Pfizer, Pharmacia, Pierre-Fabre, Proc-

Østergaard 2015 *(Continued)*

tor&Gamble, Rhone-Poulenc, Roche, Roussel, Schering-Plough, Searle, Serono, UCB Pharma and Wyeth.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	External central of randomisation
Allocation concealment (selection bias)	Low risk	IVRS
Blinding (performance bias and detection bias) ACR50	Unclear risk	Not measured at 2 weeks. Not applicable
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Due to differences in the presentation and viscosity of certolizumab pegol and placebo, all study treatments (certolizumab pegol and placebo) were administered by unblinded study centre personnel to maintain study blinding. The personnel administering the injections had no involvement in the study other than performing the ESR analysis
Incomplete outcome data (attrition bias) ACR50	Low risk	Not measured. Not applicable
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant withdrew prior to treatment and was not included in the Full Analysis Set (FAS), but it is not clear from which arm the participant withdrew. The FAS comprised 27 participants in the certolizumab pegol group and 13 in the placebo→certolizumab pegol group. During the double-blind phase, 4 participants discontinued treatment: 1 from the placebo→certolizumab pegol group due to withdrawal of consent, and 3 from the certolizumab pegol group, 2 due to AEs and 1 due to lack of efficacy. Since it is not clear at which point of the double-blind phase the withdrawals occurred, we did not input these data to the analysis
Selective reporting (reporting bias)	Low risk	All the outcomes listed in the protocol are reported in www.ClinicalTrial.gov. However, the data were measured at week 16 and so cannot be used
Other bias	Low risk	The study appears to be free of other sources of bias
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The personnel administering the injections had no involvement in the study"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Due to differences in the presentation and viscosity of certolizumab pegol and placebo, all study treatments (certolizumab pegol and placebo) were administered by unblinded study centre personnel to maintain study blinding. The personnel administering the injections had no involvement in the study other than performing the erythrocyte sedimentation rate analysis"

ACR: American College of Rheumatology
ARA: American Rheumatology Association
CDAI: coronary diffuse atheromatous index
CRP: C-reactive protein
DAS: disease activity score

DMARD: disease-modifying anti-rheumatic drug
ESR: erythrocyte sedimentation rate
HAQ-DI: health assessment questionnaire - disability index
ITT: intention-to-treat
IVRS: Interactive voice recognition system
mBPI: modified brief pain inventory
mTSS: modified total sharp score
MTX: methotrexate
NYHA: New York Heart Association
PPD: purified protein derivative
Q2W every two weeks
RA: rheumatoid arthritis
sc: subcutaneous
SDAI: Simplified Disease Activity Index
SF-36: short form 36
SJC: swollen joint count
TB: tuberculosis
TJC: tender joint count
VAS: visual analogue scale

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

Study	Reason for exclusion
Alten 2013	OLE
Bykerk 2015	The outcomes reported (Disease Burden on Workplace and Household Productivity) are not covered in our review
Curtis 2014	There is only one arm without placebo or any comparator
Curtis 2015a	There is only one arm without placebo or any comparator
Curtis 2015b	There is only one arm without placebo or any comparator
Dose Flex 2007	RCT that tested clinical efficacy of 2 dosing regimens of CZP (200 mg every 2 weeks or 400 mg every four weeks + MTX) compared to MTX alone for maintenance of clinical response up to 34 weeks in participants who have achieved ACR20 after a 16-week open-label run-in period of CZP treatment (CZP 200 mg every 2 weeks + MTX). Reason for exclusion is that participants do not have active disease at randomisation
Fleischmann 2013	OLE
Kavanaugh 2013	OLE
Kavanaugh 2014	There is only one arm without placebo or any comparator
Kivitz 2014	Phase IV clinical trial
NCT00160641	One simple group
NCT00160693	It is an OLE with just one simple group
NCT00753454	One simple group
NCT00843778	One simple group
NCT00851318	OLE

Study	Reason for exclusion
NCT00993668	Excluded because adverse events were studied in the blinded period just at 4 weeks
NCT01197066	OLE
NCT01255761 PREDICT	Phase IV. Both arms were treated with CZP 200 mg
NCT01292265	Phase IV
NCT01374971	Phase IV
NCT01443364	OLE
NCT01526434	OLE
NCT02319642	OLE
NCT02586246	OLE

OLE: open-label extension

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

NCT01295151

Trial name or title	SWITCH Clinical trial for patients with rheumatoid arthritis who have failed an initial TNF-blocking drug (SWITCH)
Methods	Randomised controlled trial
Participants	People that have failed an anti-TNF therapy (the first of the biological therapies to be introduced)
Interventions	Etanercept; abatacept; rituximab; adalimumab; certolizumab pegol; infliximab; golimumab
Outcomes	Change in disease activity at 6 months; EULAR and ACR scores; CDAI; quality of life
Starting date	2011
Contact information	Julia Brown, Director of Leeds Institute of Clinical Trials Research, University of Leeds
Notes	Only published the protocol : EXCLUDE Infliximab, adalimumab, certolizumab or golimumab if initial failure to the receptor fusion protein etanercept (choice of TNFi at investigator's discretion)

NCT01489384

Trial name or title	Cimzia treatment in rheumatoid arthritis: randomising to stop versus continue disease-modifying anti-rheumatic drug(s)
Methods	Randomised controlled trial
Participants	125 people with moderate to severe RA who are being prescribed CZP

NCT01489384 *(Continued)*

Interventions	CZP plus DMRA vs CZP alone
Outcomes	DAS28 < 3.2 at 18 months
Starting date	2011
Contact information	Janet Pope, MD (Pope Research Corporation)
Notes	The recruitment status of this study is unknown because the information has not been verified recently

NCT01491815

Trial name or title	Active conventional therapy compared to three different biologic treatments in early rheumatoid arthritis with subsequent dose reduction: NORD-STAR trial
Methods	This is an international (Nordic) trial designed to compare the safety and efficacy of active conventional therapy (ACT) and 3 biologic treatments in people with early rheumatoid arthritis (RA). The global aim of this study is to assess and compare 1. the proportion of participants who achieve remission with ACT versus 3 different biologic therapies (Certolizumab pegol, abatacept or tocilizumab) 2. 2 alternative de-escalation strategies in participants who respond to first-line therapy.
Participants	Estimated enrolment: 800
Interventions	Certolizumabl pegol, abatacept, tocilizumab
Outcomes	• The proportion of participants in remission at week 24 from baseline according to CDAI. • The proportion of participants in remission at week 24 after dose-reduction according to CDAI. • The radiographic progression of total Sharp van der Heijde score after 48 weeks from baseline
Starting date	2012; estimated completion data: 2020
Contact information	Contact: Ronald van Vollenhoven, MD, Prof. +46(0)851776077 ronald.van.vollenhoven@ki.se
Notes	

NCT01500278

Trial name or title	Study to assess the short- and long-term efficacy of certolizumab pegol plus methotrexate compared to adalimumab plus methotrexate in subjects with moderate to severe rheumatoid arthritis (RA) inadequately responding to methotrexate
Methods	RCT
Participants	916
Interventions	CZP plus MTX vs adalimumab plus MTX
Outcomes	ACR20 at 12 and 104 weeks

NCT01500278 *(Continued)*

Starting date	2011
Contact information	UCB Pharma
Notes	Without results in clinicaltrials.gov/ct2/show/study/NCT01500278?term=certolizumab&rank=34, nor abstract of proceedings

NCT01602302

Trial name or title	Ultrasound and withdrawal of biological DMARDs in rheumatoid arthritis (RA-BioStop)
Methods	Phase IV
Participants	Estimated enrolment: 110
Interventions	
Outcomes	Primary outcome measures: Active inflammation at the time of DMARD withdrawal indicated by the presence of a PD-score ≥ 1 in at least 1 joint out of a sonographic 14-joint count predicts relapse rate at week 16
Starting date	Estimated completion data: September 2017
Contact information	Contact: Christian Dejaco, MD, PhD +43-316-80595 christian.dejaco@gmx.net
Notes	This study is currently recruiting participants

NCT02151851

Trial name or title	A study of certolizumab pegol as additional therapy in Chinese patients with active rheumatoid arthritis (RAPID-C)
Methods	Phase 3, multi centre, double-blind, placebo-controlled, parallel-group, randomised 24-week trial
Participants	400 participants (300 with CZP/100 placebo)
Interventions	CZP 400 mg (200 mg prefilled syringe [PFS], i.e. 2 injections) at baseline, and weeks 2 and 4; then CZP 200 mg (1 injection) every 2 weeks until week 22
Outcomes	ACR20
Starting date	June 2014; completion data: June 2016
Contact information	UCB Cares; UCB Pharma
Notes	

NCT02293590

Trial name or title	Remission by Intra-articular injection plus CErtolizumab (RICE)

NCT02293590 *(Continued)*

Methods	An open-label, randomised study to compare the efficacy of certolizumab pegol (CZP) plus a dynamic or fixed dose treatment strategy in patients with rheumatoid arthritis; a Phase II study
Participants	48
Interventions	Intensive, adapted treatment strategy Certolizumab pegol (CZP, Cimzia (R)): 200 mg every 2 weeks after loading dose of 400 mg at Weeks 0, 2 and 4
Outcomes	ACR50 at 24 weeks
Starting date	October 2014
Contact information	Rüdiger B. Müller, Cantonal Hospital of St. Gallen
Notes	Recruiting participants

NCT02430909

Trial name or title	Multiple dose study of UCB4940 as add-on to certolizumab pegol in subjects with rheumatoid arthritis
Methods	Phase II double-blind, randomised, placebo-controlled study
Participants	No data
Interventions	Certolizumab pegol (400 mg at weeks 0, 2, and 4 followed by 200 mg every 2 weeks) until week 30 + placebo from week 8 to week 18 versus Certolizumab pegol (400 mg at weeks 0, 2, and 4 followed by 200 mg every 2 weeks) until week 30 + UCB4940 from week 8 until week 18
Outcomes	Adverse events; Change in DAS28 at week 20
Starting date	2015
Contact information	UCB Cares +1 887 822 9493 (UCB)
Notes	

NCT02466581

Trial name or title	Dose reduction for early rheumatoid arthritis patients with low disease activity
Methods	Phase IV. This is an international (Nordic) trial designed to compare the safety and efficacy of active conventional therapy (ACT) and 3 biologic treatments (certolizumab pegol, abatacept or tocilizumab) in people with early rheumatoid arthritis. The global aim of this study is to assess and compare 2 alternative de-escalation strategies in participants who achieved low disease activity during first-line therapy in the NORD-STAR study.
Participants	
Interventions	Active Comparator: Arm 1

NCT02466581 *(Continued)*	Participants keep the intervention they had in the NORD-STAR-study (NCT01491815), i.e. 1 of the 4 below: 1. Sulphasalazine + hydroxychloroquine OR prednisolone plus methotrexate and steroids 2. Cimzia plus methotrexate and steroids 3. Orencia plus methotrexate and steroids 4. RoActemra plus methotrexate and steroids Active Comparator: Arm 2 Participants keep the intervention they had in the NORD-STAR-study (NCT01491815), i.e. 1 of the 4 below: 1. Sulphasalazine + hydroxychloroquine OR prednisolone plus methotrexate and steroids 2. Cimzia plus methotrexate and steroids 3. Orencia plus methotrexate and steroids 3. RoActemra plus methotrexate and steroids. This intervention is de-escalated starting 24 weeks after randomisation
Outcomes	Proportion of participants maintaining low disease activity after dose reduction The proportion of participants, with early dose reduction vs late dose reduction, who maintain low disease activity (2.8 < CDAI ≤ 10.0) at 24 weeks after the dose was first reduced
Starting date	May 2015
Contact information	Ronald van Vollenhoven +46(0)851776077 ronald.van.vollenhoven@ki.se
Notes	This study is currently recruiting participants

CDAI: coronary diffuse atheromatous index
DMARD: disease-modifying anti-rheumatic drug

DATA AND ANALYSES

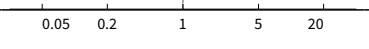
Comparison 1. Efficacy at 12 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR20	6	2902	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.79, 1.63]
1.1 certolizumab 50 mg sc	1	47	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.13, 0.57]
1.2 certolizumab 100 mg sc	2	145	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.09, 7.05]
1.3 certolizumab 200 mg sc	6	2456	Risk Ratio (M-H, Random, 95% CI)	1.66 [0.97, 2.85]

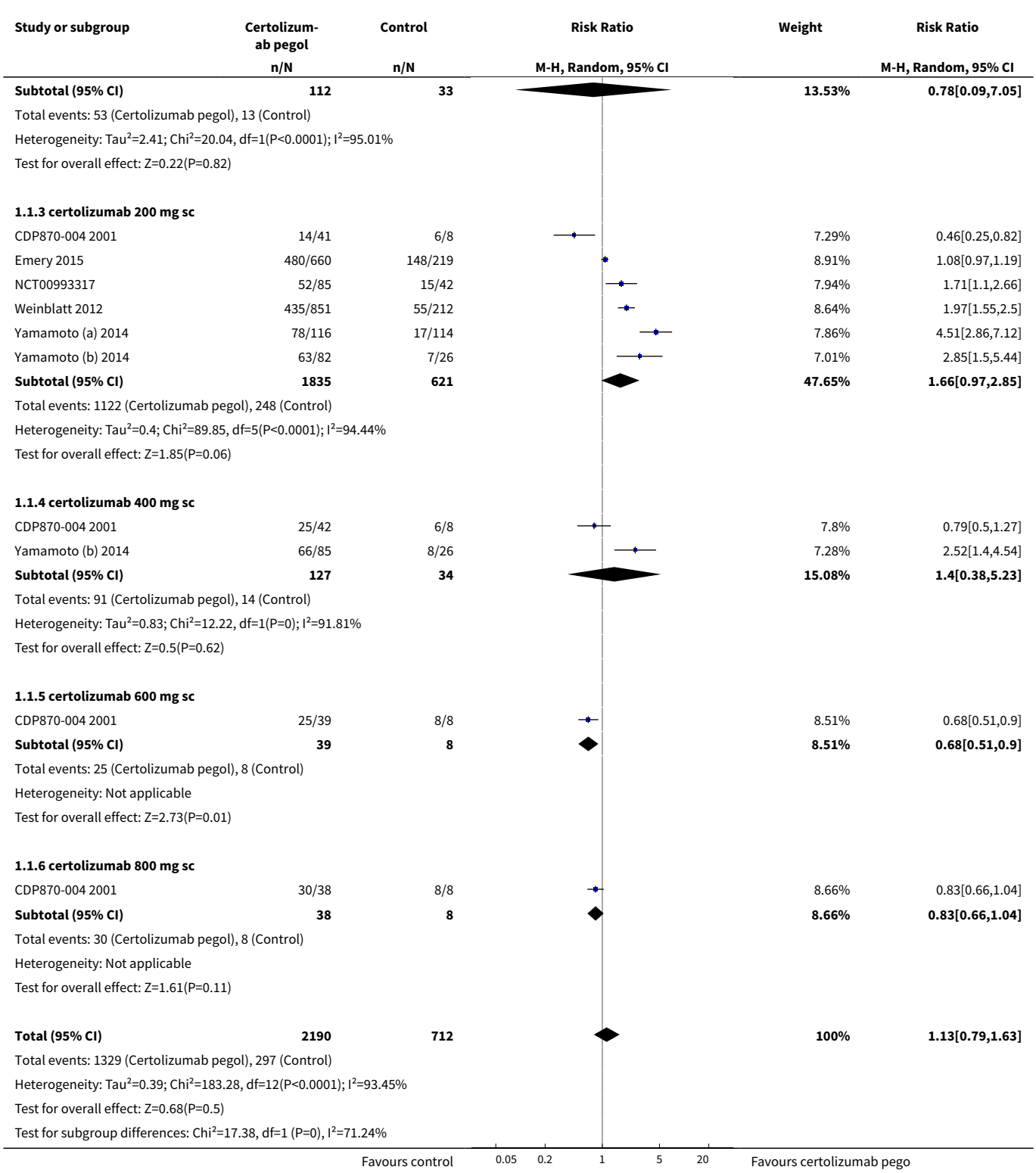
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4 certolizumab 400 mg sc	2	161	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.38, 5.23]
1.5 certolizumab 600 mg sc	1	47	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.51, 0.90]
1.6 certolizumab 800 mg sc	1	46	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.66, 1.04]
2 ACR50	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 certolizumab 50 mg sc	1	47	Risk Ratio (M-H, Random, 95% CI)	1.58 [0.09, 27.88]
2.2 certolizumab 100 mg sc	1	48	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.06, 20.96]
2.3 certolizumab 200 mg sc	4	2118	Risk Ratio (M-H, Random, 95% CI)	1.89 [1.06, 3.37]
2.4 certolizumab 400 mg sc	1	50	Risk Ratio (M-H, Random, 95% CI)	7.33 [0.48, 110.96]
3 ACR70	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 certolizumab 50 mg sc	1	47	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.06, 21.47]
3.2 certolizumab 100 mg sc	1	48	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.03, 14.89]
3.3 certolizumab 200 mg sc	4	2118	Risk Ratio (M-H, Random, 95% CI)	2.78 [1.20, 6.41]
3.4 certolizumab 400 mg sc	1	50	Risk Ratio (M-H, Random, 95% CI)	5.23 [0.34, 80.54]

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

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 certolizumab 50 mg sc					
CDP870-004 2001	8/39	6/8		6.57%	0.27[0.13,0.57]
Subtotal (95% CI)	**39**	**8**		**6.57%**	**0.27[0.13,0.57]**
Total events: 8 (Certolizumab pegol), 6 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.45(P=0)					
1.1.2 certolizumab 100 mg sc					
CDP870-004 2001	8/40	6/8		6.56%	0.27[0.13,0.56]
Yamamoto (b) 2014	45/72	7/25		6.96%	2.23[1.16,4.29]

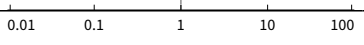


Favours control — Favours certolizumab pego



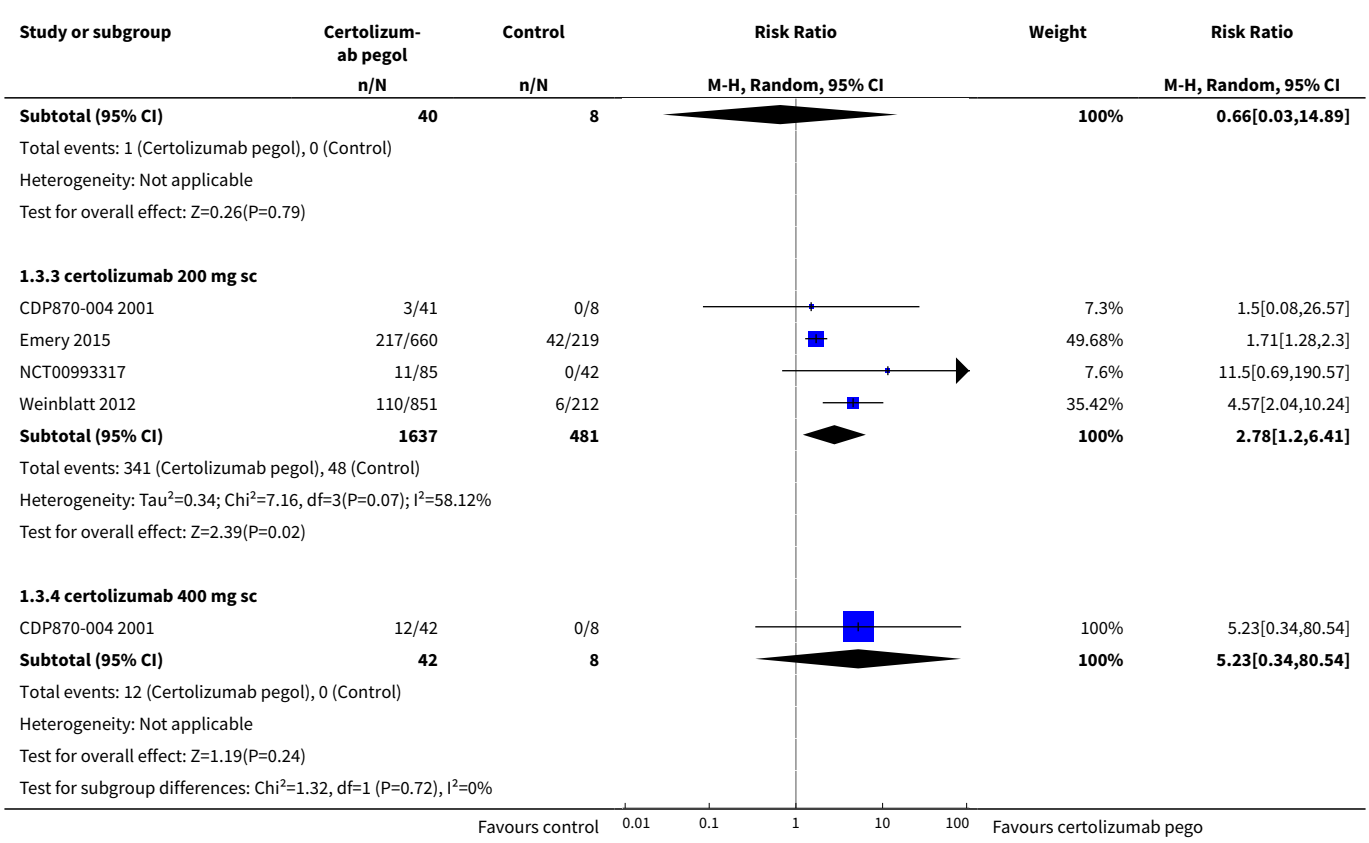
Analysis 1.2. Comparison 1 Efficacy at 12 weeks, any dose, Outcome 2 ACR50.

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 certolizumab 50 mg sc					
CDP870-004 2001	3/39	0/8		100%	1.58[0.09,27.88]
Subtotal (95% CI)	**39**	**8**		**100%**	**1.58[0.09,27.88]**
Total events: 3 (Certolizumab pegol), 0 (Control)					
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%					
Test for overall effect: Z=0.31(P=0.76)					
1.2.2 certolizumab 100 mg sc					
CDP870-004 2001	2/40	0/8		100%	1.1[0.06,20.96]
Subtotal (95% CI)	**40**	**8**		**100%**	**1.1[0.06,20.96]**
Total events: 2 (Certolizumab pegol), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.06(P=0.95)					
1.2.3 certolizumab 200 mg sc					
CDP870-004 2001	7/41	0/8		3.95%	3.21[0.2,51.33]
Emery 2015	334/660	87/219		40.66%	1.27[1.06,1.52]
NCT00993317	21/85	5/42		20.83%	2.08[0.84,5.12]
Weinblatt 2012	226/851	21/212		34.56%	2.68[1.76,4.08]
Subtotal (95% CI)	**1637**	**481**		**100%**	**1.89[1.06,3.37]**
Total events: 588 (Certolizumab pegol), 113 (Control)					
Heterogeneity: Tau²=0.21; Chi²=12.34, df=3(P=0.01); I²=75.69%					
Test for overall effect: Z=2.16(P=0.03)					
1.2.4 certolizumab 400 mg sc					
CDP870-004 2001	17/42	0/8		100%	7.33[0.48,110.96]
Subtotal (95% CI)	**42**	**8**		**100%**	**7.33[0.48,110.96]**
Total events: 17 (Certolizumab pegol), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.44(P=0.15)					
Test for subgroup differences: Chi²=1.09, df=1 (P=0.78), I²=0%					



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

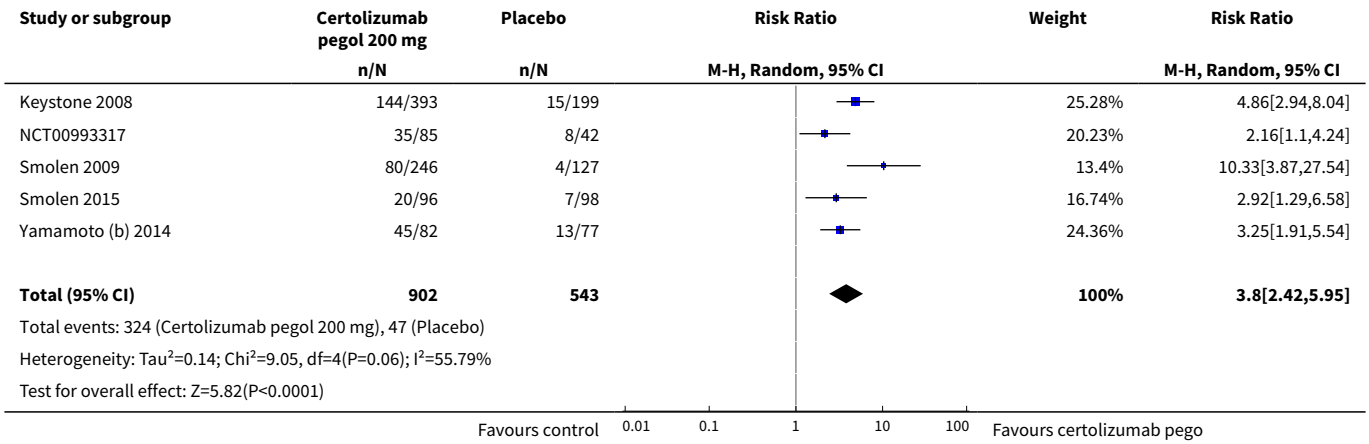
Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 certolizumab 50 mg sc					
CDP870-004 2001	2/39	0/8		100%	1.13[0.06,21.47]
Subtotal (95% CI)	**39**	**8**		**100%**	**1.13[0.06,21.47]**
Total events: 2 (Certolizumab pegol), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.08(P=0.94)					
1.3.2 certolizumab 100 mg sc					
CDP870-004 2001	1/40	0/8		100%	0.66[0.03,14.89]



Comparison 2. ACR50 24 weeks, 200 mg certolizumab pegol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR 50	5	1445	Risk Ratio (M-H, Random, 95% CI)	3.80 [2.42, 5.95]

Analysis 2.1. Comparison 2 ACR50 24 weeks, 200 mg certolizumab pegol, Outcome 1 ACR 50.

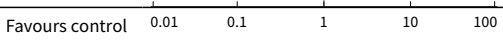


Comparison 3. ACR50 at 24 weeks, 400 mg certolizumab

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR 50	5	1591	Risk Ratio (M-H, Random, 95% CI)	4.65 [3.09, 6.99]

Analysis 3.1. Comparison 3 ACR50 at 24 weeks, 400 mg certolizumab, Outcome 1 ACR 50.

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Choy 2012	22/126	7/121		17.13%	3.02[1.34,6.81]
Fleischmann 2009	25/111	4/109		12.3%	6.14[2.21,17.05]
Keystone 2008	155/390	15/199		29.53%	5.27[3.19,8.71]
Smolen 2009	81/246	4/127		13.1%	10.45[3.92,27.88]
Yamamoto (b) 2014	46/85	13/77		27.94%	3.21[1.88,5.46]
Total (95% CI)	**958**	**633**		**100%**	**4.65[3.09,6.99]**
Total events: 329 (Certolizumab pegol), 43 (Control)					
Heterogeneity: Tau^2=0.08; Chi^2=6.53, df=4(P=0.16); I^2=38.75%					
Test for overall effect: Z=7.37(P<0.0001)					

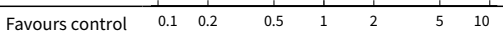


Comparison 4. ACR50 at 52 weeks, 200 mg certolizumab

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR 50	3	1790	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [1.38, 1.73]

Analysis 4.1. Comparison 4 ACR50 at 52 weeks, 200 mg certolizumab, Outcome 1 ACR 50.

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Atsumi 2016	116/161	81/158		30.3%	1.41[1.17,1.68]
Emery 2015	405/660	112/219		62.32%	1.2[1.04,1.38]
Keystone 2008	149/393	15/199		7.38%	5.03[3.04,8.32]
Total (95% CI)	**1214**	**576**		**100%**	**1.54[1.38,1.73]**
Total events: 670 (Certolizumab pegol), 208 (Control)					
Heterogeneity: Tau^2=0; Chi^2=34.25, df=2(P<0.0001); I^2=94.16%					
Test for overall effect: Z=7.38(P<0.0001)					



Comparison 5. ACR50 at 52 weeks, 400 mg certolizumab

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR 50	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 5.1. Comparison 5 ACR50 at 52 weeks, 400 mg certolizumab, Outcome 1 ACR 50.

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Keystone 2008	155/390	15/199		5.27[3.19,8.71]

Favours control 0.01 0.1 1 10 100 Favours certolizumab pego

Comparison 6. Mean HAQ-DI from baseline at week 12

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 certolizumab pegol 200 mg sc	1	1063	Mean Difference (IV, Fixed, 95% CI)	-0.22 [-0.23, -0.21]

Analysis 6.1. Comparison 6 Mean HAQ-DI from baseline at week 12, Outcome 1 certolizumab pegol 200 mg sc.

Study or subgroup	Certolizumab pegol 200 mg N	Certolizumab pegol 200 mg Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Weinblatt 2012	851	-0.4 (0)	212	-0.2 (0)		100%	-0.22[-0.23,-0.21]
Total ***	**851**		**212**			**100%**	**-0.22[-0.23,-0.21]**
Heterogeneity: Not applicable							
Test for overall effect: Z=77.7(P<0.0001)							

Favours certolizumab pego -4 -2 0 2 4 Favours control

Comparison 7. Mean HAQ-DI from baseline at week 24

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 certolizumab pegol 200 mg sc	4	1268	Mean Difference (IV, Random, 95% CI)	-0.35 [-0.43, -0.26]
2 certolizumab 400 mg sc	4	1425	Mean Difference (IV, Random, 95% CI)	-0.38 [-0.48, -0.28]

Analysis 7.1. Comparison 7 Mean HAQ-DI from baseline at week 24, Outcome 1 certolizumab pegol 200 mg sc.

Study or subgroup	Certolizumab pegol 200 mg		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Keystone 2008	393	-0.6 (0.6)	199	-0.2 (0.6)		33.94%	-0.41[-0.51,-0.31]
NCT00993317	81	-0.5 (0.5)	40	-0.2 (0.7)		9.56%	-0.37[-0.61,-0.13]
Smolen 2009	246	-0.5 (0.5)	127	-0.1 (0.5)		33.73%	-0.36[-0.46,-0.26]
Smolen 2015	91	-0.2 (0.5)	91	-0 (0.5)		22.77%	-0.22[-0.36,-0.08]
Total ***	**811**		**457**			**100%**	**-0.35[-0.43,-0.26]**
Heterogeneity: Tau^2=0; Chi^2=4.92, df=3(P=0.18); I^2=39.05%							
Test for overall effect: Z=8.32(P<0.0001)							

Favours certolizumab pego | Favours control

Analysis 7.2. Comparison 7 Mean HAQ-DI from baseline at week 24, Outcome 2 certolizumab 400 mg sc.

Study or subgroup	Certolizumab 400 mg sc		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Choy 2012	124	-0.3 (0.7)	119	-0.1 (0.2)		23.2%	-0.23[-0.36,-0.1]
Fleischmann 2009	111	-0.4 (0.5)	109	0.1 (0.5)		22.01%	-0.49[-0.62,-0.36]
Keystone 2008	390	-0.6 (0.6)	199	-0.2 (0.6)		27.43%	-0.43[-0.53,-0.33]
Smolen 2009	246	-0.5 (0.5)	127	-0.1 (0.5)		27.36%	-0.36[-0.46,-0.26]
Total ***	**871**		**554**			**100%**	**-0.38[-0.48,-0.28]**
Heterogeneity: Tau^2=0.01; Chi^2=9.17, df=3(P=0.03); I^2=67.27%							
Test for overall effect: Z=7.53(P<0.0001)							

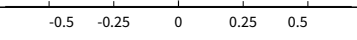
Favours certolizumab pego | Favours Control

Comparison 8. 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	5	2246	Mean Difference (IV, Random, 95% CI)	-0.36 [-0.43, -0.29]
1.1 certolizumab pegol 200 mg sc	3	985	Mean Difference (IV, Random, 95% CI)	-0.33 [-0.44, -0.23]
1.2 certolizumab pegol 400 mg sc	4	1261	Mean Difference (IV, Random, 95% CI)	-0.38 [-0.48, -0.27]

Analysis 8.1. Comparison 8 HAQ-DI at 24 weeks, any dose, Outcome 1 Change from baseline.

Study or subgroup	Certolizumab pegol N	Certolizumab pegol Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
8.1.1 certolizumab pegol 200 mg sc							
Keystone 2008	393	-0.6 (0.6)	100	-0.2 (0.6)		14.69%	-0.41[-0.53,-0.29]
Smolen 2009	246	-0.5 (0.5)	64	-0.1 (0.5)		14.63%	-0.36[-0.48,-0.24]
Smolen 2015	91	-0.2 (0.5)	91	-0 (0.5)		13.34%	-0.22[-0.36,-0.08]
Subtotal ***	**730**		**255**			**42.66%**	**-0.33[-0.44,-0.23]**
Heterogeneity: Tau²=0; Chi²=4.21, df=2(P=0.12); I²=52.53%							
Test for overall effect: Z=6.05(P<0.0001)							
8.1.2 certolizumab pegol 400 mg sc							
Choy 2012	124	-0.3 (0.7)	119	-0.1 (0.2)		14.51%	-0.23[-0.36,-0.1]
Fleischmann 2009	111	-0.4 (0.5)	109	0.1 (0.5)		13.65%	-0.49[-0.62,-0.36]
Keystone 2008	390	-0.6 (0.6)	99	-0.2 (0.6)		14.63%	-0.43[-0.55,-0.31]
Smolen 2009	246	-0.5 (0.5)	63	-0.1 (0.5)		14.55%	-0.36[-0.49,-0.23]
Subtotal ***	**871**		**390**			**57.34%**	**-0.38[-0.48,-0.27]**
Heterogeneity: Tau²=0.01; Chi²=8.67, df=3(P=0.03); I²=65.41%							
Test for overall effect: Z=6.79(P<0.0001)							
Total ***	**1601**		**645**			**100%**	**-0.36[-0.43,-0.29]**
Heterogeneity: Tau²=0.01; Chi²=13.43, df=6(P=0.04); I²=55.32%							
Test for overall effect: Z=9.67(P<0.0001)							
Test for subgroup differences: Chi²=0.3, df=1 (P=0.59), I²=0%							



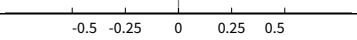
Favours certolizumab pego — Favours control

Comparison 9. HAQ-DI at 52 weeks, any dose

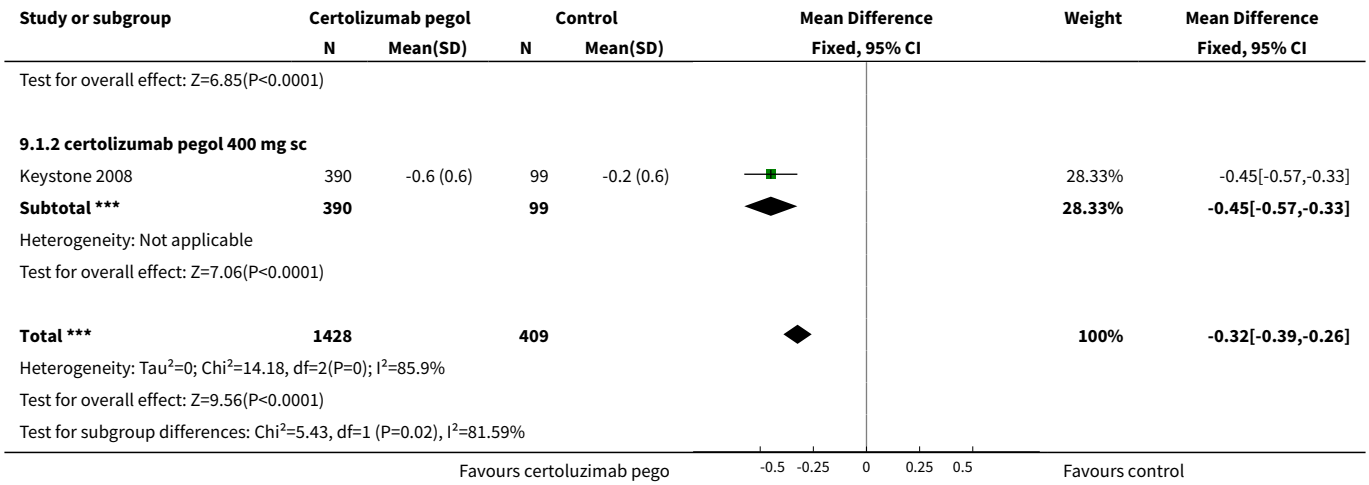
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	2	1837	Mean Difference (IV, Fixed, 95% CI)	-0.32 [-0.39, -0.26]
1.1 certolizumab pegol 200 mg sc	2	1348	Mean Difference (IV, Fixed, 95% CI)	-0.27 [-0.35, -0.20]
1.2 certolizumab pegol 400 mg sc	1	489	Mean Difference (IV, Fixed, 95% CI)	-0.45 [-0.57, -0.33]

Analysis 9.1. Comparison 9 HAQ-DI at 52 weeks, any dose, Outcome 1 Change from baseline.

Study or subgroup	Certolizumab pegol N	Certolizumab pegol Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
9.1.1 certolizumab pegol 200 mg sc							
Emery 2015	645	-1 (0.7)	210	-0.8 (0.6)		43.06%	-0.18[-0.28,-0.08]
Keystone 2008	393	-0.6 (0.6)	100	-0.2 (0.6)		28.6%	-0.42[-0.54,-0.3]
Subtotal ***	**1038**		**310**			**71.67%**	**-0.27[-0.35,-0.2]**
Heterogeneity: Tau²=0; Chi²=8.75, df=1(P=0); I²=88.57%							



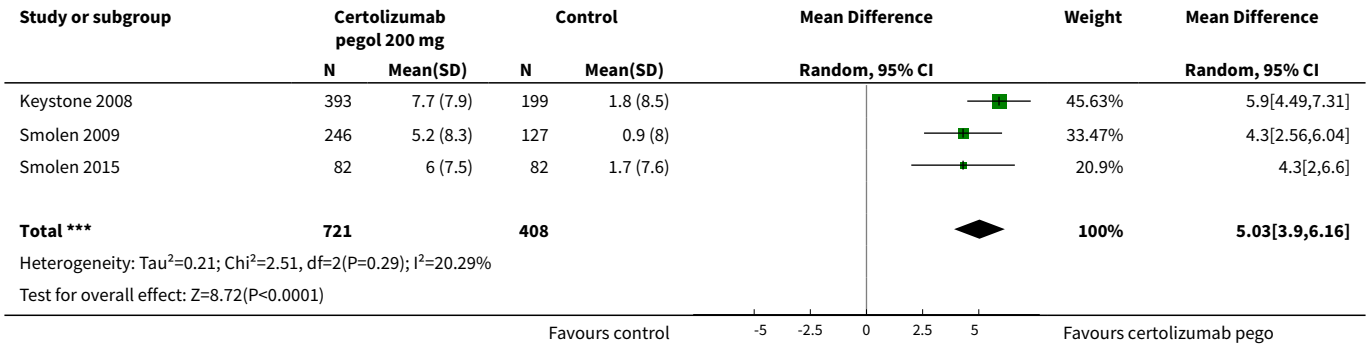
Favours certoluzimab pego — Favours control



Comparison 10. SF-36 Physical Component Summary (PCS), week 24

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 certolizumab pegol 200 mg sc	3	1129	Mean Difference (IV, Random, 95% CI)	5.03 [3.90, 6.16]
2 certolizumab pegol 400 mg sc	3	1205	Mean Difference (IV, Random, 95% CI)	5.54 [4.11, 6.97]

Analysis 10.1. Comparison 10 SF-36 Physical Component Summary (PCS), week 24, Outcome 1 certolizumab pegol 200 mg sc.



Analysis 10.2. Comparison 10 SF-36 Physical Component Summary (PCS), week 24, Outcome 2 certolizumab pegol 400 mg sc.

Study or subgroup	Certolizumab pegol 400 mg N	Mean(SD)	Control N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Choy 2012	124	8.4 (19.8)	119	3.4 (8.1)		12.44%	5[1.23,8.77]
Keystone 2008	390	8.3 (7.9)	199	1.8 (8.5)		48.5%	6.5[5.09,7.91]
Smolen 2009	246	5.5 (8.3)	127	0.9 (8)		39.06%	4.53[2.79,6.27]
Total ***	**760**		**445**			**100%**	**5.54[4.11,6.97]**
Heterogeneity: Tau^2=0.58; Chi^2=3.1, df=2(P=0.21); I^2=35.55%							
Test for overall effect: Z=7.6(P<0.0001)							

Comparison 11. SF-36 Mental Component Summary (MCS), week 24

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 certolizumab pegol 200 mg sc	2	965	Mean Difference (IV, Random, 95% CI)	4.18 [2.70, 5.66]
2 certolizumab pegol 400 mg sc	3	1205	Mean Difference (IV, Random, 95% CI)	4.05 [2.77, 5.34]

Analysis 11.1. Comparison 11 SF-36 Mental Component Summary (MCS), week 24, Outcome 1 certolizumab pegol 200 mg sc.

Study or subgroup	Certolizumab pegol 200 mg N	Mean(SD)	Control N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Keystone 2008	393	6.3 (11.9)	199	2.3 (11.3)		56.91%	4[2.04,5.96]
Smolen 2009	246	6.1 (10.8)	127	1.6 (10.4)		43.09%	4.42[2.17,6.67]
Total ***	**639**		**326**			**100%**	**4.18[2.7,5.66]**
Heterogeneity: Tau^2=0; Chi^2=0.08, df=1(P=0.78); I^2=0%							
Test for overall effect: Z=5.54(P<0.0001)							

Analysis 11.2. Comparison 11 SF-36 Mental Component Summary (MCS), week 24, Outcome 2 certolizumab pegol 400 mg sc.

Study or subgroup	Certolizumab pegol 400 mg N	Mean(SD)	Control N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Choy 2012	124	4.6 (13.9)	119	1.6 (4.8)		24.72%	3.02[0.43,5.61]
Keystone 2008	390	6.5 (11.9)	199	2.3 (11.3)		43.03%	4.2[2.24,6.16]

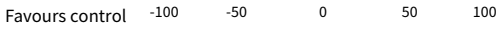
Study or subgroup	Certolizumab pegol 400 mg		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Smolen 2009	246	6.3 (11)	127	1.6 (10.4)		32.25%	4.65[2.39,6.91]
Total ***	**760**		**445**			**100%**	**4.05[2.77,5.34]**
Heterogeneity: Tau^2=0; Chi^2=0.9, df=2(P=0.64); I^2=0%							
Test for overall effect: Z=6.18(P<0.0001)							

Comparison 12. 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		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 certolizumab 400 mg sc	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

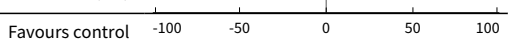
Analysis 12.1. Comparison 12 SF-36 Physical Component Summary (PCS), week 52, Outcome 1 certolizumab 200 mg sc.

Study or subgroup	Certolizumab pegol 200 mg		Control		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Keystone 2008	393	7.8 (8.7)	199	1.7 (8.6)		6.06[4.59,7.53]



Analysis 12.2. Comparison 12 SF-36 Physical Component Summary (PCS), week 52, Outcome 2 certolizumab 400 mg sc.

Study or subgroup	Certolizumab pegol 400 mg		Control		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Keystone 2008	390	8.6 (8.5)	199	1.7 (8.6)		6.88[5.42,8.34]



Comparison 13. SF-36 Mental Component Summary (MCS), week 52

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 certolizumab pegol 200 mg sc	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

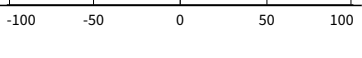
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 certolizumab pegol 400 mg sc	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 13.1. Comparison 13 SF-36 Mental Component Summary (MCS), week 52, Outcome 1 certolizumab pegol 200 mg sc.

Study or subgroup	Certolizumab 200 mg sc N	Certolizumab 200 mg sc Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Keystone 2008	393	6.4 (11.1)	199	2.1 (11.1)	+	4.3[2.4,6.2]

Analysis 13.2. Comparison 13 SF-36 Mental Component Summary (MCS), week 52, Outcome 2 certolizumab pegol 400 mg sc.

Study or subgroup	Certolizumab pegol 400 mg N	Certolizumab pegol 400 mg Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Keystone 2008	390	6.4 (11.1)	199	2.1 (11.1)	+	4.3[2.4,6.2]

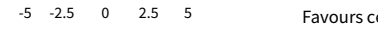


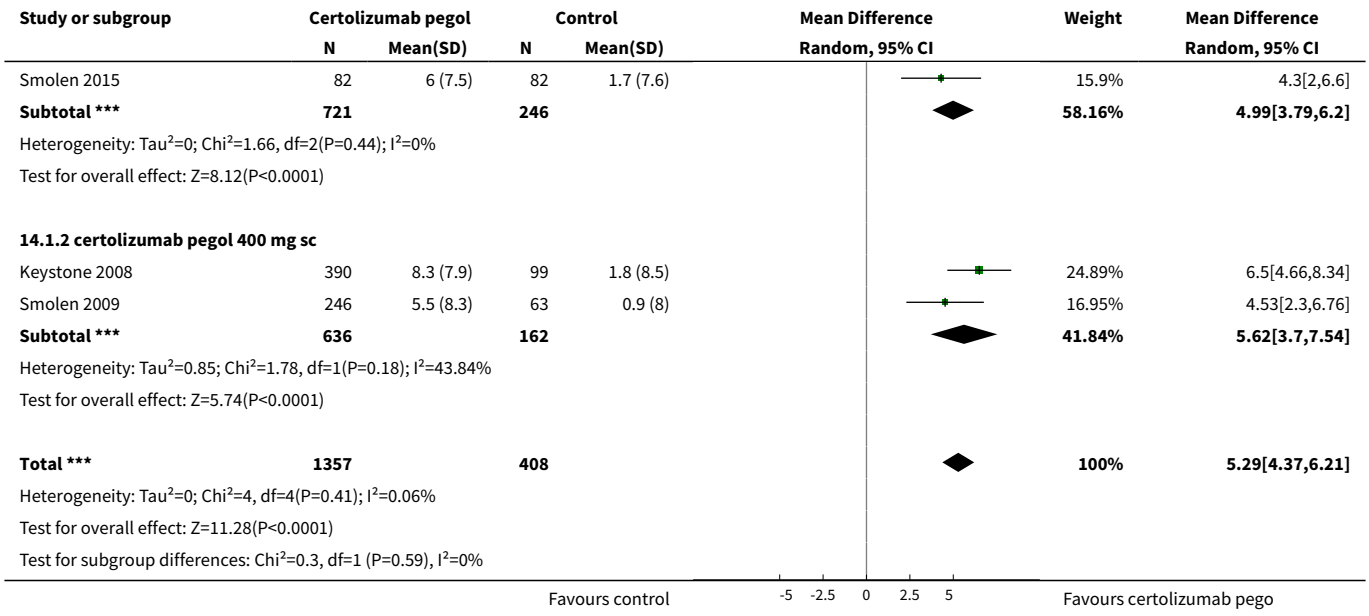
Comparison 14. SF-36 Physical Component Summary (PCS) at week 24, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	3	1765	Mean Difference (IV, Random, 95% CI)	5.29 [4.37, 6.21]
1.1 certolizumab pegol 200 mg sc	3	967	Mean Difference (IV, Random, 95% CI)	4.99 [3.79, 6.20]
1.2 certolizumab pegol 400 mg sc	2	798	Mean Difference (IV, Random, 95% CI)	5.62 [3.70, 7.54]

Analysis 14.1. Comparison 14 SF-36 Physical Component Summary (PCS) at week 24, any dose, Outcome 1 Change from baseline.

Study or subgroup	Certolizumab pegol N	Certolizumab pegol Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
14.1.1 certolizumab pegol 200 mg sc							
Keystone 2008	393	7.7 (7.9)	100	1.8 (8.5)		25.1%	5.9[4.07,7.73]
Smolen 2009	246	5.2 (8.3)	64	0.9 (8)		17.16%	4.3[2.08,6.52]

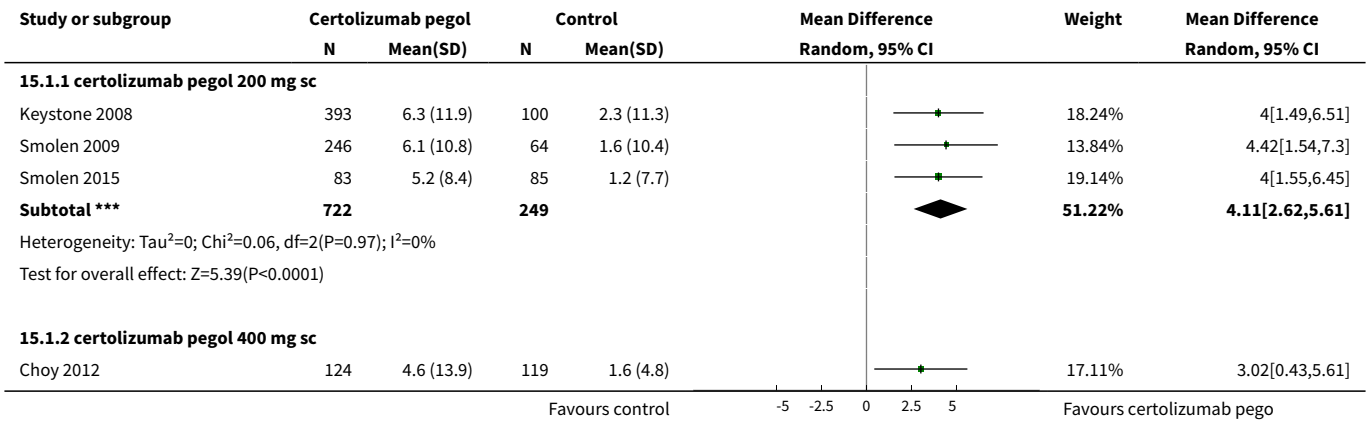


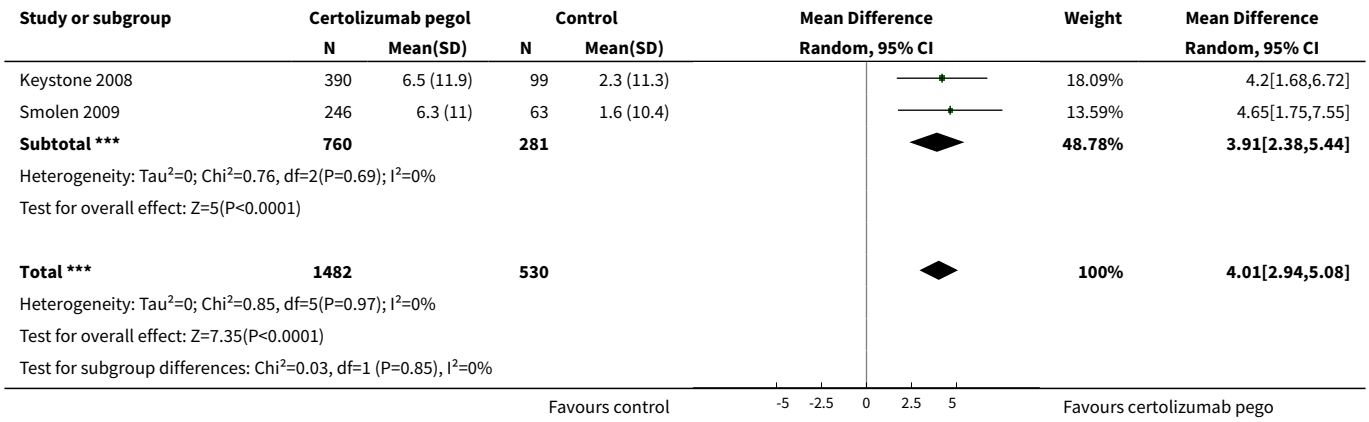


Comparison 15. SF-36 Mental Component Summary (MCS) at week 24, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	4	2012	Mean Difference (IV, Random, 95% CI)	4.01 [2.94, 5.08]
1.1 certolizumab pegol 200 mg sc	3	971	Mean Difference (IV, Random, 95% CI)	4.11 [2.62, 5.61]
1.2 certolizumab pegol 400 mg sc	3	1041	Mean Difference (IV, Random, 95% CI)	3.91 [2.38, 5.44]

Analysis 15.1. Comparison 15 SF-36 Mental Component Summary (MCS) at week 24, any dose, Outcome 1 Change from baseline.

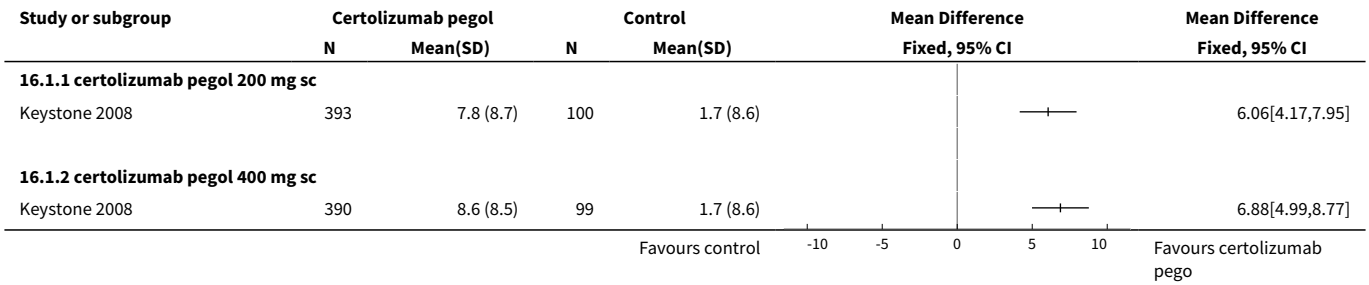




Comparison 16. SF-36 Physical Component Summary (PCS) at week 52, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 certolizumab pegol 200 mg sc	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 certolizumab pegol 400 mg sc	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 16.1. Comparison 16 SF-36 Physical Component Summary (PCS) at week 52, any dose, Outcome 1 Change from baseline.



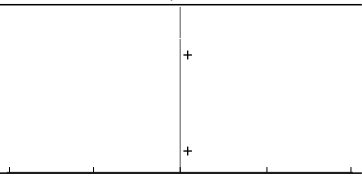
Comparison 17. SF-36 Mental Component Summary (MCS) at week 52, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 certolizumab pegol 200 mg sc	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 certolizumab pegol 400 mg sc	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 17.1. Comparison 17 SF-36 Mental Component Summary (MCS) at week 52, any dose, Outcome 1 Change from baseline.

Study or subgroup	Certolizumab pegol N	Certolizumab pegol Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
17.1.1 certolizumab pegol 200 mg sc						
Keystone 2008	393	6.4 (11.1)	100	2.1 (11.1)		4.3[1.86,6.74]
17.1.2 certolizumab pegol 400 mg sc						
Keystone 2008	390	6.4 (11.1)	99	2.1 (11.1)		4.3[1.85,6.75]

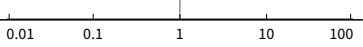


Comparison 18. Disease Activity Score (DAS-28) (ESR) remission (< 2.6), any doses, 12 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of participants achieving remission 12 weeks certolizumab 200 mg	2	1942	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.94 [1.44, 2.61]

Analysis 18.1. Comparison 18 Disease Activity Score (DAS-28) (ESR) remission (< 2.6), any doses, 12 weeks, Outcome 1 Proportion of participants achieving remission 12 weeks certolizumab 200 mg.

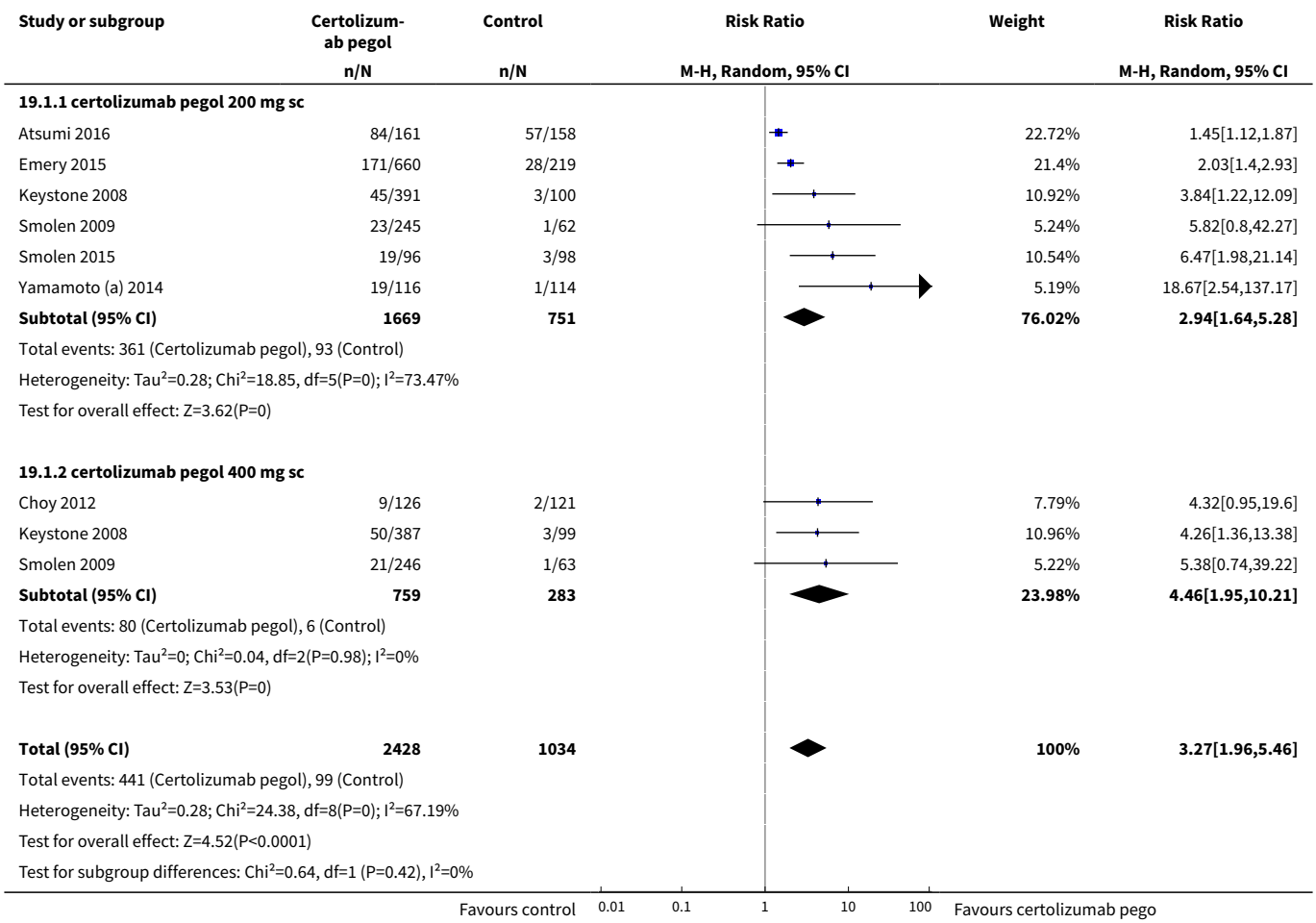
Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Emery 2015	124/660	26/219		53.37%	1.63[1.09,2.45]
Weinblatt 2012	136/851	12/212		46.63%	2.36[1.53,3.65]
Total (95% CI)	**1511**	**431**		**100%**	**1.94[1.44,2.61]**
Total events: 260 (Certolizumab pegol 200 mg), 38 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.51, df=1(P=0.22); I^2=33.59%					
Test for overall effect: Z=4.37(P<0.0001)					



Comparison 19. Disease Activity Score (DAS-28) (ESR) remission (< 2.6), any dose, 24 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of participants achieving remission 24 weeks	7	3462	Risk Ratio (M-H, Random, 95% CI)	3.27 [1.96, 5.46]
1.1 certolizumab pegol 200 mg sc	6	2420	Risk Ratio (M-H, Random, 95% CI)	2.94 [1.64, 5.28]
1.2 certolizumab pegol 400 mg sc	3	1042	Risk Ratio (M-H, Random, 95% CI)	4.46 [1.95, 10.21]

Analysis 19.1. Comparison 19 Disease Activity Score (DAS-28) (ESR) remission (< 2.6), any dose, 24 weeks, Outcome 1 Proportion of participants achieving remission 24 weeks.

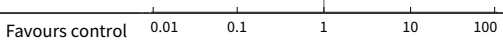


Comparison 20. Disease Activity Score (DAS-28) (ESR) remission (< 2.6), any dose, 52 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of participants achieving remission 52 weeks	3	2175	Risk Ratio (M-H, Fixed, 95% CI)	1.85 [1.55, 2.21]
1.1 certolizumab pegol 200 mg sc	3	1689	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [1.43, 2.04]
1.2 certolizumab pegol 400 mg sc	1	486	Risk Ratio (M-H, Fixed, 95% CI)	6.31 [2.03, 19.59]

Analysis 20.1. Comparison 20 Disease Activity Score (DAS-28) (ESR) remission (< 2.6), any dose, 52 weeks, Outcome 1 Proportion of participants achieving remission 52 weeks.

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
20.1.1 certolizumab pegol 200 mg sc					
Atsumi 2016	91/161	58/158		38.09%	1.54[1.2,1.97]
Emery 2015	279/660	57/219		55.69%	1.62[1.28,2.07]
Keystone 2008	62/391	3/100		3.11%	5.29[1.69,16.49]
Subtotal (95% CI)	**1212**	**477**		**96.89%**	**1.71[1.43,2.04]**
Total events: 432 (Certolizumab pegol), 118 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.65, df=2(P=0.1); I^2=56.94%					
Test for overall effect: Z=5.99(P<0.0001)					
20.1.2 certolizumab pegol 400 mg sc					
Keystone 2008	74/387	3/99		3.11%	6.31[2.03,19.59]
Subtotal (95% CI)	**387**	**99**		**3.11%**	**6.31[2.03,19.59]**
Total events: 74 (Certolizumab pegol), 3 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.19(P=0)					
Total (95% CI)	**1599**	**576**		**100%**	**1.85[1.55,2.21]**
Total events: 506 (Certolizumab pegol), 121 (Control)					
Heterogeneity: Tau^2=0; Chi^2=11.07, df=3(P=0.01); I^2=72.91%					
Test for overall effect: Z=6.88(P<0.0001)					
Test for subgroup differences: Chi^2=4.99, df=1 (P=0.03), I^2=79.96%					



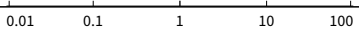
Comparison 21. Disease Activity Score (DAS-28) (ESR) remission (< 2.6), any time

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of participants achieving remission 12 weeks certolizumab 200 mg	2	1942	Risk Ratio (M-H, Fixed, 95% CI)	1.99 [1.44, 2.76]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Proportion of participants achieving remission 24 weeks certolizumab 200 mg	6	2579	Risk Ratio (M-H, Random, 95% CI)	3.79 [1.90, 7.56]
3 Proportion of participants achieving remission 24 weeks certolizumab 400 mg	3	1201	Risk Ratio (M-H, Random, 95% CI)	7.18 [3.12, 16.50]
4 Proportion of participants achieving remission 52 weeks certolizumab 200 mg	3	1785	Risk Ratio (M-H, Fixed, 95% CI)	1.83 [1.53, 2.18]
5 Proportion of participants achieving remission 52 weeks certolizumab 400 mg	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 21.1. Comparison 21 Disease Activity Score (DAS-28) (ESR) remission (< 2.6), any time, Outcome 1 Proportion of participants achieving remission 12 weeks certolizumab 200 mg.

Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Emery 2015	124/660	26/219		67.02%	1.58[1.07,2.35]
Weinblatt 2012	136/851	12/212		32.98%	2.82[1.6,5]
Total (95% CI)	**1511**	**431**		**100%**	**1.99[1.44,2.76]**
Total events: 260 (Certolizumab pegol 200 mg), 38 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.74, df=1(P=0.1); I^2=63.55%					
Test for overall effect: Z=4.15(P<0.0001)					



Favours control — Favours certolizumab pego

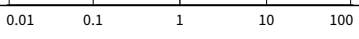
Analysis 21.2. Comparison 21 Disease Activity Score (DAS-28) (ESR) remission (< 2.6), any time, Outcome 2 Proportion of participants achieving remission 24 weeks certolizumab 200 mg.

Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Atsumi 2016	84/161	57/158		26.68%	1.45[1.12,1.87]
Emery 2015	171/660	28/219		25.66%	2.03[1.4,2.93]
Smolen 2015	19/96	3/98		15.27%	6.47[1.98,21.14]
Keystone 2008	45/391	3/196		15.61%	7.52[2.37,23.89]
Smolen 2009	23/245	1/125		8.4%	11.73[1.6,85.89]
Yamamoto (a) 2014	19/116	1/114		8.38%	18.67[2.54,137.17]
Total (95% CI)	**1669**	**910**		**100%**	**3.79[1.9,7.56]**
Total events: 361 (Certolizumab pegol 200 mg), 93 (Control)					
Heterogeneity: Tau^2=0.45; Chi^2=27.23, df=5(P<0.0001); I^2=81.64%					
Test for overall effect: Z=3.78(P=0)					

Favours control — Favours certolizumab pego

Analysis 21.3. Comparison 21 Disease Activity Score (DAS-28) (ESR) remission (< 2.6), any time, Outcome 3 Proportion of participants achieving remission 24 weeks certolizumab 400 mg.

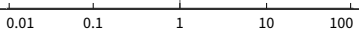
Study or subgroup	Certolizumab 400 mg n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Choy 2012	9/126	2/121		30.34%	4.32[0.95,19.6]
Keystone 2008	50/387	3/196		52.23%	8.44[2.67,26.72]
Smolen 2009	21/246	1/125		17.43%	10.67[1.45,78.41]
Total (95% CI)	**759**	**442**		**100%**	**7.18[3.12,16.5]**
Total events: 80 (Certolizumab 400 mg), 6 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.69, df=2(P=0.71); I^2=0%					
Test for overall effect: Z=4.64(P<0.0001)					



Favours control — Favours certolizumab 400 mg sc

Analysis 21.4. Comparison 21 Disease Activity Score (DAS-28) (ESR) remission (< 2.6), any time, Outcome 4 Proportion of participants achieving remission 52 weeks certolizumab 200 mg.

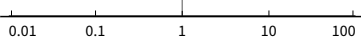
Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Atsumi 2016	91/161	58/158		39.52%	1.54[1.2,1.97]
Emery 2015	279/660	57/219		57.78%	1.62[1.28,2.07]
Keystone 2008	62/391	3/196		2.7%	10.36[3.29,32.58]
Total (95% CI)	**1212**	**573**		**100%**	**1.83[1.53,2.18]**
Total events: 432 (Certolizumab pegol 200 mg), 118 (Control)					
Heterogeneity: Tau^2=0; Chi^2=11.59, df=2(P=0); I^2=82.74%					
Test for overall effect: Z=6.76(P<0.0001)					



Favours experimental — Favours certolizumab pego

Analysis 21.5. Comparison 21 Disease Activity Score (DAS-28) (ESR) remission (< 2.6), any time, Outcome 5 Proportion of participants achieving remission 52 weeks certolizumab 400 mg.

Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Keystone 2008	74/387	3/196		12.49[3.99,39.12]



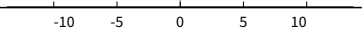
Favours control — Favours certolizumab pego

Comparison 22. DAS-28 at 12 weeks, 200 mg certolizumab

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 DAS 28 (ESR) change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 22.1. Comparison 22 DAS-28 at 12 weeks, 200 mg certolizumab, Outcome 1 DAS 28 (ESR) change from baseline.

Study or subgroup	Certolizumab 200 mg		Control		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Weinblatt 2012	851	-1.6 (0)	212	-0.8 (0)		Not estimable



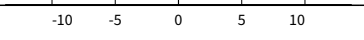
Favours certolizumab pego | Favours control

Comparison 23. DAS-28 at 24 weeks, 400 mg 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, Random, 95% CI)	-1.46 [-2.49, -0.42]

Analysis 23.1. Comparison 23 DAS-28 at 24 weeks, 400 mg certolizumab, Outcome 1 DAS 28 (ESR) change from baseline.

Study or subgroup	Certolizumab pegol 400 mg		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Fleischmann 2009	111	-1.5 (2)	109	-0.6 (2)		47.46%	-0.9[-1.43,-0.37]
Smolen 2009	246	-2.5 (1.3)	127	-0.5 (1.1)		52.54%	-1.96[-2.21,-1.71]
Total ***	**357**		**236**			**100%**	**-1.46[-2.49,-0.42]**
Heterogeneity: Tau^2=0.52; Chi^2=12.71, df=1(P=0); I^2=92.13%							
Test for overall effect: Z=2.75(P=0.01)							



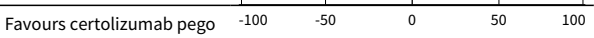
Favours certolizumab pego | Favours control

Comparison 24. 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		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 24.1. Comparison 24 DAS-28 at week 52, certolizumab 200 mg, Outcome 1 DAS 28 (ESR) Change from baseline.

Study or subgroup	Certolizumab pegol 200 mg N	Mean(SD)	Control N	Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Keystone 2008	393	-3.3 (1.3)	199	-2.4 (1.3)		-0.9[-1.12,-0.68]

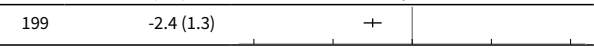


Comparison 25. DAS-28 at week 52, certolizumab 400 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 DAS 28 (ESR) Change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 25.1. Comparison 25 DAS-28 at week 52, certolizumab 400 mg, Outcome 1 DAS 28 (ESR) Change from baseline.

Study or subgroup	Certolizumab pegol 400 mg N	Mean(SD)	Control N	Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Keystone 2008	390	-3.4 (1.4)	199	-2.4 (1.3)		-1[-1.23,-0.77]

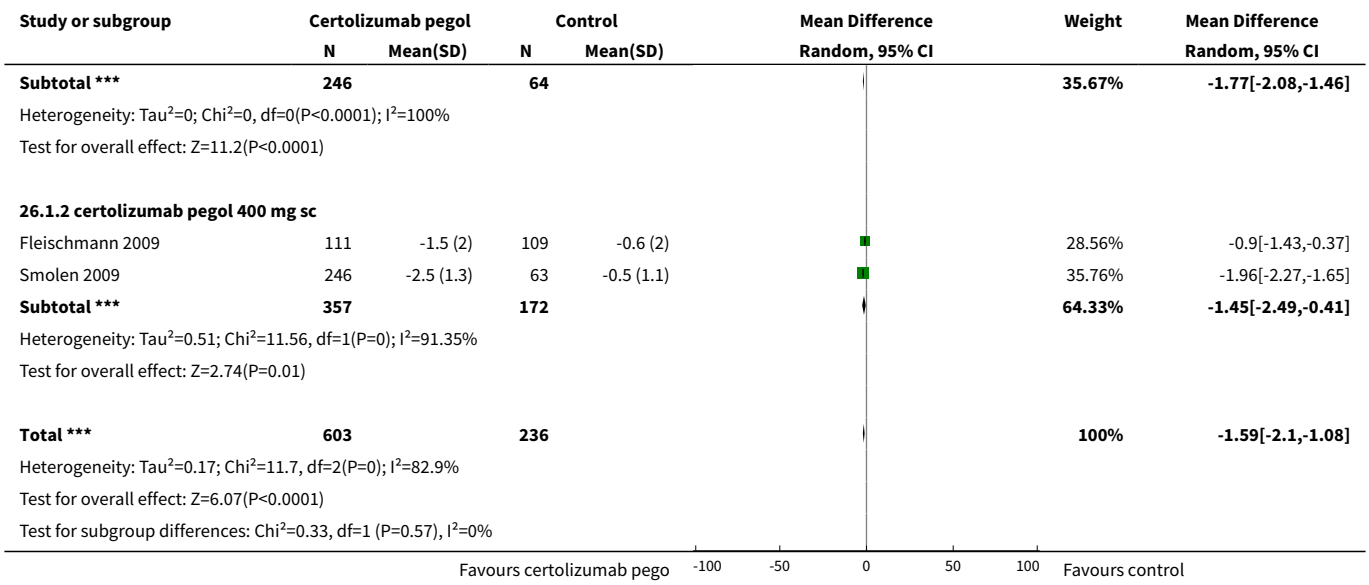


Comparison 26. DAS-28 at 24 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	2	839	Mean Difference (IV, Random, 95% CI)	-1.59 [-2.10, -1.08]
1.1 certolizumab pegol 200 mg sc	1	310	Mean Difference (IV, Random, 95% CI)	-1.77 [-2.08, -1.46]
1.2 certolizumab pegol 400 mg sc	2	529	Mean Difference (IV, Random, 95% CI)	-1.45 [-2.49, -0.41]

Analysis 26.1. Comparison 26 DAS-28 at 24 weeks, any dose, Outcome 1 Change from baseline.

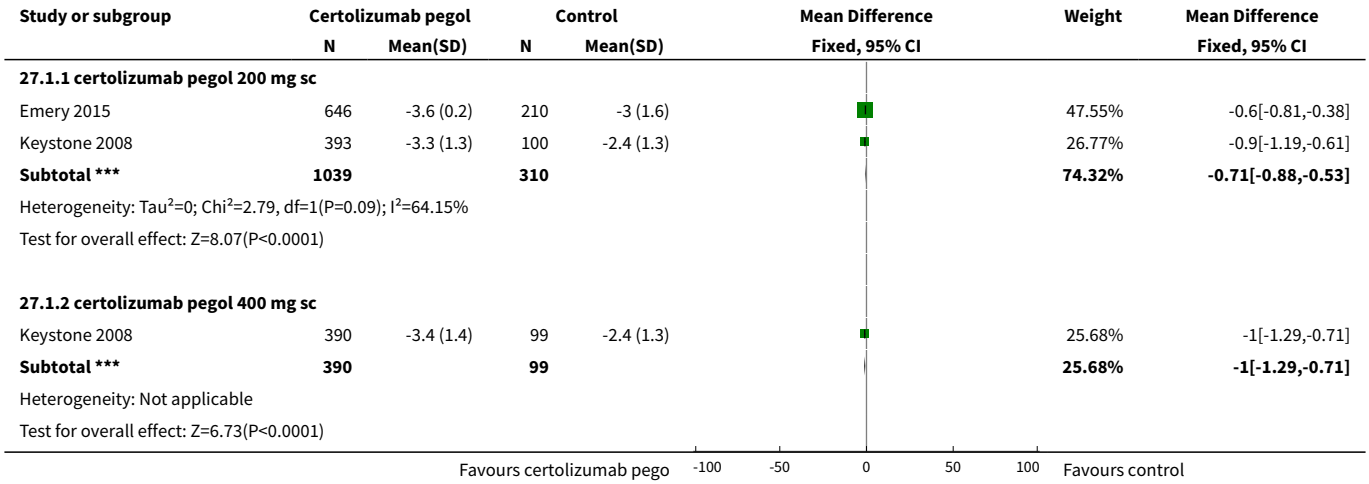
Study or subgroup	Certolizumab pegol N	Mean(SD)	Control N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
26.1.1 certolizumab pegol 200 mg sc							
Smolen 2009	246	-2.3 (1.4)	64	-0.5 (1.1)		35.67%	-1.77[-2.08,-1.46]

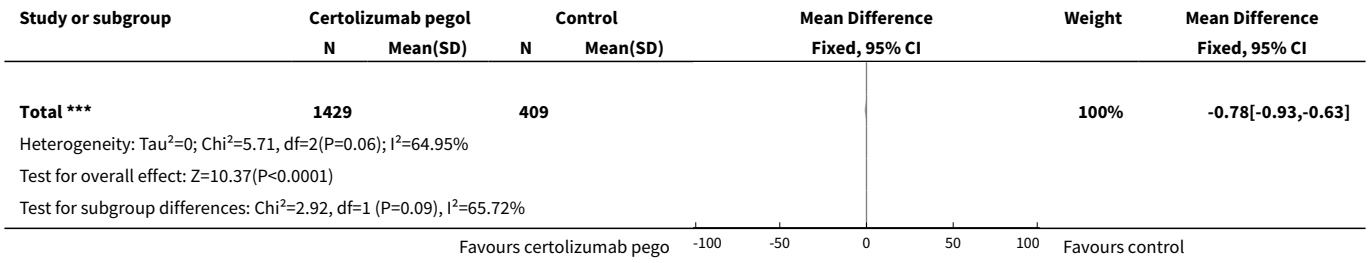


Comparison 27. DAS-28 at 52 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	2	1838	Mean Difference (IV, Fixed, 95% CI)	-0.78 [-0.93, -0.63]
1.1 certolizumab pegol 200 mg sc	2	1349	Mean Difference (IV, Fixed, 95% CI)	-0.71 [-0.88, -0.53]
1.2 certolizumab pegol 400 mg sc	1	489	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-1.29, -0.71]

Analysis 27.1. Comparison 27 DAS-28 at 52 weeks, any dose, Outcome 1 Change from baseline.

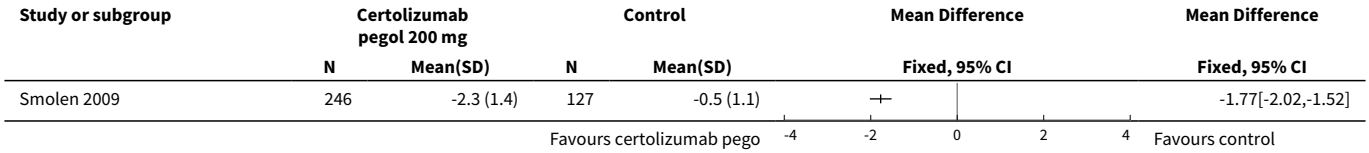




Comparison 28. DAS-28 at 24 weeks, 200 mg certolizumab

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 DAS 28 (ESR) change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 28.1. Comparison 28 DAS-28 at 24 weeks, 200 mg certolizumab, Outcome 1 DAS 28 (ESR) change from baseline.

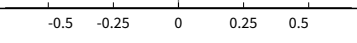


Comparison 29. Erosion score (ES)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from the baseline mean ES at week 24, certolizumab pegol 200 mg	2	859	Std. Mean Difference (IV, Fixed, 95% CI)	-0.35 [-0.50, -0.21]
2 Change from the baseline mean ES at week 24, certolizumab pegol 400 mg	2	869	Mean Difference (IV, Random, 95% CI)	-0.76 [-1.14, -0.37]
3 Change from the baseline mean ES at week 52, certolizumab pegol 200 mg	2	1235	Mean Difference (IV, Fixed, 95% CI)	-1.14 [-1.54, -0.74]
4 Change from the baseline mean ES at week 52, certolizumab pegol 400 mg	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 29.1. Comparison 29 Erosion score (ES), Outcome 1 Change from the baseline mean ES at week 24, certolizumab pegol 200 mg.

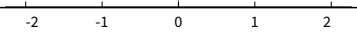
Study or subgroup	Certolizumab pegol 200 mg N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Keystone 2008	353	0 (1.5)	180	0.7 (2.1)		61.62%	-0.41[-0.59,-0.22]
Smolen 2009	214	0.1 (2)	112	0.7 (2.6)		38.38%	-0.27[-0.5,-0.04]
Total ***	**567**		**292**			**100%**	**-0.35[-0.5,-0.21]**
Heterogeneity: Tau^2=0; Chi^2=0.83, df=1(P=0.36); I^2=0%							
Test for overall effect: Z=4.86(P<0.0001)							



Favours certolizumab pego — Favours control

Analysis 29.2. Comparison 29 Erosion score (ES), Outcome 2 Change from the baseline mean ES at week 24, certolizumab pegol 400 mg.

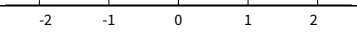
Study or subgroup	Certolizumab pegol N	Mean(SD)	Control N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Keystone 2008	355	0.1 (2.4)	180	0.7 (2.1)		60.7%	-0.6[-1,-0.2]
Smolen 2009	222	-0.3 (1.8)	112	0.7 (2.6)		39.3%	-1[-1.54,-0.46]
Total ***	**577**		**292**			**100%**	**-0.76[-1.14,-0.37]**
Heterogeneity: Tau^2=0.02; Chi^2=1.38, df=1(P=0.24); I^2=27.7%							
Test for overall effect: Z=3.88(P=0)							



Favours certolizumab pego — Favours control

Analysis 29.3. Comparison 29 Erosion score (ES), Outcome 3 Change from the baseline mean ES at week 52, certolizumab pegol 200 mg.

Study or subgroup	Certolizumab pegol N	Mean(SD)	Control N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Emery 2015	528	0.1 (2.1)	163	1.1 (3)		65.35%	-1[-1.49,-0.51]
Keystone 2008	364	0.1 (2.5)	180	1.5 (4.3)		34.65%	-1.4[-2.08,-0.72]
Total ***	**892**		**343**			**100%**	**-1.14[-1.54,-0.74]**
Heterogeneity: Tau^2=0; Chi^2=0.87, df=1(P=0.35); I^2=0%							
Test for overall effect: Z=5.59(P<0.0001)							



Favours certolizumab pego — Favours control

Analysis 29.4. Comparison 29 Erosion score (ES), Outcome 4 Change from the baseline mean ES at week 52, certolizumab pegol 400 mg.

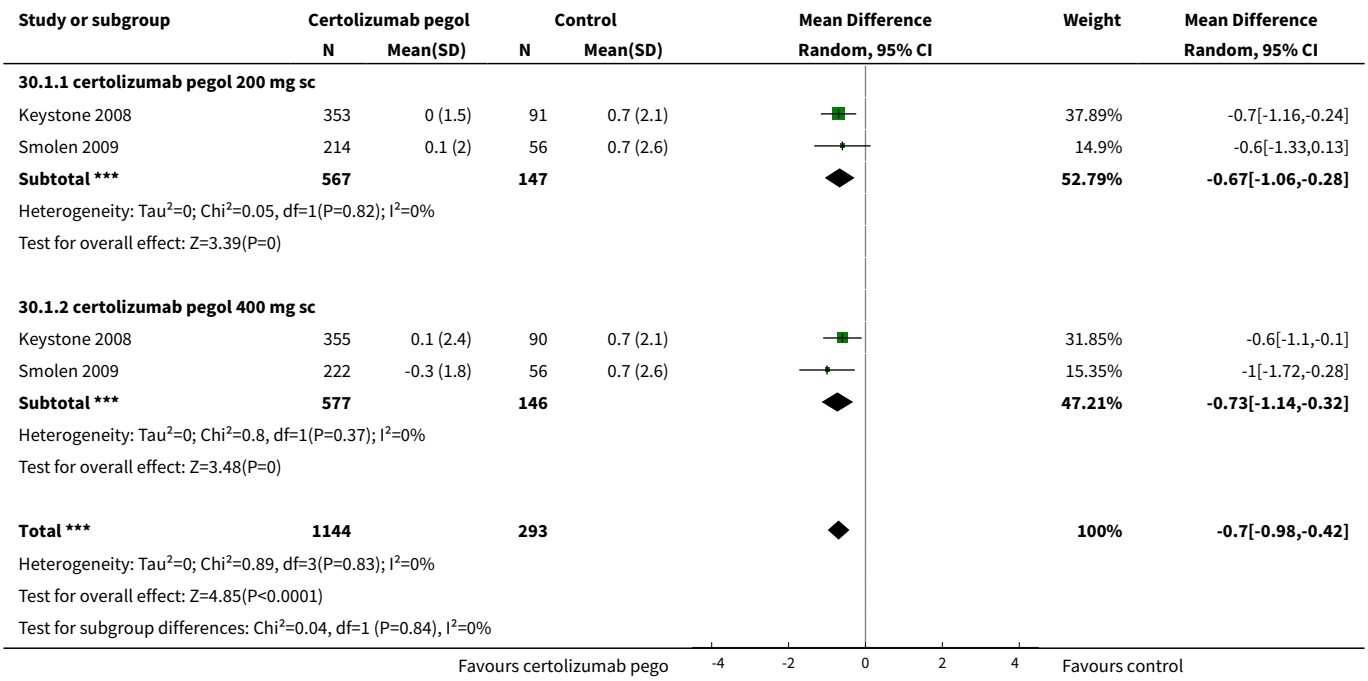
Study or subgroup	Certolizumab pegol N	Mean(SD)	Control N	Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Keystone 2008	363	0 (3)	180	1.5 (4.3)		-1.5[-2.2,-0.8]

Favours Certolizumab pego — Favours control

Comparison 30. 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, Random, 95% CI)	-0.70 [-0.98, -0.42]
1.1 certolizumab pegol 200 mg sc	2	714	Mean Difference (IV, Random, 95% CI)	-0.67 [-1.06, -0.28]
1.2 certolizumab pegol 400 mg sc	2	723	Mean Difference (IV, Random, 95% CI)	-0.73 [-1.14, -0.32]

Analysis 30.1. Comparison 30 Erosion score (ES) at 24 weeks, any dose, Outcome 1 Change from baseline.



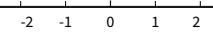
Comparison 31. Erosion score (ES) at 52 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	2	1599	Mean Difference (IV, Fixed, 95% CI)	-1.16 [-1.56, -0.77]
1.1 certolizumab pegol 200 mg sc	2	1146	Mean Difference (IV, Fixed, 95% CI)	-1.09 [-1.52, -0.65]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 certolizumab pegol 400 mg sc	1	453	Mean Difference (IV, Fixed, 95% CI)	-1.5 [-2.44, -0.56]

Analysis 31.1. Comparison 31 Erosion score (ES) at 52 weeks, any dose, Outcome 1 Change from baseline.

Study or subgroup	Certolizumab pegol N	Certolizumab pegol Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
31.1.1 certolizumab pegol 200 mg sc							
Emery 2015	528	0.1 (2.1)	163	1.1 (3)		63.92%	-1[-1.49,-0.51]
Keystone 2008	364	0.1 (2.5)	91	1.5 (4.3)		18.44%	-1.4[-2.32,-0.48]
Subtotal ***	**892**		**254**			**82.35%**	**-1.09[-1.52,-0.65]**
Heterogeneity: Tau^2=0; Chi^2=0.56, df=1(P=0.45); I^2=0%							
Test for overall effect: Z=4.91(P<0.0001)							
31.1.2 certolizumab pegol 400 mg sc							
Keystone 2008	363	0 (3)	90	1.5 (4.3)		17.65%	-1.5[-2.44,-0.56]
Subtotal ***	**363**		**90**			**17.65%**	**-1.5[-2.44,-0.56]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.13(P=0)							
Total ***	**1255**		**344**			**100%**	**-1.16[-1.56,-0.77]**
Heterogeneity: Tau^2=0; Chi^2=1.17, df=2(P=0.56); I^2=0%							
Test for overall effect: Z=5.76(P<0.0001)							
Test for subgroup differences: Chi^2=0.6, df=1 (P=0.44), I^2=0%							



Favours certolizumab pego

Favours control

Comparison 32. Joint space narrowing (JSN)

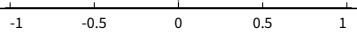
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from the baseline mean JSN 24 weeks, certolizumab pegol 200 mg	2	861	Mean Difference (IV, Random, 95% CI)	-0.45 [-0.77, -0.13]
2 Change from the baseline mean JSN 24 weeks,certolizumab pegol 400 mg	2	869	Mean Difference (IV, Random, 95% CI)	-0.55 [-0.86, -0.24]
3 Change from the baseline mean JSN 52 weeks,certolizumab pegol 200 mg	2	1239	Mean Difference (IV, Fixed, 95% CI)	-0.67 [-1.02, -0.32]
4 Change from the baseline mean JSN 52 weeks, certolizumab pegol 400 mg	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 32.1. Comparison 32 Joint space narrowing (JSN), Outcome 1 Change from the baseline mean JSN 24 weeks, certolizumab pegol 200 mg.

Study or subgroup	Certolizumab pegol 200 mg N	Mean(SD)	Control N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Keystone 2008	355	0.2 (2.5)	180	0.7 (2.4)		53.2%	-0.5[-0.94,-0.06]
Smolen 2009	214	0.1 (1.4)	112	0.5 (2.3)		46.8%	-0.4[-0.87,0.07]
Total ***	**569**		**292**			**100%**	**-0.45[-0.77,-0.13]**

Heterogeneity: Tau²=0; Chi²=0.09, df=1(P=0.76); I²=0%

Test for overall effect: Z=2.79(P=0.01)



Favours certolizumab pego | Favours control

Analysis 32.2. Comparison 32 Joint space narrowing (JSN), Outcome 2 Change from the baseline mean JSN 24 weeks,certolizumab pegol 400 mg.

Study or subgroup	Certolizumab pegol 400 mg N	Mean(SD)	Control N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Keystone 2008	355	0.2 (2.4)	180	0.7 (2.4)		51.76%	-0.5[-0.93,-0.07]
Smolen 2009	222	-0.1 (1)	112	0.5 (2.3)		48.24%	-0.6[-1.05,-0.15]
Total ***	**577**		**292**			**100%**	**-0.55[-0.86,-0.24]**

Heterogeneity: Tau²=0; Chi²=0.1, df=1(P=0.75); I²=0%

Test for overall effect: Z=3.47(P=0)

Favours certolizumab pego | Favours control

Analysis 32.3. Comparison 32 Joint space narrowing (JSN), Outcome 3 Change from the baseline mean JSN 52 weeks,certolizumab pegol 200 mg.

Study or subgroup	Certolizumab pegol N	Mean(SD)	Control N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Emery 2015	528	0.1 (1.7)	163	0.7 (2.3)		83.08%	-0.6[-0.98,-0.22]
Keystone 2008	367	0.4 (4.2)	181	1.4 (5)		16.92%	-1[-1.85,-0.15]
Total ***	**895**		**344**			**100%**	**-0.67[-1.02,-0.32]**

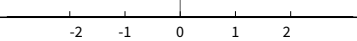
Heterogeneity: Tau²=0; Chi²=0.71, df=1(P=0.4); I²=0%

Test for overall effect: Z=3.76(P=0)

Favours certolizumab pego | Favours control

Analysis 32.4. Comparison 32 Joint space narrowing (JSN), Outcome 4 Change from the baseline mean JSN 52 weeks, certolizumab pegol 400 mg.

Study or subgroup	Certolizumab N	Mean(SD)	Control N	Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Keystone 2008	363	0.2 (2.8)	181	1.4 (5)		-1.2[-1.98,-0.42]



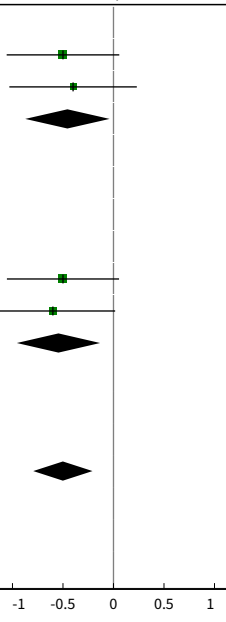
Favours certolizumab | Favours control

Comparison 33. 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, Random, 95% CI)	-0.50 [-0.79, -0.21]
1.1 certolizumab pegol 200 mg sc	2	716	Mean Difference (IV, Random, 95% CI)	-0.46 [-0.87, -0.04]
1.2 certolizumab pegol 400 mg sc	2	723	Mean Difference (IV, Random, 95% CI)	-0.54 [-0.96, -0.13]

Analysis 33.1. Comparison 33 Joint space narrowing (JSN) at 24 weeks, any dose, Outcome 1 Change from baseline.

Study or subgroup	Certolizumab pegol N	Certolizumab pegol Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
33.1.1 certolizumab pegol 200 mg sc							
Keystone 2008	355	0.2 (2.5)	91	0.7 (2.4)		27.73%	-0.5[-1.06,0.06]
Smolen 2009	214	0.1 (1.4)	56	0.5 (2.3)		21.65%	-0.4[-1.03,0.23]
Subtotal ***	**569**		**147**			**49.37%**	**-0.46[-0.87,-0.04]**
Heterogeneity: Tau^2=0; Chi^2=0.05, df=1(P=0.82); I^2=0%							
Test for overall effect: Z=2.14(P=0.03)							
33.1.2 certolizumab pegol 400 mg sc							
Keystone 2008	355	0.2 (2.4)	90	0.7 (2.4)		27.96%	-0.5[-1.06,0.06]
Smolen 2009	222	-0.1 (1)	56	0.5 (2.3)		22.67%	-0.6[-1.22,0.02]
Subtotal ***	**577**		**146**			**50.63%**	**-0.54[-0.96,-0.13]**
Heterogeneity: Tau^2=0; Chi^2=0.06, df=1(P=0.81); I^2=0%							
Test for overall effect: Z=2.59(P=0.01)							
Total ***	**1146**		**293**			**100%**	**-0.5[-0.79,-0.21]**
Heterogeneity: Tau^2=0; Chi^2=0.2, df=3(P=0.98); I^2=0%							
Test for overall effect: Z=3.35(P=0)							
Test for subgroup differences: Chi^2=0.09, df=1 (P=0.77), I^2=0%							

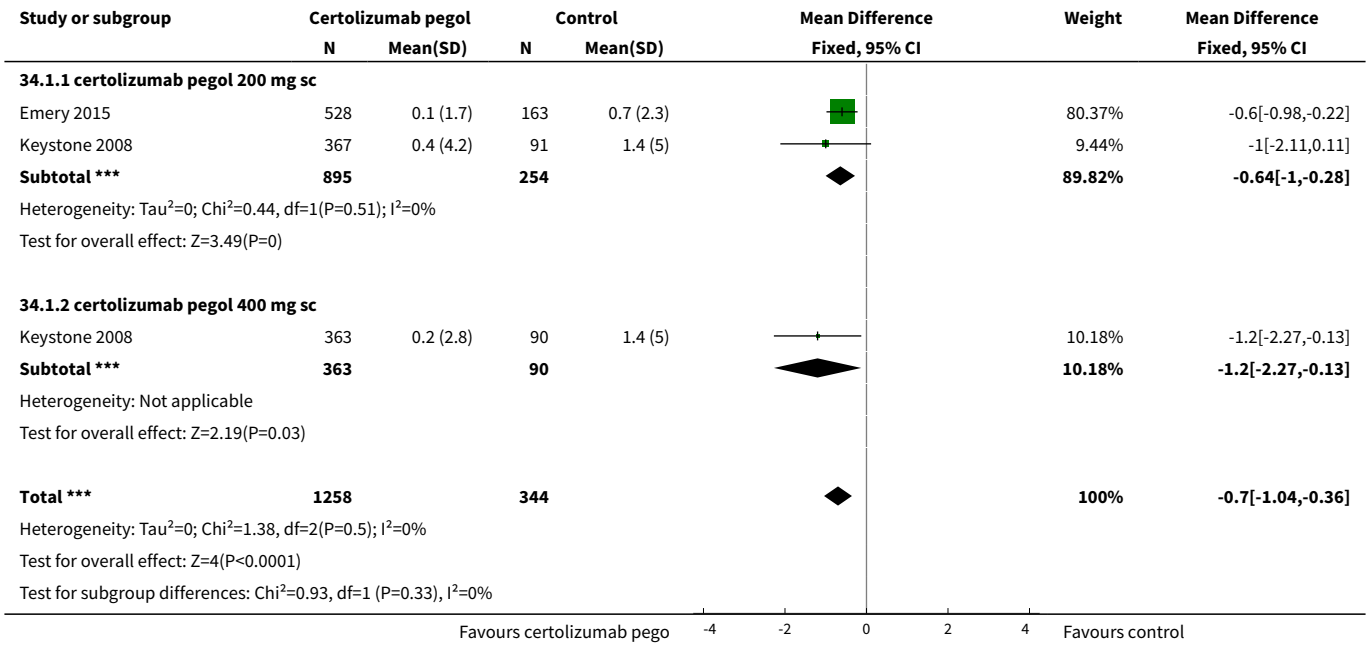


Comparison 34. Joint space narrowing (JSN) at 52 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	2	1602	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-1.04, -0.36]
1.1 certolizumab pegol 200 mg sc	2	1149	Mean Difference (IV, Fixed, 95% CI)	-0.64 [-1.00, -0.28]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 certolizumab pegol 400 mg sc	1	453	Mean Difference (IV, Fixed, 95% CI)	-1.2 [-2.27, -0.13]

Analysis 34.1. Comparison 34 Joint space narrowing (JSN) at 52 weeks, any dose, Outcome 1 Change from baseline.

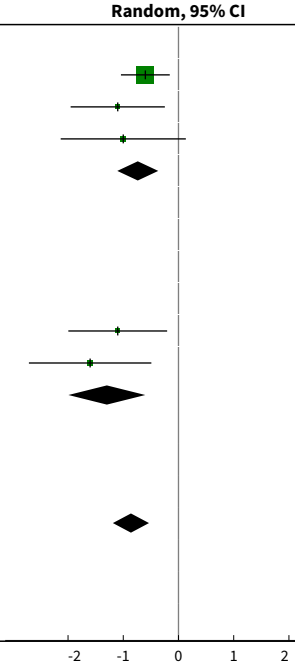


Comparison 35. Modified Total Sharp Scores (mTSS) at 24 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	3	1753	Mean Difference (IV, Random, 95% CI)	-0.86 [-1.19, -0.53]
1.1 certolizumab pegol 200 mg sc	3	1029	Mean Difference (IV, Random, 95% CI)	-0.74 [-1.11, -0.37]
1.2 certolizumab pegol 400 mg sc	2	724	Mean Difference (IV, Random, 95% CI)	-1.30 [-1.99, -0.60]

Analysis 35.1. Comparison 35 Modified Total Sharp Scores (mTSS) at 24 weeks, any dose, Outcome 1 Change from baseline.

Study or subgroup	Certolizumab pegol N	Certolizumab pegol Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
35.1.1 certolizumab pegol 200 mg sc							
Atsumi 2016	159	0.3 (1.6)	157	0.9 (2.4)		54.82%	-0.6[-1.04,-0.16]
Keystone 2008	353	0.2 (3.2)	90	1.3 (3.8)		14.73%	-1.1[-1.95,-0.25]
Smolen 2009	214	0.2 (2.7)	56	1.2 (4.1)		8.35%	-1[-2.13,0.13]
Subtotal ***	**726**		**303**			**77.89%**	**-0.74[-1.11,-0.37]**
Heterogeneity: Tau²=0; Chi²=1.27, df=2(P=0.53); I²=0%							
Test for overall effect: Z=3.9(P<0.0001)							
35.1.2 certolizumab pegol 400 mg sc							
Keystone 2008	355	0.2 (4.2)	91	1.3 (3.8)		13.39%	-1.1[-1.99,-0.21]
Smolen 2009	222	-0.4 (2.1)	56	1.2 (4.1)		8.72%	-1.6[-2.71,-0.49]
Subtotal ***	**577**		**147**			**22.11%**	**-1.3[-1.99,-0.6]**
Heterogeneity: Tau²=0; Chi²=0.47, df=1(P=0.49); I²=0%							
Test for overall effect: Z=3.65(P=0)							
Total ***	**1303**		**450**			**100%**	**-0.86[-1.19,-0.53]**
Heterogeneity: Tau²=0; Chi²=3.68, df=4(P=0.45); I²=0%							
Test for overall effect: Z=5.16(P<0.0001)							
Test for subgroup differences: Chi²=1.93, df=1 (P=0.16), I²=48.3%							

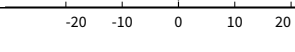


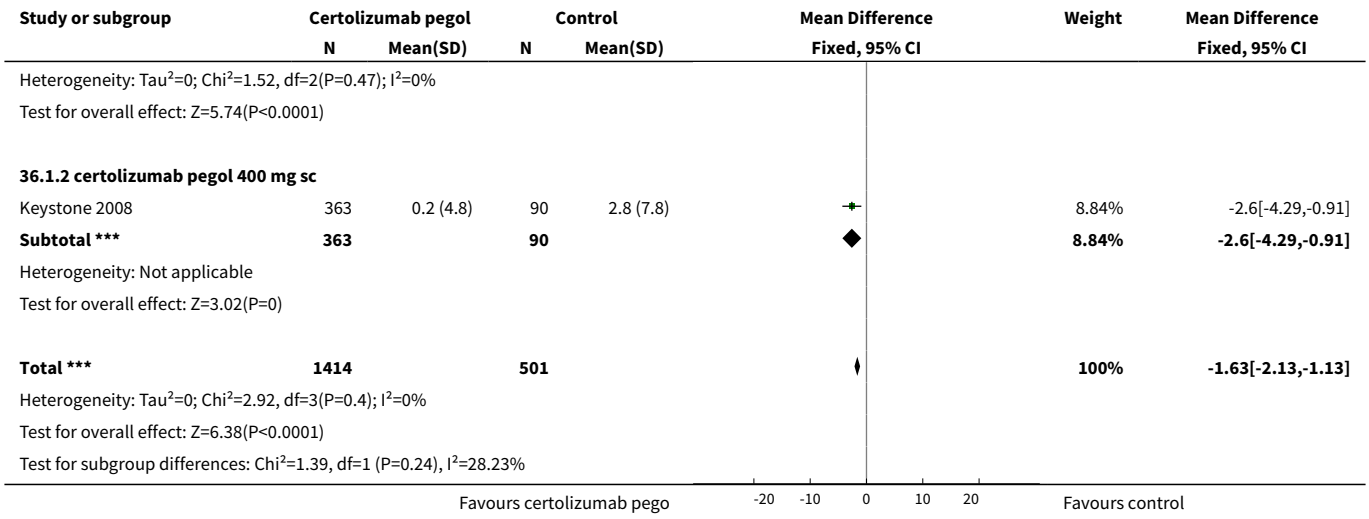
Comparison 36. Modified Total Sharp Scores (mTSS) at 52 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	3	1915	Mean Difference (IV, Fixed, 95% CI)	-1.63 [-2.13, -1.13]
1.1 certolizumab pegol 200 mg sc	3	1462	Mean Difference (IV, Fixed, 95% CI)	-1.54 [-2.06, -1.01]
1.2 certolizumab pegol 400 mg sc	1	453	Mean Difference (IV, Fixed, 95% CI)	-2.60 [-4.29, -0.91]

Analysis 36.1. Comparison 36 Modified Total Sharp Scores (mTSS) at 52 weeks, any dose, Outcome 1 Change from baseline.

Study or subgroup	Certolizumab pegol N	Certolizumab pegol Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
36.1.1 certolizumab pegol 200 mg sc							
Atsumi 2016	159	0.4 (2.7)	157	1.6 (4.9)		33.31%	-1.22[-2.09,-0.35]
Emery 2015	528	0.2 (3.2)	163	1.8 (4.3)		49.22%	-1.6[-2.31,-0.89]
Keystone 2008	364	0.4 (5.7)	91	2.8 (7.8)		8.63%	-2.4[-4.11,-0.69]
Subtotal ***	**1051**		**411**			**91.16%**	**-1.54[-2.06,-1.01]**

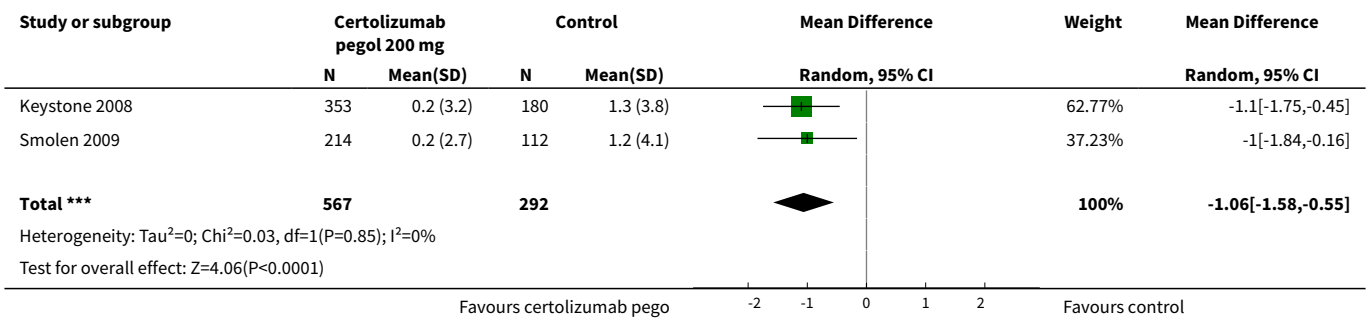




Comparison 37. Modified total Sharp scores (mTSS)

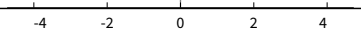
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from the baseline mean mTSS 24 weeks, certolizumab pegol 200 mg	2	859	Mean Difference (IV, Random, 95% CI)	-1.06 [-1.58, -0.55]
2 Change from the baseline mean mTSS 24 weeks, certolizumab 400 mg	2	869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

Analysis 37.1. Comparison 37 Modified total Sharp scores (mTSS), Outcome 1 Change from the baseline mean mTSS 24 weeks, certolizumab pegol 200 mg.



Analysis 37.2. Comparison 37 Modified total Sharp scores (mTSS), Outcome 2 Change from the baseline mean mTSS 24 weeks, certolizumab 400 mg.

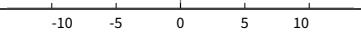
Study or subgroup	Certolizumab pegol 400 mg N	Mean(SD)	Control N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Keystone 2008	355	0.2 (4.2)	180	1.3 (3.8)		56.68%	-1.1[-1.81,-0.39]
Smolen 2009	222	-0.4 (2.1)	112	1.2 (4.1)		43.32%	-1.6[-2.41,-0.79]
Total ***	**577**		**292**			**100%**	**-1.32[-1.85,-0.78]**
Heterogeneity: Tau^2=0; Chi^2=0.83, df=1(P=0.36); I^2=0%							
Test for overall effect: Z=4.85(P<0.0001)							



Favours certolizumab pego — Favours control

Analysis 37.3. Comparison 37 Modified total Sharp scores (mTSS), Outcome 3 Change from the baseline mean mTSS 52 weeks, certolizumab pegol 200 mg.

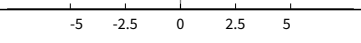
Study or subgroup	Certolizumab pegol 200mg N	Mean(SD)	Control N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Keystone 2008	364	0.4 (5.7)	181	2.8 (7.8)		100%	-2.4[-3.68,-1.12]
Total ***	**364**		**181**			**100%**	**-2.4[-3.68,-1.12]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.68(P=0)							



Favours certolizumab pego — Favours control

Analysis 37.4. Comparison 37 Modified total Sharp scores (mTSS), Outcome 4 Change from the baseline mean mTSS 52 weeks, certolizumab pegol 400 mg.

Study or subgroup	Certolizumab pegol 400 mg N	Mean(SD)	Control N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Keystone 2008	363	0.2 (4.8)	181	2.8 (7.8)		100%	-2.6[-3.84,-1.36]
Total ***	**363**		**181**			**100%**	**-2.6[-3.84,-1.36]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.11(P<0.0001)							



Favours certolizumab pego — Favours control

Comparison 38. Certolizumab pegol 1mg/kg/day sc

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Headache	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Lower respiratory tract infection	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
3 Adverse events Intensity severe	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
4 Antinuclear antibodies (ANA)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
5 Urinary tract infection	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected

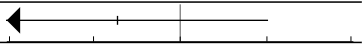
Analysis 38.1. Comparison 38 Certolizumab pegol 1mg/kg/day sc, Outcome 1 Headache.

Study or subgroup	certolizumab pegol 1 mg n/N	control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Choy 2002	3/8	1/12		5.65[0.64,49.98]

Favours certolizumab pego | Favours control

Analysis 38.2. Comparison 38 Certolizumab pegol 1mg/kg/day sc, Outcome 2 Lower respiratory tract infection.

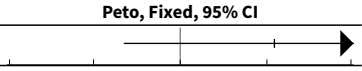
Study or subgroup	certolizumab pegol 1 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Choy 2002	0/8	1/12		0.19[0,10.32]



Favours certolizumab 1mg/Kg/day sc | Favours control

Analysis 38.3. Comparison 38 Certolizumab pegol 1mg/kg/day sc, Outcome 3 Adverse events Intensity severe.

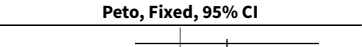
Study or subgroup	certolizumab pegol 1 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Choy 2002	1/8	0/12		12.18[0.22,665.65]



Favours certolizumab pego | Favours control

Analysis 38.4. Comparison 38 Certolizumab pegol 1mg/kg/day sc, Outcome 4 Antinuclear antibodies (ANA).

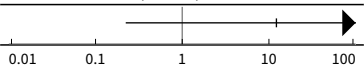
Study or subgroup	certolizumab pegol 1 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Choy 2002	2/8	1/12		3.46[0.3,39.8]



Favours certolizumab pego | Favours control

Analysis 38.5. Comparison 38 Certolizumab pegol 1mg/kg/day sc, Outcome 5 Urinary tract infection.

Study or subgroup	certolizumab pegol 1 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Choy 2002	1/8	0/12		12.18[0.22,665.65]

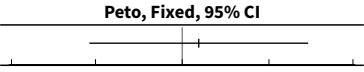


Comparison 39. Certolizumab 5 mg/kg/day sc

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Lower respiratory tract infection	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
2 Urinary tract infection	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected

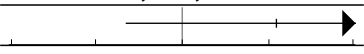
Analysis 39.1. Comparison 39 Certolizumab 5 mg/kg/day sc, Outcome 1 Lower respiratory tract infection.

Study or subgroup	certolizumab pegol 5 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Choy 2002	1/8	1/12		1.55[0.08,28.4]



Analysis 39.2. Comparison 39 Certolizumab 5 mg/kg/day sc, Outcome 2 Urinary tract infection.

Study or subgroup	certolizumab pegol 5 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Choy 2002	1/8	0/12		12.18[0.22,665.65]



Comparison 40. Certolizumab 20 mg/kg/day sc

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Headache	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Lower respiratory tract infection	1	20	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.32, 27.83]
3 Death	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
4 Antinuclear antibodies (ANA)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Urinary tract infection	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected

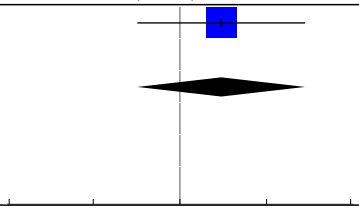
Analysis 40.1. Comparison 40 Certolizumab 20 mg/kg/day sc, Outcome 1 Headache.

Study or subgroup	certolizumab pegol 20 mg n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Choy 2002	3/8	1/12		4.5[0.56,35.98]

Favours certolizumab pego | Control

Analysis 40.2. Comparison 40 Certolizumab 20 mg/kg/day sc, Outcome 2 Lower respiratory tract infection.

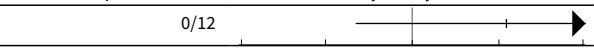
Study or subgroup	certolizumab pegol 20 mg n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Choy 2002	2/8	1/12		100%	3[0.32,27.83]
Total (95% CI)	**8**	**12**		**100%**	**3[0.32,27.83]**
Total events: 2 (certolizumab pegol 20 mg), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.97(P=0.33)					



Favours certolizumab pego | Favours control

Analysis 40.3. Comparison 40 Certolizumab 20 mg/kg/day sc, Outcome 3 Death.

Study or subgroup	certolizumab pegol 20 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Choy 2002	1/8	0/12		12.18[0.22,665.65]



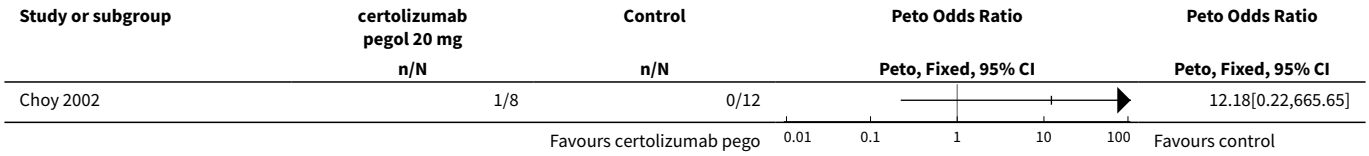
Favours certolizumab pego | Favours control

Analysis 40.4. Comparison 40 Certolizumab 20 mg/kg/day sc, Outcome 4 Antinuclear antibodies (ANA).

Study or subgroup	certolizumab pegol 20 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Choy 2002	1/8	1/12		1.55[0.08,28.4]

Favours certolizumab pego | Favours control

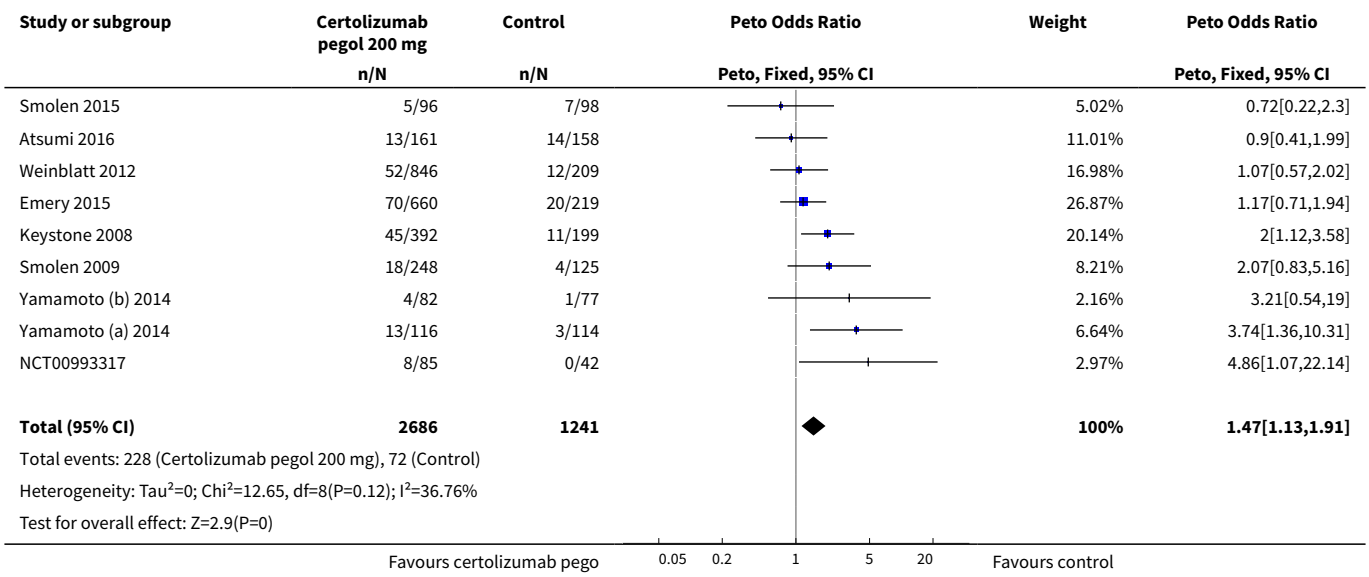
Analysis 40.5. Comparison 40 Certolizumab 20 mg/kg/day sc, Outcome 5 Urinary tract infection.



Comparison 41. Safety, SAE certolizumab 200 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serious Adverse Events (SAE)	9	3927	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.47 [1.13, 1.91]

Analysis 41.1. Comparison 41 Safety, SAE certolizumab 200 mg, Outcome 1 Serious Adverse Events (SAE).



Comparison 42. Safety, SAE certolizumab 400 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serious Adverse Events (SAEs)	6	1624	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.98 [1.36, 2.90]

Analysis 42.1. Comparison 42 Safety, SAE certolizumab 400 mg, Outcome 1 Serious Adverse Events (SAEs).

Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Choy 2012	16/124	12/119		23.17%	1.32[0.6,2.89]
Fleischmann 2009	8/111	3/109		9.78%	2.54[0.76,8.53]
Keystone 2008	48/389	11/199		44.37%	2.12[1.2,3.75]
Smolen 2009	18/246	4/125		17.28%	2.09[0.84,5.19]
Yamamoto (b) 2014	5/85	1/77		5.4%	3.59[0.7,18.26]
Østergaard 2015	0/27	0/13			Not estimable
Total (95% CI)	**982**	**642**		**100%**	**1.98[1.36,2.9]**
Total events: 95 (Certolizumab pegol 400 mg), 31 (Control)					
Heterogeneity: Tau²=0; Chi²=1.78, df=4(P=0.78); I²=0%					
Test for overall effect: Z=3.55(P=0)					

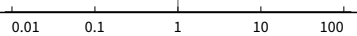
Favours certolizumab pego — Favours control

Comparison 43. Withdrawals

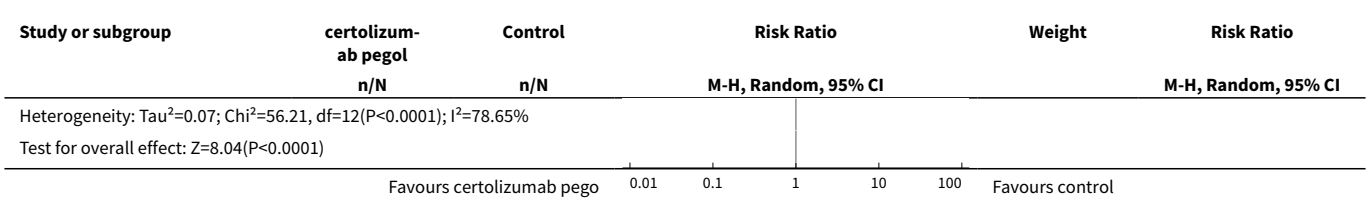
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All Withdrawn: any doses any follow-up	13	5200	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.39, 0.56]
2 Withdrawals due to adverse events	12	5236	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.45 [1.09, 1.94]

Analysis 43.1. Comparison 43 Withdrawals, Outcome 1 All Withdrawn: any doses any follow-up.

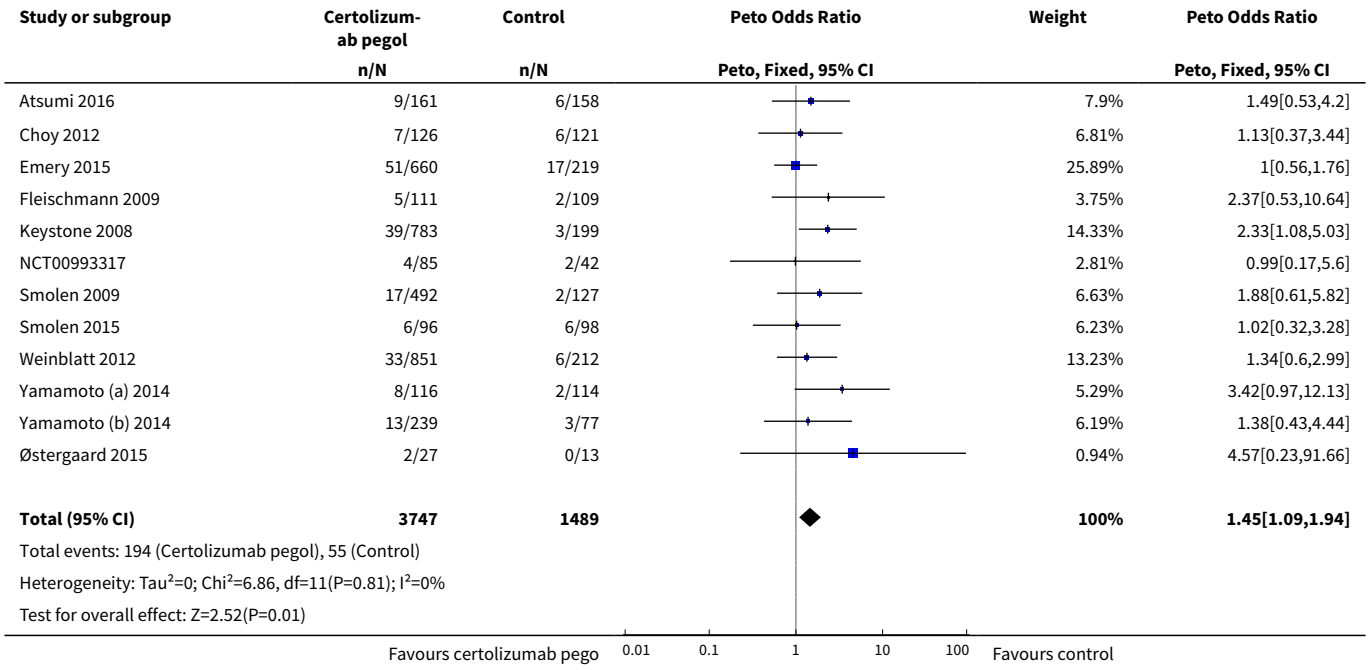
Study or subgroup	certolizumab pegol n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Atsumi 2016	50/161	85/158		9.66%	0.58[0.44,0.76]
Choy 2002	2/24	6/12		1.46%	0.17[0.04,0.71]
Choy 2012	28/126	56/121		8.09%	0.48[0.33,0.7]
Emery 2015	160/660	76/219		10.31%	0.7[0.56,0.88]
Fleischmann 2009	35/111	81/109		9.31%	0.42[0.32,0.57]
Keystone 2008	254/783	156/199		11.54%	0.41[0.37,0.47]
NCT00993317	25/85	21/42		7.15%	0.59[0.38,0.92]
Smolen 2009	137/492	110/127		11.19%	0.32[0.27,0.38]
Smolen 2015	12/96	18/98		4.69%	0.68[0.35,1.34]
Weinblatt 2012	80/851	28/212		7.74%	0.71[0.48,1.07]
Yamamoto (a) 2014	34/116	96/114		9.34%	0.35[0.26,0.47]
Yamamoto (b) 2014	36/167	52/77		8.83%	0.32[0.23,0.44]
Østergaard 2015	3/27	1/13		0.7%	1.44[0.17,12.58]
Total (95% CI)	**3699**	**1501**		**100%**	**0.47[0.39,0.56]**
Total events: 856 (certolizumab pegol), 786 (Control)					



Favours certolizumab pego — Favours control



Analysis 43.2. Comparison 43 Withdrawals, Outcome 2 Withdrawals due to adverse events.



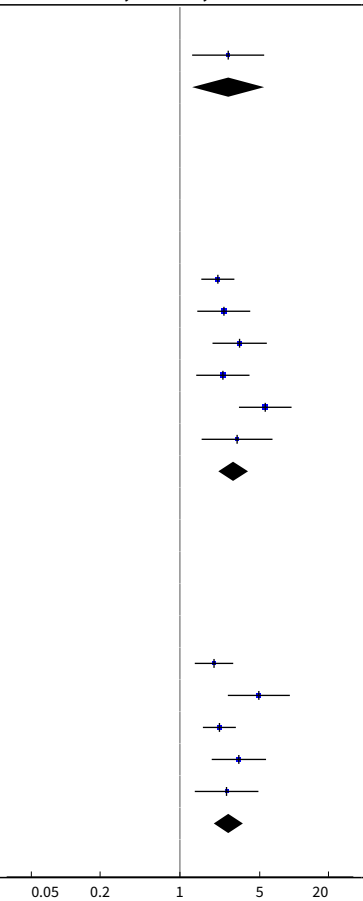
Comparison 44. ACR at 24 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR20	8	2935	Risk Ratio (M-H, Random, 95% CI)	2.76 [2.29, 3.33]
1.1 certolizumab 100 mg sc	1	98	Risk Ratio (M-H, Random, 95% CI)	2.65 [1.28, 5.47]
1.2 certolizumab 200 mg sc	6	1462	Risk Ratio (M-H, Random, 95% CI)	2.92 [2.17, 3.95]
1.3 certolizumab 400 mg sc	5	1375	Risk Ratio (M-H, Random, 95% CI)	2.65 [1.98, 3.56]
2 ACR50	7	2705	Risk Ratio (M-H, Random, 95% CI)	2.95 [2.37, 3.68]
2.1 certolizumab 100 mg sc	1	98	Risk Ratio (M-H, Random, 95% CI)	2.89 [1.13, 7.38]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 certolizumab 200 mg sc	5	1232	Risk Ratio (M-H, Random, 95% CI)	2.76 [2.02, 3.78]
2.3 certolizumab 400 mg sc	5	1375	Risk Ratio (M-H, Random, 95% CI)	3.18 [2.29, 4.41]
3 ACR70	7	2705	Risk Ratio (M-H, Random, 95% CI)	4.15 [2.68, 6.42]
3.1 certolizumab 100 mg sc	1	98	Risk Ratio (M-H, Random, 95% CI)	6.86 [0.97, 48.72]
3.2 certolizumab 200 mg sc	5	1232	Risk Ratio (M-H, Random, 95% CI)	4.29 [2.36, 7.77]
3.3 certolizumab 400 mg sc	5	1375	Risk Ratio (M-H, Random, 95% CI)	4.04 [1.37, 11.90]

Analysis 44.1. Comparison 44 ACR at 24 weeks, any dose, Outcome 1 ACR20.

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
44.1.1 certolizumab 100 mg sc					
Yamamoto (b) 2014	44/72	6/26		5.15%	2.65[1.28,5.47]
Subtotal (95% CI)	**72**	**26**		**5.15%**	**2.65[1.28,5.47]**
Total events: 44 (Certolizumab pegol), 6 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.63(P=0.01)					
44.1.2 certolizumab 200 mg sc					
Keystone 2008	228/393	27/100		13.08%	2.15[1.54,3]
NCT00993317	54/85	11/42		7.97%	2.43[1.42,4.13]
Smolen 2009	141/246	11/64		7.68%	3.33[1.93,5.77]
Smolen 2015	35/96	15/98		7.92%	2.38[1.39,4.07]
Yamamoto (a) 2014	74/116	13/114		8.03%	5.59[3.29,9.5]
Yamamoto (b) 2014	60/82	6/26		5.28%	3.17[1.55,6.47]
Subtotal (95% CI)	**1018**	**444**		**49.96%**	**2.92[2.17,3.95]**
Total events: 592 (Certolizumab pegol), 83 (Control)					
Heterogeneity: Tau^2=0.07; Chi^2=10.25, df=5(P=0.07); I^2=51.2%					
Test for overall effect: Z=7.01(P<0.0001)					
44.1.3 certolizumab 400 mg sc					
Choy 2012	56/126	27/121		11.48%	1.99[1.35,2.93]
Fleischmann 2009	50/111	10/109		6.42%	4.91[2.63,9.18]
Keystone 2008	236/390	27/99		13.13%	2.22[1.59,3.09]
Smolen 2009	141/246	11/63		7.69%	3.28[1.9,5.68]
Yamamoto (b) 2014	61/85	7/25		6.17%	2.56[1.35,4.87]
Subtotal (95% CI)	**958**	**417**		**44.89%**	**2.65[1.98,3.56]**
Total events: 544 (Certolizumab pegol), 82 (Control)					



Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0.05; Chi²=7.42, df=4(P=0.12); I²=46.13%					
Test for overall effect: Z=6.53(P<0.0001)					
Total (95% CI)	**2048**	**887**		**100%**	**2.76[2.29,3.33]**
Total events: 1180 (Certolizumab pegol), 171 (Control)					
Heterogeneity: Tau²=0.04; Chi²=18.18, df=11(P=0.08); I²=39.49%					
Test for overall effect: Z=10.61(P<0.0001)					
Test for subgroup differences: Chi²=0.22, df=1 (P=0.89), I²=0%					

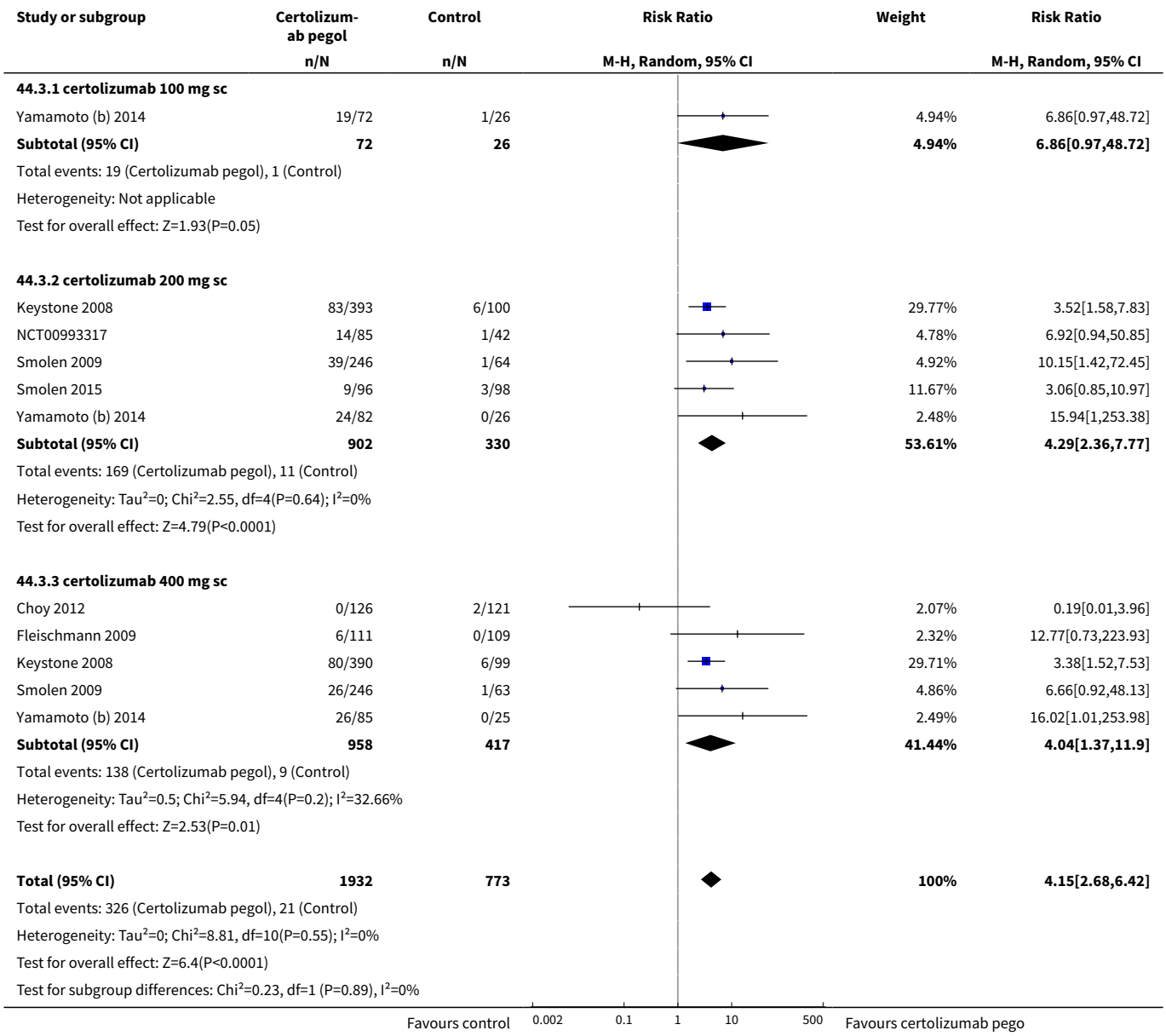
Favours control 0.05 0.2 1 5 20 Favours certolizumab pego

Analysis 44.2. Comparison 44 ACR at 24 weeks, any dose, Outcome 2 ACR50.

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
44.2.1 certolizumab 100 mg sc					
Yamamoto (b) 2014	32/72	4/26		5.48%	2.89[1.13,7.38]
Subtotal (95% CI)	**72**	**26**		**5.48%**	**2.89[1.13,7.38]**
Total events: 32 (Certolizumab pegol), 4 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.22(P=0.03)					
44.2.2 certolizumab 200 mg sc					
Keystone 2008	144/393	15/100		20.55%	2.44[1.5,3.96]
NCT00993317	35/85	8/42		10.63%	2.16[1.1,4.24]
Smolen 2009	80/246	4/64		5.17%	5.2[1.98,13.67]
Smolen 2015	20/96	7/98		7.29%	2.92[1.29,6.58]
Yamamoto (b) 2014	45/82	4/26		5.66%	3.57[1.42,8.97]
Subtotal (95% CI)	**902**	**330**		**49.3%**	**2.76[2.02,3.78]**
Total events: 324 (Certolizumab pegol), 38 (Control)					
Heterogeneity: Tau²=0; Chi²=2.81, df=4(P=0.59); I²=0%					
Test for overall effect: Z=6.37(P<0.0001)					
44.2.3 certolizumab 400 mg sc					
Choy 2012	22/126	7/121		7.29%	3.02[1.34,6.81]
Fleischmann 2009	25/111	4/109		4.62%	6.14[2.21,17.05]
Keystone 2008	155/390	15/99		20.76%	2.62[1.62,4.25]
Smolen 2009	81/246	4/63		5.18%	5.19[1.98,13.61]
Yamamoto (b) 2014	46/85	5/25		7.38%	2.71[1.21,6.07]
Subtotal (95% CI)	**958**	**417**		**45.22%**	**3.18[2.29,4.41]**
Total events: 329 (Certolizumab pegol), 35 (Control)					
Heterogeneity: Tau²=0; Chi²=3.42, df=4(P=0.49); I²=0%					
Test for overall effect: Z=6.94(P<0.0001)					
Total (95% CI)	**1932**	**773**		**100%**	**2.95[2.37,3.68]**
Total events: 685 (Certolizumab pegol), 77 (Control)					
Heterogeneity: Tau²=0; Chi²=6.62, df=10(P=0.76); I²=0%					
Test for overall effect: Z=9.66(P<0.0001)					
Test for subgroup differences: Chi²=0.38, df=1 (P=0.83), I²=0%					

Favours control 0.01 0.1 1 10 100 Favours certolizumab pego

Analysis 44.3. Comparison 44 ACR at 24 weeks, any dose, Outcome 3 ACR70.



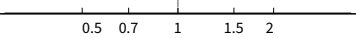
Comparison 45. ACR at 52 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR20	3	2180	Risk Ratio (M-H, Random, 95% CI)	1.46 [1.11, 1.93]
1.1 certolizumab 200 mg sc	3	1691	Risk Ratio (M-H, Random, 95% CI)	1.30 [1.03, 1.65]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 certolizumab 400 mg sc	1	489	Risk Ratio (M-H, Random, 95% CI)	2.08 [1.48, 2.93]
2 ACR50	3	2180	Risk Ratio (M-H, Random, 95% CI)	1.69 [1.22, 2.33]
2.1 certolizumab 200 mg sc	3	1691	Risk Ratio (M-H, Random, 95% CI)	1.48 [1.11, 1.96]
2.2 certolizumab 400 mg sc	1	489	Risk Ratio (M-H, Random, 95% CI)	2.62 [1.62, 4.25]
3 ACR70	3	2180	Risk Ratio (M-H, Random, 95% CI)	1.89 [1.44, 2.48]
3.1 certolizumab 200 mg sc	3	1691	Risk Ratio (M-H, Random, 95% CI)	1.71 [1.39, 2.11]
3.2 certolizumab 400 mg sc	1	489	Risk Ratio (M-H, Random, 95% CI)	3.26 [1.56, 6.82]

Analysis 45.1. Comparison 45 ACR at 52 weeks, any dose, Outcome 1 ACR20.

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
45.1.1 certolizumab 200 mg sc					
Atsumi 2016	125/161	108/158		28.8%	1.14[0.99,1.3]
Emery 2015	452/660	131/219		29.2%	1.14[1.02,1.29]
Keystone 2008	208/393	26/100		20.97%	2.04[1.44,2.87]
Subtotal (95% CI)	**1214**	**477**		**78.98%**	**1.3[1.03,1.65]**
Total events: 785 (Certolizumab pegol), 265 (Control)					
Heterogeneity: Tau^2=0.03; Chi^2=11.66, df=2(P=0); I^2=82.85%					
Test for overall effect: Z=2.16(P=0.03)					
45.1.2 certolizumab 400 mg sc					
Keystone 2008	213/390	26/99		21.02%	2.08[1.48,2.93]
Subtotal (95% CI)	**390**	**99**		**21.02%**	**2.08[1.48,2.93]**
Total events: 213 (Certolizumab pegol), 26 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=4.19(P<0.0001)					
Total (95% CI)	**1604**	**576**		**100%**	**1.46[1.11,1.93]**
Total events: 998 (Certolizumab pegol), 291 (Control)					
Heterogeneity: Tau^2=0.06; Chi^2=24.18, df=3(P<0.0001); I^2=87.59%					
Test for overall effect: Z=2.68(P=0.01)					
Test for subgroup differences: Chi^2=4.84, df=1 (P=0.03), I^2=79.32%					

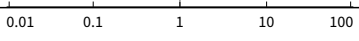


Favours control

Favours certoluzimab pego

Analysis 45.2. Comparison 45 ACR at 52 weeks, any dose, Outcome 2 ACR50.

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
45.2.1 certolizumab 200 mg sc					
Atsumi 2016	116/161	81/158		30.31%	1.41[1.17,1.68]
Emery 2015	405/660	112/219		31.4%	1.2[1.04,1.38]
Keystone 2008	149/393	15/100		19.12%	2.53[1.56,4.1]
Subtotal (95% CI)	**1214**	**477**		**80.83%**	**1.48[1.11,1.96]**
Total events: 670 (Certolizumab pegol), 208 (Control)					
Heterogeneity: Tau^2=0.05; Chi^2=9.68, df=2(P=0.01); I^2=79.34%					
Test for overall effect: Z=2.7(P=0.01)					
45.2.2 certolizumab 400 mg sc					
Keystone 2008	155/390	15/99		19.17%	2.62[1.62,4.25]
Subtotal (95% CI)	**390**	**99**		**19.17%**	**2.62[1.62,4.25]**
Total events: 155 (Certolizumab pegol), 15 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.92(P<0.0001)					
Total (95% CI)	**1604**	**576**		**100%**	**1.69[1.22,2.33]**
Total events: 825 (Certolizumab pegol), 223 (Control)					
Heterogeneity: Tau^2=0.08; Chi^2=18.63, df=3(P=0); I^2=83.89%					
Test for overall effect: Z=3.17(P=0)					
Test for subgroup differences: Chi^2=4.04, df=1 (P=0.04), I^2=75.26%					



Analysis 45.3. Comparison 45 ACR at 52 weeks, any dose, Outcome 3 ACR70.

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
45.3.1 certolizumab 200 mg sc					
Atsumi 2016	91/161	54/158		38.22%	1.65[1.28,2.13]
Emery 2015	279/660	57/219		39.73%	1.62[1.28,2.07]
Keystone 2008	83/393	7/100		10.99%	3.02[1.44,6.32]
Subtotal (95% CI)	**1214**	**477**		**88.94%**	**1.71[1.39,2.11]**
Total events: 453 (Certolizumab pegol), 118 (Control)					
Heterogeneity: Tau^2=0.01; Chi^2=2.59, df=2(P=0.27); I^2=22.65%					
Test for overall effect: Z=5.11(P<0.0001)					
45.3.2 certolizumab 400 mg sc					
Keystone 2008	90/390	7/99		11.06%	3.26[1.56,6.82]
Subtotal (95% CI)	**390**	**99**		**11.06%**	**3.26[1.56,6.82]**
Total events: 90 (Certolizumab pegol), 7 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.15(P=0)					
Total (95% CI)	**1604**	**576**		**100%**	**1.89[1.44,2.48]**
Total events: 543 (Certolizumab pegol), 125 (Control)					
Heterogeneity: Tau^2=0.03; Chi^2=5.77, df=3(P=0.12); I^2=47.98%					

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=4.58(P<0.0001)					
Test for subgroup differences: Chi^2=2.72, df=1 (P=0.1), I^2=63.25%					

Favours control 0.01 0.1 1 10 100 Favours certoluzimab pego

Comparison 46. ACR20-ACR70, 24 weeks, 200 mg certolizumab pegol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR 20	6	1675	Risk Ratio (M-H, Random, 95% CI)	3.71 [2.68, 5.13]
2 ACR 70	5	1445	Risk Ratio (M-H, Random, 95% CI)	7.26 [3.83, 13.76]

Analysis 46.1. Comparison 46 ACR20-ACR70, 24 weeks, 200 mg certolizumab pegol, Outcome 1 ACR 20.

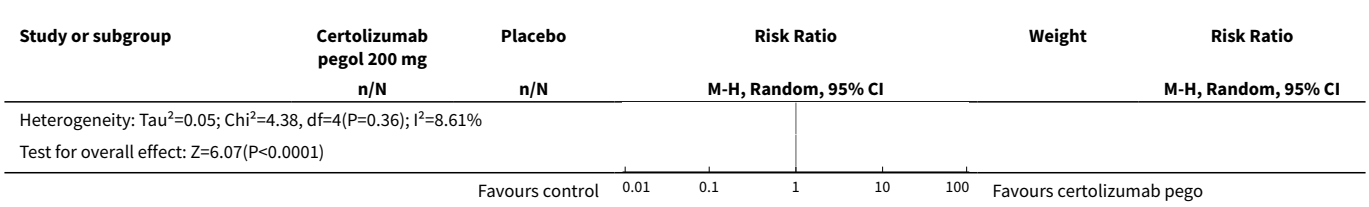
Study or subgroup	Certolizumab pegol 200 mg n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Smolen 2015	35/96	15/98		15.48%	2.38[1.39,4.07]
NCT00993317	54/85	11/42		15.55%	2.43[1.42,4.13]
Yamamoto (b) 2014	60/82	19/77		18.7%	2.97[1.96,4.48]
Keystone 2008	228/393	27/199		20.11%	4.28[2.98,6.13]
Yamamoto (a) 2014	74/116	13/114		15.62%	5.59[3.29,9.5]
Smolen 2009	141/246	11/127		14.54%	6.62[3.72,11.76]
Total (95% CI)	**1018**	**657**		**100%**	**3.71[2.68,5.13]**
Total events: 592 (Certolizumab pegol 200 mg), 96 (Placebo)					
Heterogeneity: Tau^2=0.1; Chi^2=13.68, df=5(P=0.02); I^2=63.46%					
Test for overall effect: Z=7.92(P<0.0001)					

Favours control 0.01 0.1 1 10 100 Favours certolizumab pego

Analysis 46.2. Comparison 46 ACR20-ACR70, 24 weeks, 200 mg certolizumab pegol, Outcome 2 ACR 70.

Study or subgroup	Certolizumab pegol 200 mg n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Keystone 2008	83/393	6/199		47.83%	7[3.11,15.76]
NCT00993317	14/85	1/42		9.79%	6.92[0.94,50.85]
Smolen 2009	39/246	1/127		10%	20.13[2.8,144.86]
Smolen 2015	9/96	3/98		22.4%	3.06[0.85,10.97]
Yamamoto (b) 2014	24/82	1/77		9.97%	22.54[3.12,162.58]
Total (95% CI)	**902**	**543**		**100%**	**7.26[3.83,13.76]**
Total events: 169 (Certolizumab pegol 200 mg), 12 (Placebo)					

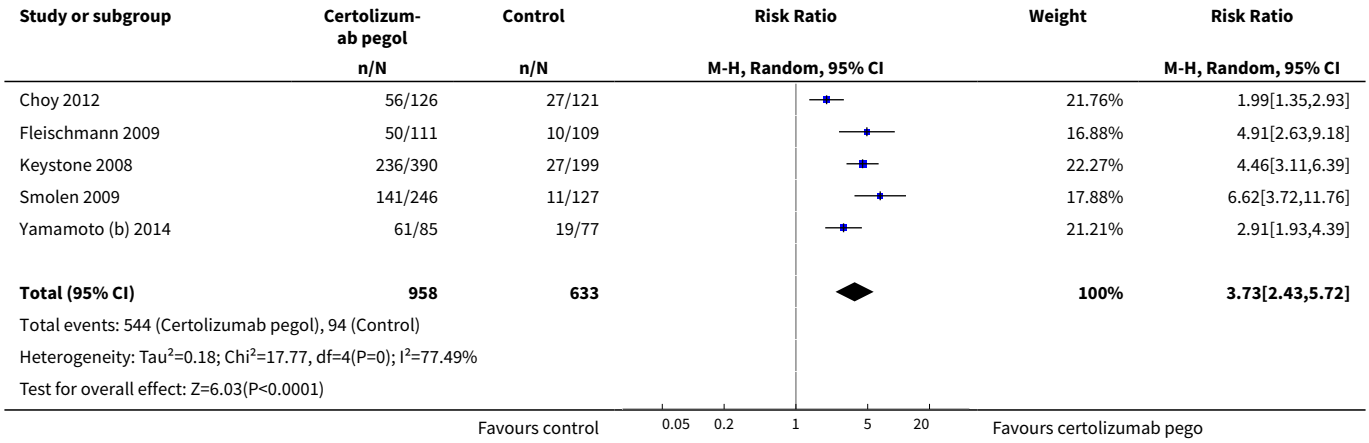
Favours control 0.01 0.1 1 10 100 Favours certolizumab pego



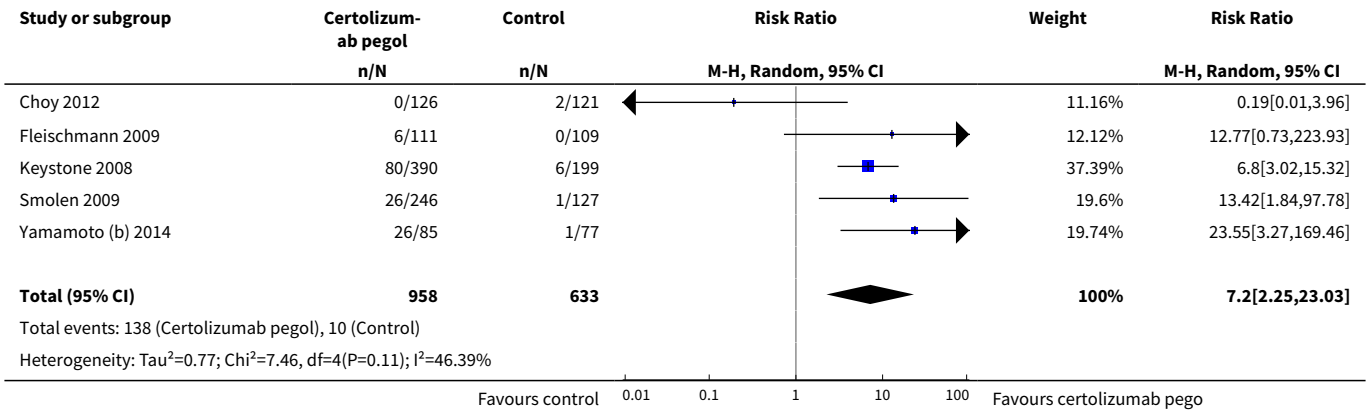
Comparison 47. ACR20-ACR70 at 24 weeks, 400 mg certolizumab

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR 20	5	1591	Risk Ratio (M-H, Random, 95% CI)	3.73 [2.43, 5.72]
2 ACR 70	5	1591	Risk Ratio (M-H, Random, 95% CI)	7.20 [2.25, 23.03]

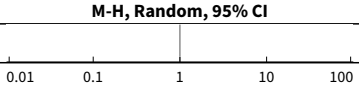
Analysis 47.1. Comparison 47 ACR20-ACR70 at 24 weeks, 400 mg certolizumab, Outcome 1 ACR 20.



Analysis 47.2. Comparison 47 ACR20-ACR70 at 24 weeks, 400 mg certolizumab, Outcome 2 ACR 70.



Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=3.33(P=0)					

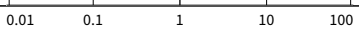


Comparison 48. ACR20-ACR70 at 52 weeks, 200 mg certolizumab

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR 20	3	1790	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [1.30, 1.58]
2 ACR 70	3	1790	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [1.41, 1.90]

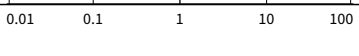
Analysis 48.1. Comparison 48 ACR20-ACR70 at 52 weeks, 200 mg certolizumab, Outcome 1 ACR 20.

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Atsumi 2016	125/161	108/158		32.04%	1.14[0.99,1.3]
Emery 2015	452/660	131/219		57.82%	1.14[1.02,1.29]
Keystone 2008	208/393	26/199		10.15%	4.05[2.8,5.87]
Total (95% CI)	**1214**	**576**		**100%**	**1.44[1.3,1.58]**
Total events: 785 (Certolizumab pegol), 265 (Control)					
Heterogeneity: Tau^2=0; Chi^2=55.5, df=2(P<0.0001); I^2=96.4%					
Test for overall effect: Z=7.37(P<0.0001)					



Analysis 48.2. Comparison 48 ACR20-ACR70 at 52 weeks, 200 mg certolizumab, Outcome 2 ACR 70.

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Atsumi 2016	91/161	54/158		28.47%	1.65[1.28,2.13]
Emery 2015	336/660	85/219		66.67%	1.31[1.09,1.57]
Keystone 2008	83/393	7/199		4.85%	6[2.83,12.74]
Total (95% CI)	**1214**	**576**		**100%**	**1.64[1.41,1.9]**
Total events: 510 (Certolizumab pegol), 146 (Control)					
Heterogeneity: Tau^2=0; Chi^2=17.14, df=2(P=0); I^2=88.33%					
Test for overall effect: Z=6.5(P<0.0001)					

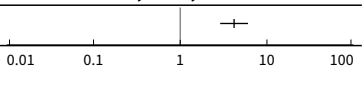


Comparison 49. ACR20-ACR70 at 52 weeks, 400 mg certolizumab

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR 20	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 ACR 70	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 49.1. Comparison 49 ACR20-ACR70 at 52 weeks, 400 mg certolizumab, Outcome 1 ACR 20.

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Keystone 2008	213/390	26/199		4.18[2.89,6.05]



Analysis 49.2. Comparison 49 ACR20-ACR70 at 52 weeks, 400 mg certolizumab, Outcome 2 ACR 70.

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Keystone 2008	90/390	7/199		6.56[3.1,13.89]

Comparison 50. Safety

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any adverse event certolizumab 200 mg	9	3927	Risk Ratio (M-H, Random, 95% CI)	1.16 [1.03, 1.31]
2 Any adverse events certolizumab 400 mg	6	1624	Risk Ratio (M-H, Random, 95% CI)	1.19 [1.05, 1.34]
3 Adverse events: Intensity mild certolizumab 200 mg	4	2249	Risk Ratio (M-H, Random, 95% CI)	1.18 [1.00, 1.41]
4 Adverse events: Intensity mild certolizumab 400 mg	5	1462	Risk Ratio (M-H, Random, 95% CI)	1.25 [1.06, 1.47]
5 Adverse events: Intensity moderate certolizumab 200 mg	4	2249	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.86, 1.32]
6 Adverse events: Intensity moderate certolizumab 400 mg	5	1462	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.99, 1.47]
7 Adverse events: Intensity severe certolizumab 200 mg	4	2249	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.14 [0.78, 1.65]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Adverse events: Intensity severe certolizumab 400 mg	5	1462	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.23 [0.83, 1.81]
9 Adverse events related to study drug certolizumab 200 mg	2	964	Risk Ratio (M-H, Random, 95% CI)	1.59 [1.27, 1.99]
10 Adverse events related to study drug certolizumab 400 mg	4	1219	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [1.20, 1.80]
11 Serious Infections certolizumab 200 mg	3	1283	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.94 [0.99, 3.80]
12 Serious infections certolizumab 400 mg	4	1422	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.25 [1.65, 6.39]
13 Adverse events leading to death certolizumab 200 mg	6	3322	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.63 [0.41, 6.47]
14 Adverse events leading to death certolizumab 400 mg	3	1179	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.16 [0.40, 11.79]
15 Adverse events leading to withdrawal certolizumab 200 mg	8	3608	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.32 [0.95, 1.84]
16 Adverse events leading to withdrawal certolizumab 400 mg	6	1624	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.01 [1.20, 3.36]
17 Death certolizumab 200 mg	6	3320	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.66 [0.63, 11.16]
18 Death certolizumab 400 mg	5	1462	Risk Ratio (M-H, Fixed, 95% CI)	1.87 [0.31, 11.34]
19 Deaths overall	10	4745	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.63 [0.78, 8.91]
19.1 Certolizumab pegol 200 mg	7	3266	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.10 [0.44, 10.08]
19.2 Certolizumab pegol 400 mg	5	1349	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.53 [0.40, 31.39]
19.3 Other doses	2	130	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.48 [0.07, 286.49]
20 Tuberculosis certolizumab 200 mg	7	3538	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.90 [0.55, 6.58]
21 Tuberculosis certolizumab 400 mg	3	1179	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.55 [0.71, 29.11]
22 Tuberculosis overall	7	4074	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.91 [0.61, 5.96]
22.1 Certolizumab pegol 200 mg	6	3058	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.53 [0.40, 5.77]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22.2 Certolizumab pegol 400 mg	3	1016	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.52 [0.40, 31.33]
23 Malignancies included lymphoma certolizumab 200 mg	8	3768	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.92 [0.40, 2.11]
24 Malignancies included lymphoma certolizumab 400 mg	3	1179	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.26 [0.26, 6.08]
25 Injection side reactions certolizumab 200 mg	5	2497	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.34 [1.85, 6.06]
26 Injection side reactions certolizumab 400 mg	5	1584	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.34 [0.20, 0.56]
27 Antinuclear antibodies (ANA) Anti-certolizumab pegol antibodies certolizumab 200 mg	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
28 Anti-certolizumab pegol antibodies certolizumab 400 mg	2	591	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.70 [2.18, 20.55]
29 Systemic lupus erythematosus certolizumab 200 mg	2	567	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.50 [0.07, 286.06]
30 Prolonged activated partial thromboplastin time (aPTT) certolizumab 200 mg	2	500	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.73 [0.98, 7.61]
31 Prolonged activated partial thromboplastin time (aPTT) certolizumab 400 mg	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
32 Urinary tract infection certolizumab 200 mg	6	3219	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.68, 1.40]
33 Urinary tract infection certolizumab 400 mg	2	959	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.87 [0.50, 1.52]
34 Upper respiratory tract infection certolizumab 200 mg	8	3608	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.68 [1.28, 2.20]
35 Upper respiratory tract infection certolizumab 400 mg	4	1364	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.42 [0.77, 2.61]
36 Lower respiratory tract infection/lung infection certolizumab 200 mg	6	2356	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.12 [0.76, 5.95]
37 Lower respiratory tract infection/lung infection certolizumab 400 mg	3	993	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.11 [0.75, 5.95]
38 Pneumonia certolizumab 200 mg	6	2804	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.94 [0.45, 1.97]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
39 Pneumonitis certolizumab 400 mg	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
40 Headache certolizumab 200 mg	6	3251	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.33 [0.94, 1.87]
41 Headache certolizumab 400 mg	4	1364	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.30 [0.76, 2.20]
42 Bacteriuria certolizumab 200 mg	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
43 Bacteriuria certolizumab 400 mg	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
44 Nasopharyngitis/Pharyngitis certolizumab 200 mg	7	2553	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.37 [1.01, 1.84]
45 Nasopharyngitis/Pharyngitis certolizumab 400 mg	4	1364	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.98 [1.26, 3.11]
46 Injection site pain certolizumab 200 mg	3	1091	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.85 [0.49, 6.92]
47 Injection site pain certolizumab 400 mg	3	1179	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.74 [0.41, 7.42]
48 Hypertension certolizumab 200 mg	4	1353	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.09 [1.64, 5.84]
49 Hypertension certolizumab 400 mg	3	1121	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.35 [1.80, 6.20]
50 Hematuria certolizumab 200 mg	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
51 Haematuria certolizumab 400 mg	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
52 Hepatic enzyme increased certolizumab 200 mg	3	851	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.84 [0.56, 1.27]
53 Hepatic enzyme increased certolizumab 400 mg	2	533	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.69 [0.25, 1.92]
54 AST increased certolizumab 200 mg	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
55 AST increased certolizumab 400 mg	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
56 ALT increased certolizumab 200 mg	2	1252	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.85 [0.48, 1.50]

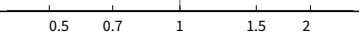
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
57 ALT increased certolizumab 400 mg	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
58 Diarrhoea certolizumab 200 mg	3	1200	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.71 [0.25, 2.03]
59 Gastroenteritis certolizumab 200 mg	2	785	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.33, 2.87]
60 Gastrointestinal disorders certolizumab 400 mg	2	831	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.05 [0.54, 2.03]
61 Back pain certolizumab 200 mg	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
62 Back pain certolizumab 400 mg	2	831	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.11 [1.48, 6.55]
63 Hematologic abnormalities certolizumab 200 mg	2	821	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.02 [0.27, 15.21]
64 Haematologic abnormalities certolizumab 400 mg	2	750	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.13 [0.21, 6.07]
65 Herpes viral infection certolizumab 200 mg	2	821	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.80 [0.34, 100.23]
66 Herpes viral infection certolizumab 400 mg	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
67 Bacterial peritonitis certolizumab 200 mg	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
68 Bacterial peritonitis certolizumab 400 mg	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
69 Opportunistic infections certolizumab 200 mg	4	2070	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.33 [0.46, 117.85]
70 Opportunistic infections certolizumab 400 mg	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
71 Infections and infestations certolizumab 200 mg	9	3910	Risk Ratio (M-H, Random, 95% CI)	1.27 [1.10, 1.46]
72 Infections and infestations certolizumab 400 mg	5	1404	Risk Ratio (M-H, Random, 95% CI)	1.43 [1.03, 1.98]
73 Decreased haemoglobin certolizumab 200 mg	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
74 Decreased haemoglobin certolizumab 400 mg	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
75 Increased platelet count certolizumab 200 mg	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
76 Increased platelet count certolizumab 400 mg	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
77 Cerebral haemorrhage including subarachnoid certolizumab 200 mg	2	321	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.27 [0.12, 13.50]
78 Ischaemic stroke certolizumab 400 mg	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
79 Nausea/vomiting certolizumab 200 mg	4	2447	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.13 [0.84, 1.54]
80 Vomiting certolizumab 400 mg	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
81 Acute miocardial infarction certolizumab 200 mg	2	1073	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.79 [0.04, 351.89]
82 Acute myocardial infarction certolizumab 400 mg	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
83 Abdominal pain/discomfort/dyspepsia certolizumab 200 mg	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
84 Constipation certolizumab 200 mg	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
85 Skin and subcutaneous tissue disorders certolizumab 200 mg	4	1395	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.83 [1.46, 5.48]
86 Skin and subcutaneous tissue disorders certolizumab 400 mg	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
87 Cough certolizumab 200 mg	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
88 Pruritus certolizumab 200 mg	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
89 Fatigue certolizumab 200 mg	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
90 Fatigue certolizumab 400 mg	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
91 Periodontitis certolizumab 200 mg	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
92 Arthritis bacterial certolizumab 400 mg	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
93 Mastitis certolizumab 400 mg	1	220	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.26 [0.14, 365.79]
94 Benign tumour certolizumab 400 mg	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
95 Dizziness postural certolizumab 400 mg	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
96 Menorrhagia certolizumab 400 mg	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
97 Corneal perforation certolizumab 400 mg	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
98 Conjunctivitis allergic certolizumab 400 mg	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
99 Periodontitis certolizumab 400 mg	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 50.1. Comparison 50 Safety, Outcome 1 Any adverse event certolizumab 200 mg.

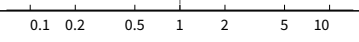
Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Atsumi 2016	153/161	148/158		18.18%	1.01[0.96,1.07]
Emery 2015	113/660	31/219		6.74%	1.21[0.84,1.75]
Keystone 2008	293/392	115/199		15.31%	1.29[1.13,1.48]
NCT00993317	60/85	21/42		7.62%	1.41[1.01,1.97]
Smolen 2009	139/248	66/125		12.33%	1.06[0.87,1.3]
Smolen 2015	37/96	41/98		7.3%	0.92[0.65,1.3]
Weinblatt 2012	571/846	129/209		15.98%	1.09[0.97,1.23]
Yamamoto (a) 2014	59/116	44/114		8.79%	1.32[0.98,1.77]
Yamamoto (b) 2014	48/82	31/77		7.75%	1.45[1.05,2.02]
Total (95% CI)	**2686**	**1241**		**100%**	**1.16[1.03,1.31]**
Total events: 1473 (Certolizumab pegol 200 mg), 626 (Control)					
Heterogeneity: Tau^2=0.02; Chi^2=31.27, df=8(P=0); I^2=74.42%					
Test for overall effect: Z=2.48(P=0.01)					



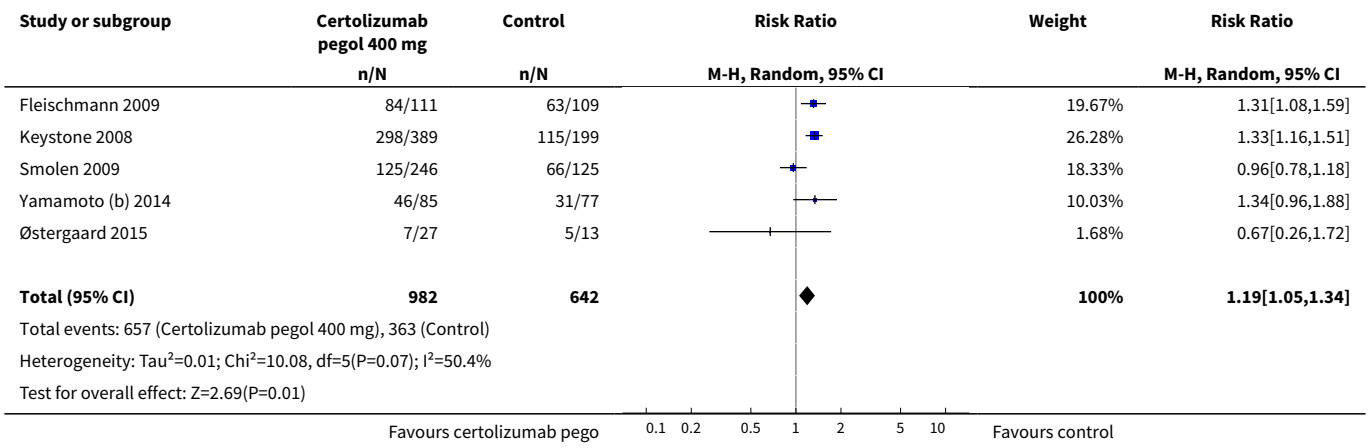
Favours certolizumab pego — Favours control

Analysis 50.2. Comparison 50 Safety, Outcome 2 Any adverse events certolizumab 400 mg.

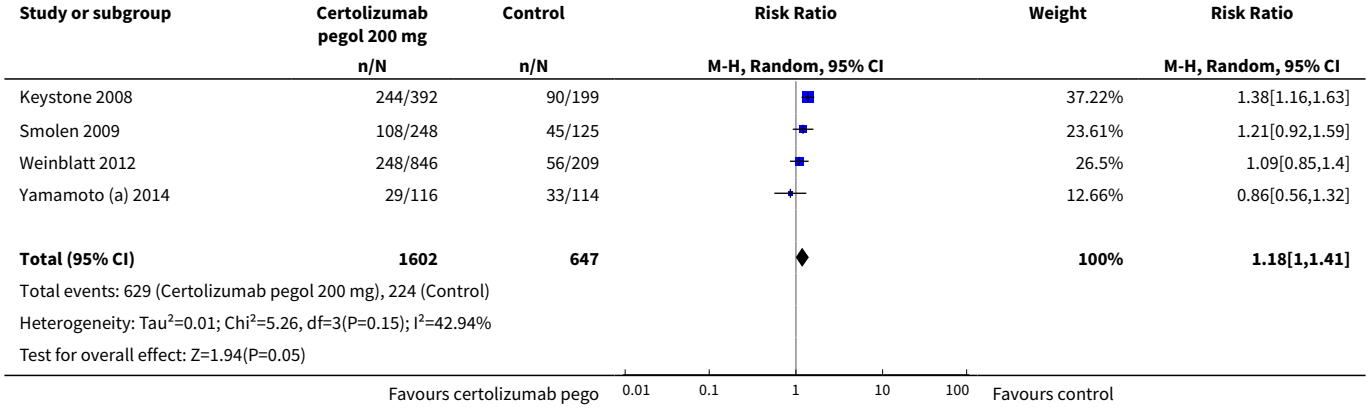
Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Choy 2012	97/124	83/119		24.02%	1.12[0.96,1.3]



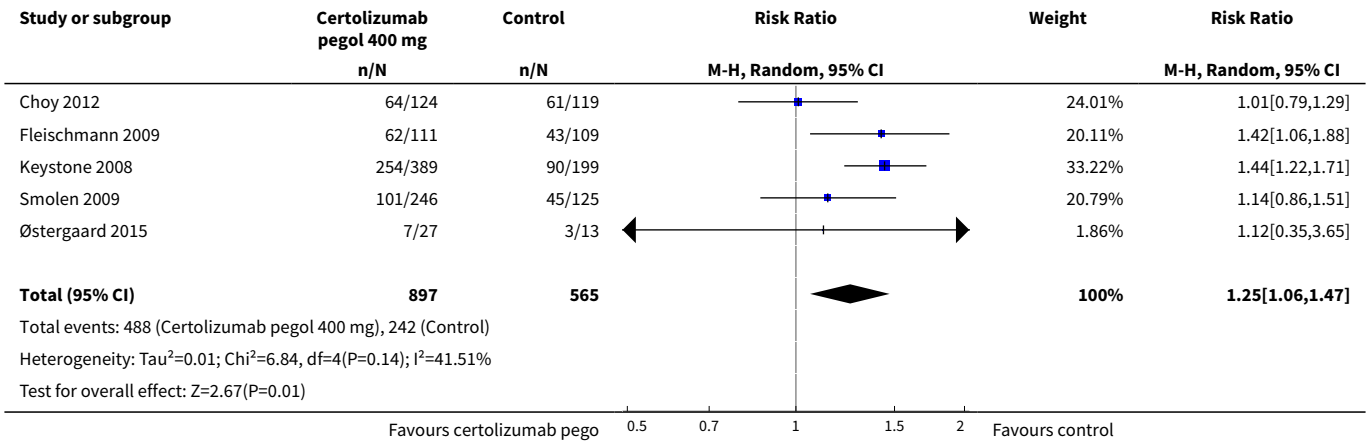
Favours certolizumab pego — Favours control



Analysis 50.3. Comparison 50 Safety, Outcome 3 Adverse events: Intensity mild certolizumab 200 mg.



Analysis 50.4. Comparison 50 Safety, Outcome 4 Adverse events: Intensity mild certolizumab 400 mg.



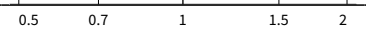
Analysis 50.5. Comparison 50 Safety, Outcome 5 Adverse events: Intensity moderate certolizumab 200 mg.

Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Keystone 2008	174/392	66/199		30.95%	1.34[1.07,1.68]
Smolen 2009	61/248	32/125		19.36%	0.96[0.66,1.39]
Weinblatt 2012	257/846	58/209		29.49%	1.09[0.86,1.39]
Yamamoto (a) 2014	36/116	44/114		20.21%	0.8[0.56,1.15]
Total (95% CI)	**1602**	**647**		**100%**	**1.07[0.86,1.32]**
Total events: 528 (Certolizumab pegol 200 mg), 200 (Control)					
Heterogeneity: Tau^2=0.02; Chi^2=6.36, df=3(P=0.1); I^2=52.85%					
Test for overall effect: Z=0.61(P=0.54)					

Favours certolizumab pego — Favours control

Analysis 50.6. Comparison 50 Safety, Outcome 6 Adverse events: Intensity moderate certolizumab 400 mg.

Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Choy 2012	59/124	45/119		25.05%	1.26[0.94,1.69]
Fleischmann 2009	52/111	40/109		23.13%	1.28[0.93,1.75]
Keystone 2008	177/389	66/199		32.81%	1.37[1.1,1.72]
Smolen 2009	57/246	32/125		18.57%	0.91[0.62,1.32]
Østergaard 2015	0/27	2/13		0.44%	0.1[0.01,1.94]
Total (95% CI)	**897**	**565**		**100%**	**1.21[0.99,1.47]**
Total events: 345 (Certolizumab pegol 400 mg), 185 (Control)					
Heterogeneity: Tau^2=0.02; Chi^2=6.32, df=4(P=0.18); I^2=36.66%					
Test for overall effect: Z=1.89(P=0.06)					



Favours certolizumab pego — Favours control

Analysis 50.7. Comparison 50 Safety, Outcome 7 Adverse events: Intensity severe certolizumab 200 mg.

Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Yamamoto (a) 2014	2/116	6/114		6.98%	0.35[0.09,1.43]
Weinblatt 2012	66/846	15/209		42.84%	1.09[0.62,1.93]
Keystone 2008	32/392	13/199		33.51%	1.26[0.66,2.4]
Smolen 2009	17/248	5/125		16.66%	1.67[0.67,4.16]
Total (95% CI)	**1602**	**647**		**100%**	**1.14[0.78,1.65]**
Total events: 117 (Certolizumab pegol 200 mg), 39 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.49, df=3(P=0.32); I^2=14.1%					
Test for overall effect: Z=0.67(P=0.5)					

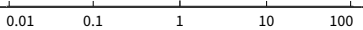
Favours certolizumab pego — Favours control

Analysis 50.8. Comparison 50 Safety, Outcome 8 Adverse events: Intensity severe certolizumab 400 mg.

Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Choy 2012	17/124	14/119		26.48%	1.19[0.56,2.53]
Fleischmann 2009	8/111	11/109		17.01%	0.69[0.27,1.78]
Keystone 2008	38/389	13/199		40.76%	1.5[0.82,2.76]
Smolen 2009	14/246	5/125		15.76%	1.41[0.53,3.75]
Østergaard 2015	0/27	0/13			Not estimable
Total (95% CI)	**897**	**565**		**100%**	**1.23[0.83,1.81]**
Total events: 77 (Certolizumab pegol 400 mg), 43 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.93, df=3(P=0.59); I^2=0%					
Test for overall effect: Z=1.04(P=0.3)					

Analysis 50.9. Comparison 50 Safety, Outcome 9 Adverse events related to study drug certolizumab 200 mg.

Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Keystone 2008	167/392	50/199		72.21%	1.7[1.3,2.21]
Smolen 2009	61/248	23/125		27.79%	1.34[0.87,2.05]
Total (95% CI)	**640**	**324**		**100%**	**1.59[1.27,1.99]**
Total events: 228 (Certolizumab pegol 200 mg), 73 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.85, df=1(P=0.36); I^2=0%					
Test for overall effect: Z=4.01(P<0.0001)					

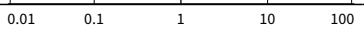


Analysis 50.10. Comparison 50 Safety, Outcome 10 Adverse events related to study drug certolizumab 400 mg.

Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Fleischmann 2009	27/111	24/109		19.81%	1.1[0.68,1.79]
Keystone 2008	166/389	50/199		54.13%	1.7[1.3,2.22]
Smolen 2009	56/246	23/125		24.95%	1.24[0.8,1.91]
Østergaard 2015	4/27	1/13		1.1%	1.93[0.24,15.56]
Total (95% CI)	**773**	**446**		**100%**	**1.47[1.2,1.8]**
Total events: 253 (Certolizumab pegol 400 mg), 98 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.15, df=3(P=0.37); I^2=4.69%					
Test for overall effect: Z=3.7(P=0)					

Analysis 50.11. Comparison 50 Safety, Outcome 11 Serious Infections certolizumab 200 mg.

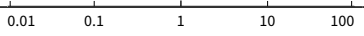
Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Atsumi 2016	5/161	7/158		33.87%	0.69[0.22,2.2]
Keystone 2008	16/392	2/199		45.67%	2.83[1.05,7.63]
Smolen 2009	8/248	0/125		20.46%	4.63[1.05,20.39]
Total (95% CI)	**801**	**482**		**100%**	**1.94[0.99,3.8]**
Total events: 29 (Certolizumab pegol 200 mg), 9 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.94, df=2(P=0.08); I^2=59.5%					
Test for overall effect: Z=1.94(P=0.05)					



Favours certolizumab pego — Favours control

Analysis 50.12. Comparison 50 Safety, Outcome 12 Serious infections certolizumab 400 mg.

Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Choy 2012	3/124	2/119		14.6%	1.44[0.25,8.44]
Fleischmann 2009	2/111	0/109		5.91%	7.32[0.46,117.84]
Keystone 2008	23/389	2/199		63.78%	3.33[1.43,7.76]
Smolen 2009	6/246	0/125		15.71%	4.61[0.84,25.36]
Total (95% CI)	**870**	**552**		**100%**	**3.25[1.65,6.39]**
Total events: 34 (Certolizumab pegol 400 mg), 4 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.31, df=3(P=0.73); I^2=0%					
Test for overall effect: Z=3.42(P=0)					



Favours certolizumab pego — Favours control

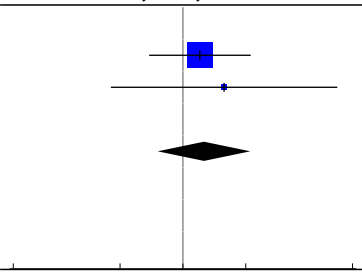
Analysis 50.13. Comparison 50 Safety, Outcome 13 Adverse events leading to death certolizumab 200 mg.

Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Emery 2015	2/660	1/219		27.75%	0.64[0.05,8.74]
Keystone 2008	2/392	1/199		33.09%	1.02[0.09,11.18]
Smolen 2009	1/248	0/125		11.04%	4.5[0.07,286.06]
Smolen 2015	0/96	0/98			Not estimable
Weinblatt 2012	2/846	0/209		15.73%	3.48[0.11,112.96]
Yamamoto (a) 2014	1/116	0/114		12.39%	7.26[0.14,366.07]
Total (95% CI)	**2358**	**964**		**100%**	**1.63[0.41,6.47]**
Total events: 8 (Certolizumab pegol 200 mg), 2 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.62, df=4(P=0.81); I^2=0%					
Test for overall effect: Z=0.69(P=0.49)					

Favours certolizumab pego — Favours control

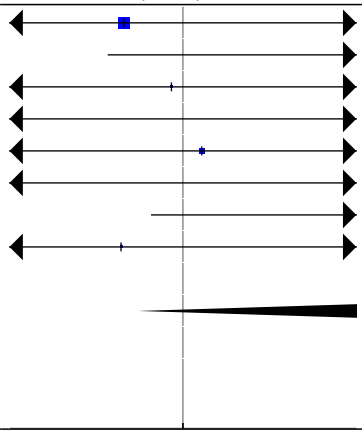
Analysis 50.14. Comparison 50 Safety, Outcome 14 Adverse events leading to death certolizumab 400 mg.

Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Fleischmann 2009	0/111	0/109			Not estimable
Keystone 2008	4/389	1/199		83.27%	1.86[0.29,11.96]
Smolen 2009	1/246	0/125		16.73%	4.52[0.07,285.66]
Total (95% CI)	**746**	**433**		**100%**	**2.16[0.4,11.79]**
Total events: 5 (Certolizumab pegol 400 mg), 1 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.15, df=1(P=0.7); I^2=0%					
Test for overall effect: Z=0.89(P=0.37)					



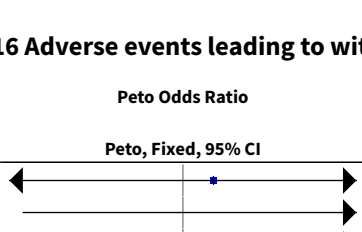
Analysis 50.15. Comparison 50 Safety, Outcome 15 Adverse events leading to withdrawal certolizumab 200 mg.

Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Emery 2015	57/660	20/219		36.82%	0.94[0.55,1.61]
Keystone 2008	17/392	3/199		12.1%	2.37[0.92,6.09]
NCT00993317	4/85	2/42		3.57%	0.99[0.17,5.6]
Smolen 2009	12/248	2/125		8.42%	2.45[0.79,7.57]
Smolen 2015	6/96	6/98		7.92%	1.02[0.32,3.28]
Weinblatt 2012	40/846	8/209		20.39%	1.23[0.6,2.54]
Yamamoto (a) 2014	8/116	2/114		6.72%	3.42[0.97,12.13]
Yamamoto (b) 2014	3/82	3/77		4.06%	0.94[0.18,4.77]
Total (95% CI)	**2525**	**1083**		**100%**	**1.32[0.95,1.84]**
Total events: 147 (Certolizumab pegol 200 mg), 46 (Control)					
Heterogeneity: Tau^2=0; Chi^2=6.83, df=7(P=0.45); I^2=0%					
Test for overall effect: Z=1.68(P=0.09)					

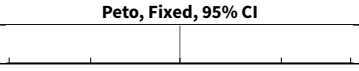


Analysis 50.16. Comparison 50 Safety, Outcome 16 Adverse events leading to withdrawal certolizumab 400 mg.

Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Choy 2012	7/124	6/119		21.32%	1.13[0.37,3.44]
Fleischmann 2009	5/111	2/109		11.75%	2.37[0.53,10.64]
Keystone 2008	22/389	3/199		37.08%	2.77[1.19,6.44]
Smolen 2009	7/246	2/125		13.59%	1.69[0.42,6.84]
Yamamoto (b) 2014	7/85	3/77		16.26%	2.11[0.59,7.55]
Østergaard 2015	0/27	0/13			Not estimable
Total (95% CI)	**982**	**642**		**100%**	**2.01[1.2,3.36]**
Total events: 48 (Certolizumab pegol 400 mg), 16 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.69, df=4(P=0.79); I^2=0%					



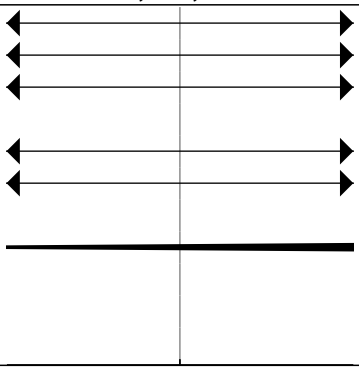
Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Test for overall effect: Z=2.65(P=0.01)					



Favours certolizumab pego | Favours control

Analysis 50.17. Comparison 50 Safety, Outcome 17 Death certolizumab 200 mg.

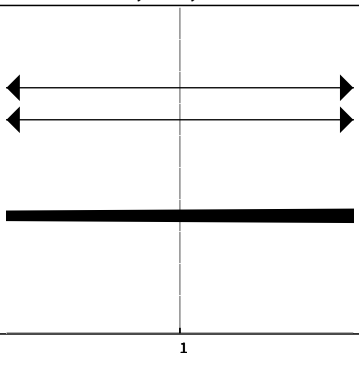
Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Emery 2015	1/660	0/219		10.02%	3.79[0.04,351.89]
Keystone 2008	3/392	1/199		47.61%	1.48[0.18,11.81]
Smolen 2009	1/246	0/125		11.97%	4.52[0.07,285.66]
Smolen 2015	0/96	0/98			Not estimable
Weinblatt 2012	2/846	0/209		17%	3.48[0.11,112.96]
Yamamoto (a) 2014	1/116	0/114		13.39%	7.26[0.14,366.07]
Total (95% CI)	**2356**	**964**		**100%**	**2.66[0.63,11.16]**
Total events: 8 (Certolizumab pegol 200 mg), 1 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.67, df=4(P=0.96); I^2=0%					
Test for overall effect: Z=1.34(P=0.18)					



Favours certolizumab pego | Favours control

Analysis 50.18. Comparison 50 Safety, Outcome 18 Death certolizumab 400 mg.

Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Choy 2012	0/124	0/119			Not estimable
Fleischmann 2009	0/111	0/109			Not estimable
Keystone 2008	4/389	1/199		66.65%	2.05[0.23,18.19]
Smolen 2009	1/246	0/125		33.35%	1.53[0.06,37.3]
Østergaard 2015	0/27	0/13			Not estimable
Total (95% CI)	**897**	**565**		**100%**	**1.87[0.31,11.34]**
Total events: 5 (Certolizumab pegol 400 mg), 1 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.88); I^2=0%					
Test for overall effect: Z=0.68(P=0.49)					

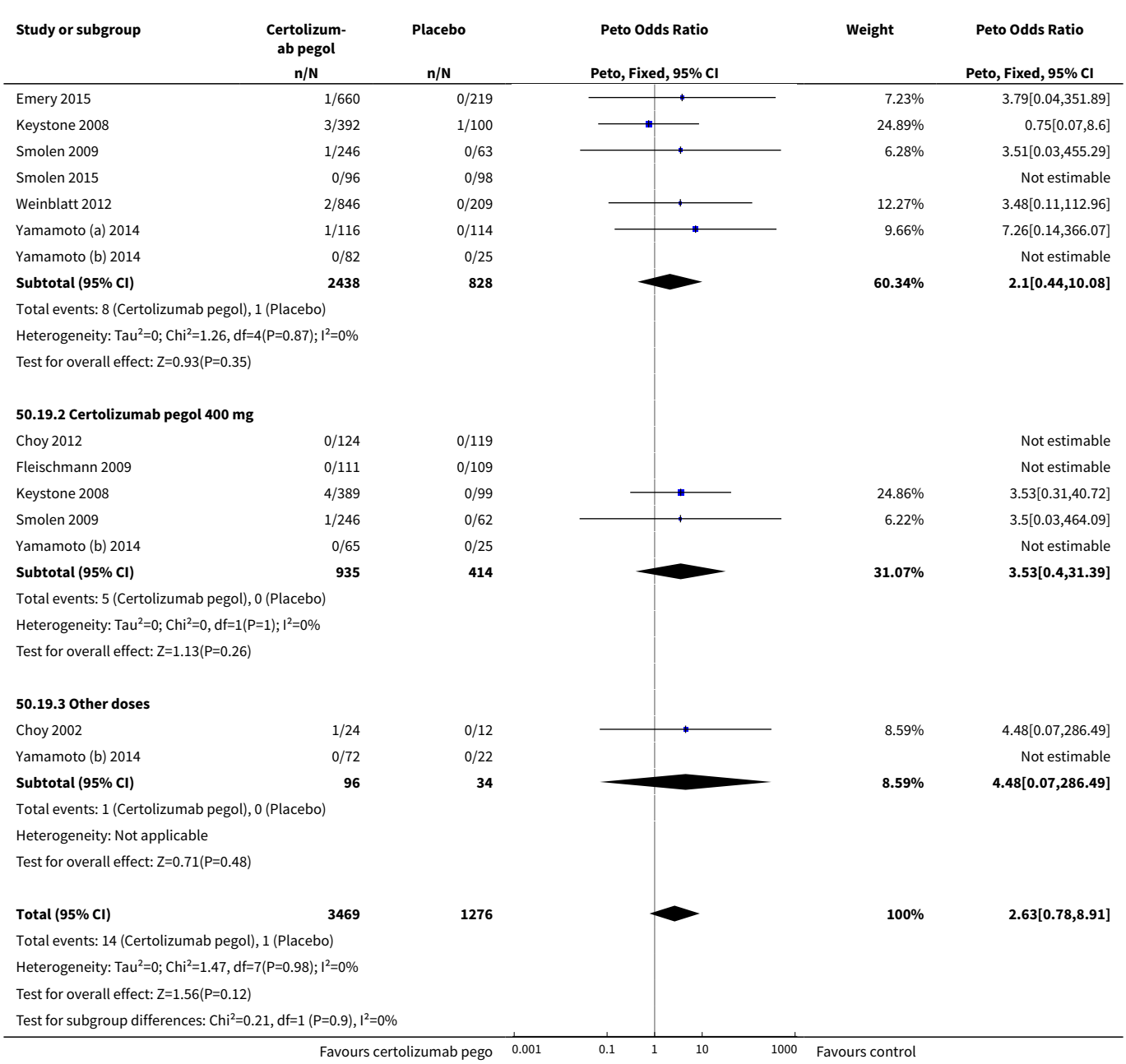


Favours certolizumab pego | Favours control

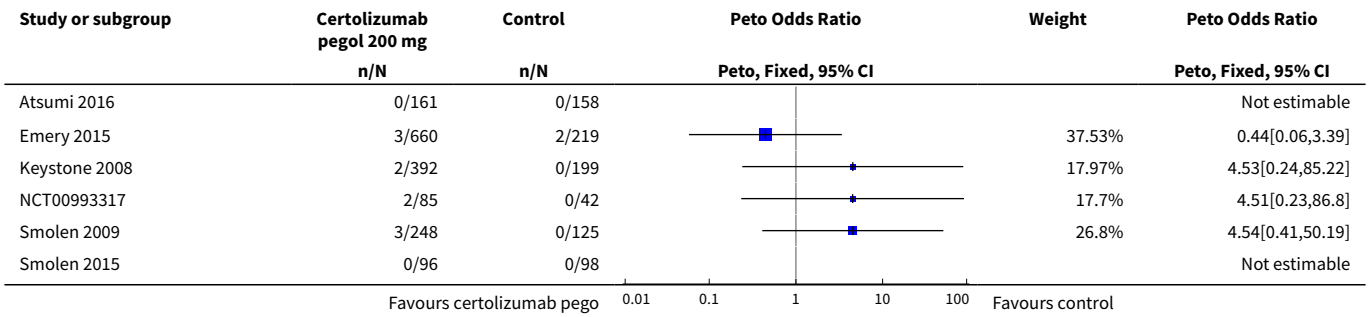
Analysis 50.19. Comparison 50 Safety, Outcome 19 Deaths overall.

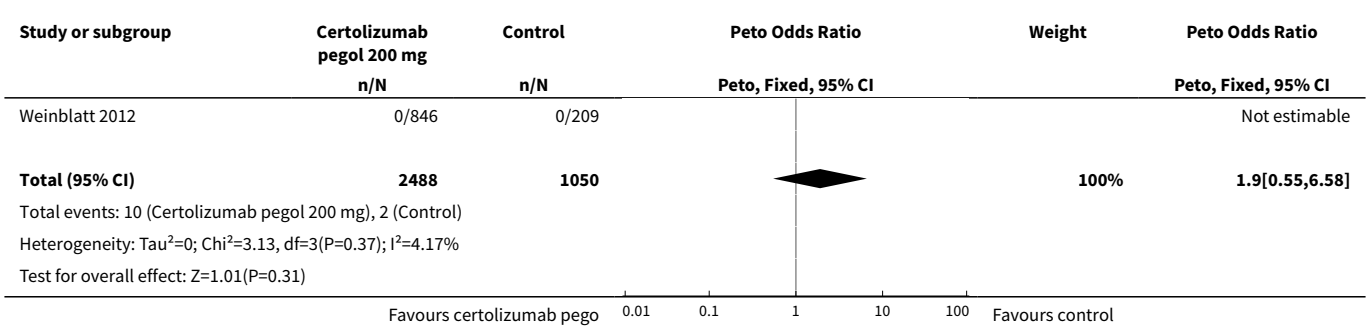
Study or subgroup	Certolizum-ab pegol n/N	Placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
50.19.1 Certolizumab pegol 200 mg					

Favours certolizumab pego | Favours control

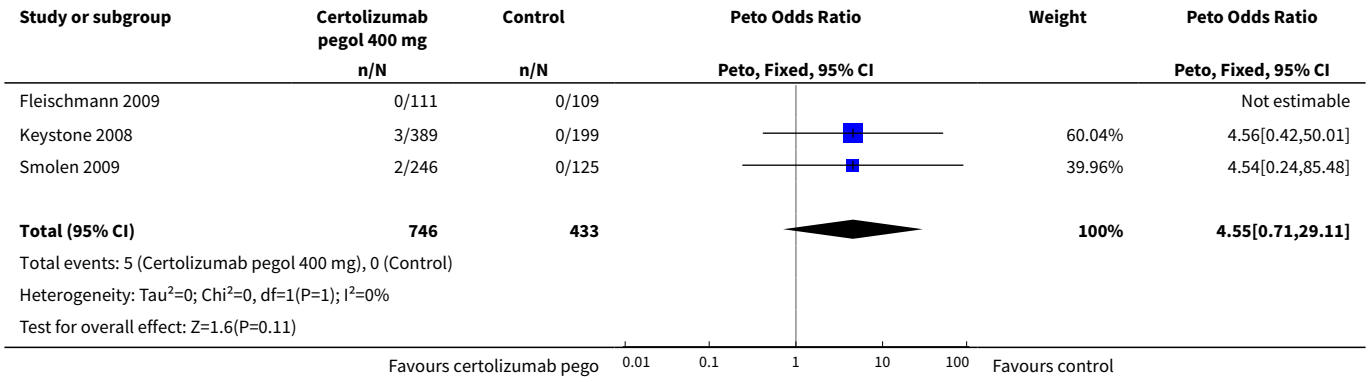


Analysis 50.20. Comparison 50 Safety, Outcome 20 Tuberculosis certolizumab 200 mg.

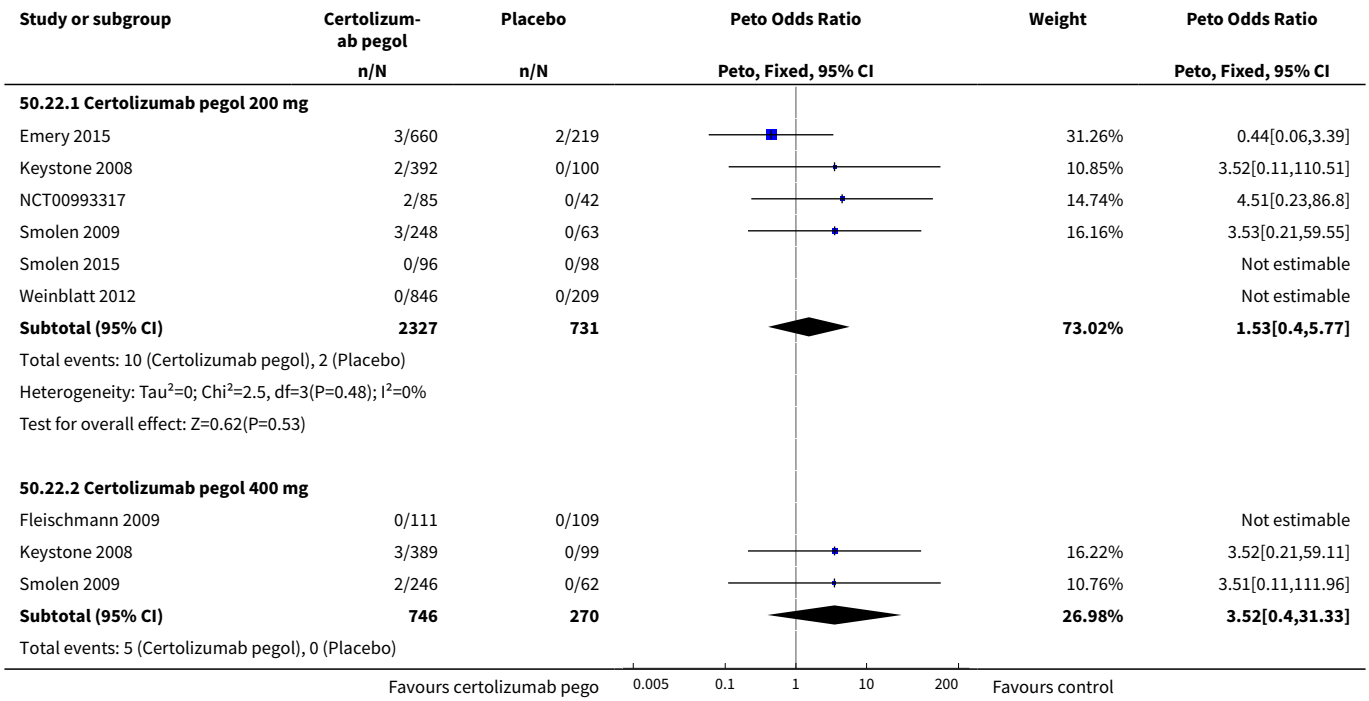


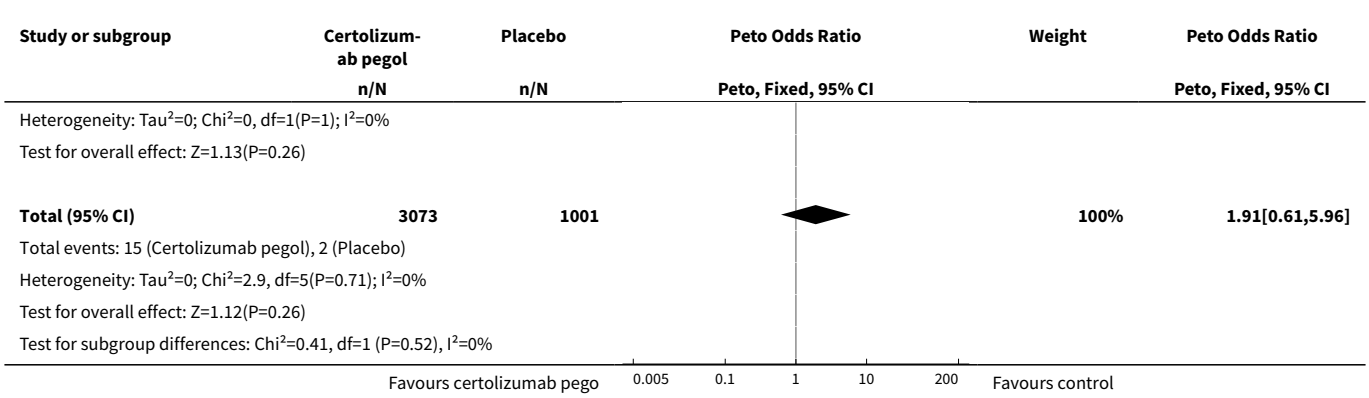


Analysis 50.21. Comparison 50 Safety, Outcome 21 Tuberculosis certolizumab 400 mg.

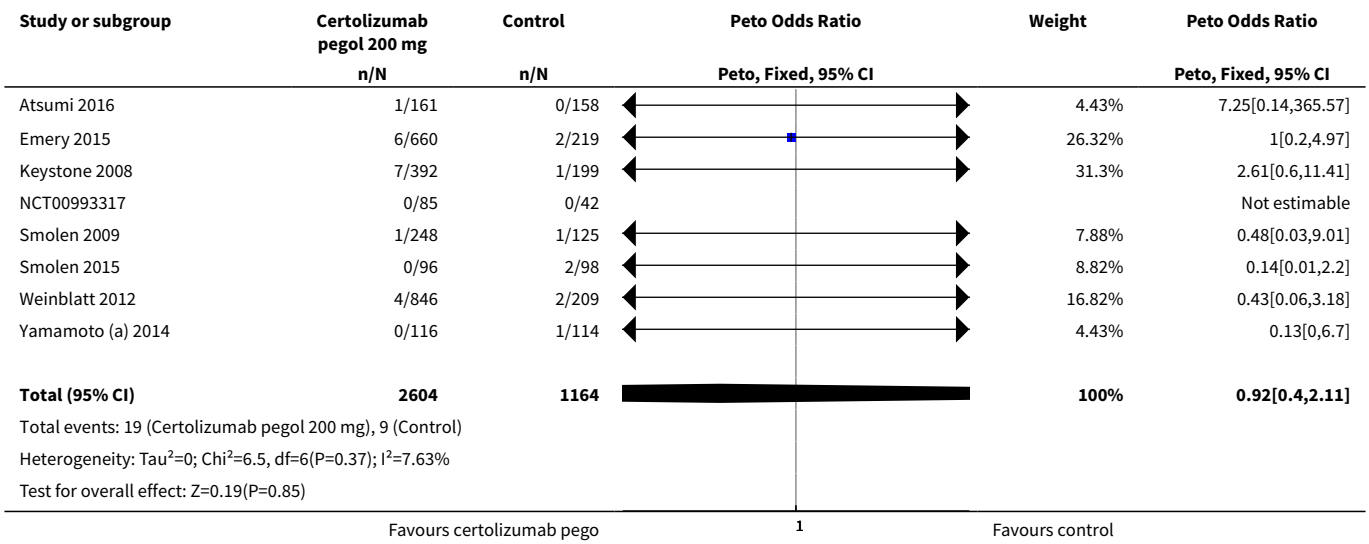


Analysis 50.22. Comparison 50 Safety, Outcome 22 Tuberculosis overall.

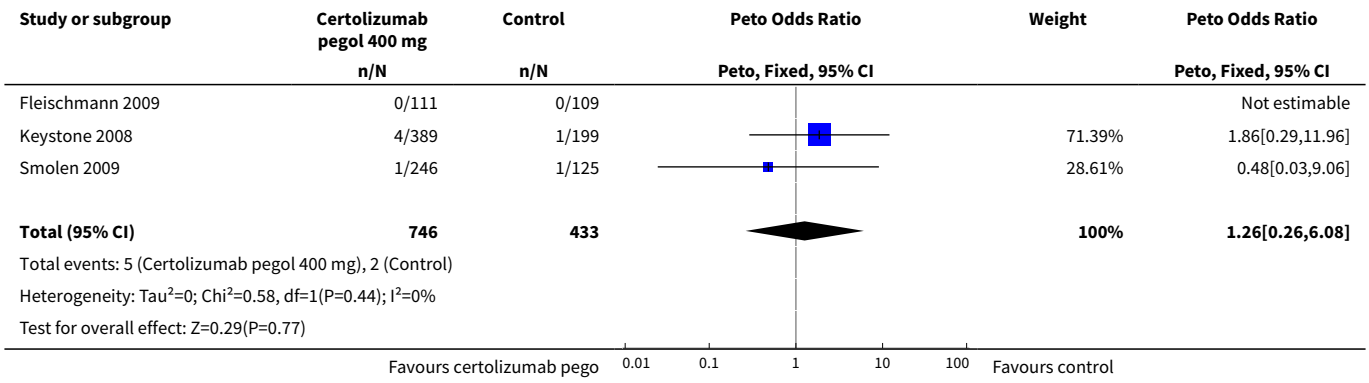




Analysis 50.23. Comparison 50 Safety, Outcome 23 Malignancies included lymphoma certolizumab 200 mg.



Analysis 50.24. Comparison 50 Safety, Outcome 24 Malignancies included lymphoma certolizumab 400 mg.



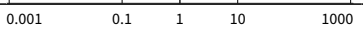
Analysis 50.25. Comparison 50 Safety, Outcome 25 Injection side reactions certolizumab 200 mg.

Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Atsumi 2016	1/161	0/158		2.3%	7.25[0.14,365.57]
Keystone 2008	9/392	0/199		18.25%	4.61[1.15,18.55]
Smolen 2009	3/248	0/125		6.12%	4.54[0.41,50.19]
Weinblatt 2012	49/846	2/209		71.03%	2.86[1.41,5.79]
Yamamoto (b) 2014	1/82	0/77		2.3%	6.95[0.14,351.04]
Total (95% CI)	**1729**	**768**		**100%**	**3.34[1.85,6.06]**
Total events: 63 (Certolizumab pegol 200 mg), 2 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.74, df=4(P=0.95); I^2=0%					
Test for overall effect: Z=3.98(P<0.0001)					

Favours certolizumab pego — Favours control

Analysis 50.26. Comparison 50 Safety, Outcome 26 Injection side reactions certolizumab 400 mg.

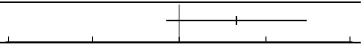
Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Choy 2012	5/124	34/119		54.58%	0.16[0.08,0.32]
Fleischmann 2009	5/111	15/109		30.33%	0.33[0.13,0.82]
Keystone 2008	3/389	0/199		4.45%	4.56[0.42,50.01]
Smolen 2009	5/246	0/125		7.34%	4.59[0.71,29.64]
Yamamoto (b) 2014	2/85	0/77		3.29%	6.81[0.42,110.13]
Total (95% CI)	**955**	**629**		**100%**	**0.34[0.2,0.56]**
Total events: 20 (Certolizumab pegol 400 mg), 49 (Control)					
Heterogeneity: Tau^2=0; Chi^2=20.89, df=4(P=0); I^2=80.85%					
Test for overall effect: Z=4.21(P<0.0001)					



Favours certolizumab pego — Favours control

Analysis 50.27. Comparison 50 Safety, Outcome 27 Antinuclear antibodies (ANA) Anti-certolizumab pegol antibodies certolizumab 200 mg.

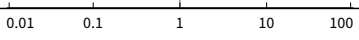
Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Smolen 2009	5/248	0/125		4.57[0.71,29.59]



Favours certolizumab pego — Favours control

Analysis 50.28. Comparison 50 Safety, Outcome 28 Anti-certolizumab pegol antibodies certolizumab 400 mg.

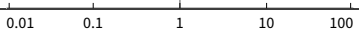
Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Fleischmann 2009	9/111	0/109		70.98%	7.82[2.07,29.62]
Smolen 2009	4/246	0/125		29.02%	4.57[0.57,36.68]
Total (95% CI)	**357**	**234**		**100%**	**6.7[2.18,20.55]**
Total events: 13 (Certolizumab pegol 400 mg), 0 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.18, df=1(P=0.67); I^2=0%					
Test for overall effect: Z=3.32(P=0)					



Favours certolizumab pego — Favours control

Analysis 50.29. Comparison 50 Safety, Outcome 29 Systemic lupus erythematosus certolizumab 200 mg.

Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Smolen 2009	1/248	0/125		100%	4.5[0.07,286.06]
Smolen 2015	0/96	0/98			Not estimable
Total (95% CI)	**344**	**223**		**100%**	**4.5[0.07,286.06]**
Total events: 1 (Certolizumab pegol 200 mg), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.71(P=0.48)					



Favours certolizumab pego — Favours control

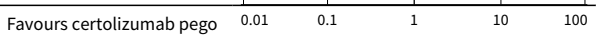
Analysis 50.30. Comparison 50 Safety, Outcome 30 Prolonged activated partial thromboplastin time (aPTT) certolizumab 200 mg.

Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
NCT00993317	3/85	0/42		17.84%	4.56[0.4,51.56]
Smolen 2009	12/248	2/125		82.16%	2.45[0.79,7.57]
Total (95% CI)	**333**	**167**		**100%**	**2.73[0.98,7.61]**
Total events: 15 (Certolizumab pegol 200 mg), 2 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.21, df=1(P=0.65); I^2=0%					
Test for overall effect: Z=1.92(P=0.05)					

Favours certolizumab pego — Favours control

Analysis 50.31. Comparison 50 Safety, Outcome 31 Prolonged activated partial thromboplastin time (aPTT) certolizumab 400 mg.

Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Smolen 2009	12/246	2/125		2.46[0.8,7.6]

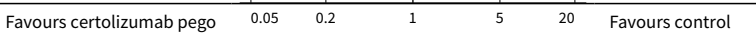


Analysis 50.32. Comparison 50 Safety, Outcome 32 Urinary tract infection certolizumab 200 mg.

Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Emery 2015	63/660	18/219		46.69%	1.17[0.69,1.99]
Keystone 2008	23/392	13/199		25.64%	0.89[0.44,1.82]
NCT00993317	1/85	0/42		0.75%	4.46[0.07,287.18]
Smolen 2009	11/248	9/125		14.34%	0.58[0.22,1.51]
Smolen 2015	6/96	5/98		8.84%	1.24[0.37,4.17]
Weinblatt 2012	5/846	2/209		3.75%	0.57[0.09,3.7]
Total (95% CI)	**2327**	**892**		**100%**	**0.98[0.68,1.4]**
Total events: 109 (Certolizumab pegol 200 mg), 47 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.63, df=5(P=0.76); I^2=0%					
Test for overall effect: Z=0.13(P=0.89)					

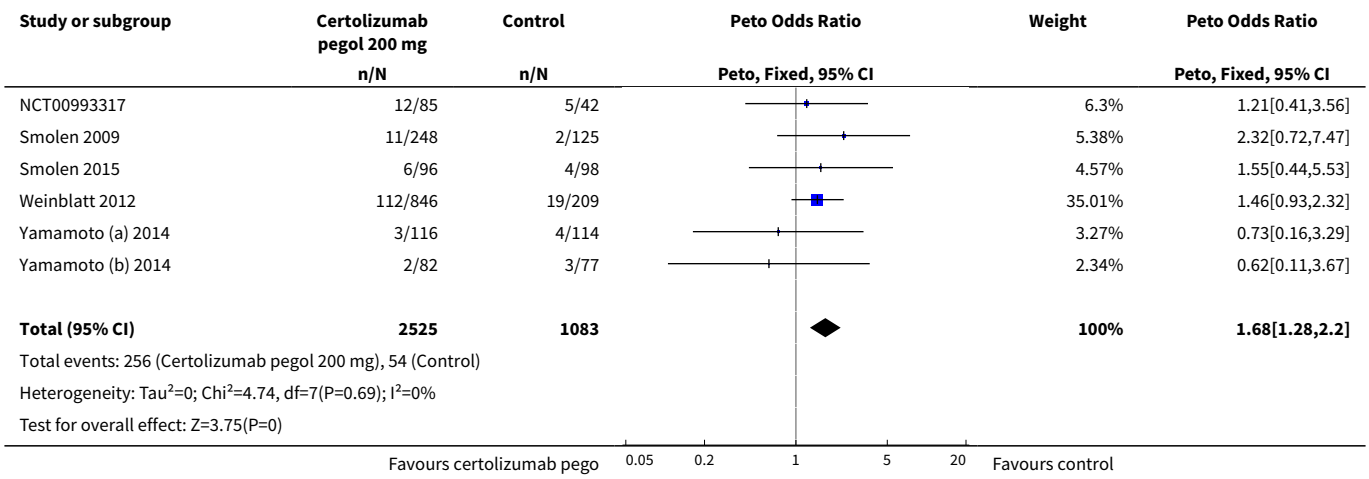
Analysis 50.33. Comparison 50 Safety, Outcome 33 Urinary tract infection certolizumab 400 mg.

Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Keystone 2008	33/389	13/199		75.91%	1.31[0.69,2.47]
Smolen 2009	5/246	9/125		24.09%	0.24[0.08,0.75]
Total (95% CI)	**635**	**324**		**100%**	**0.87[0.5,1.52]**
Total events: 38 (Certolizumab pegol 400 mg), 22 (Control)					
Heterogeneity: Tau^2=0; Chi^2=6.54, df=1(P=0.01); I^2=84.7%					
Test for overall effect: Z=0.48(P=0.63)					

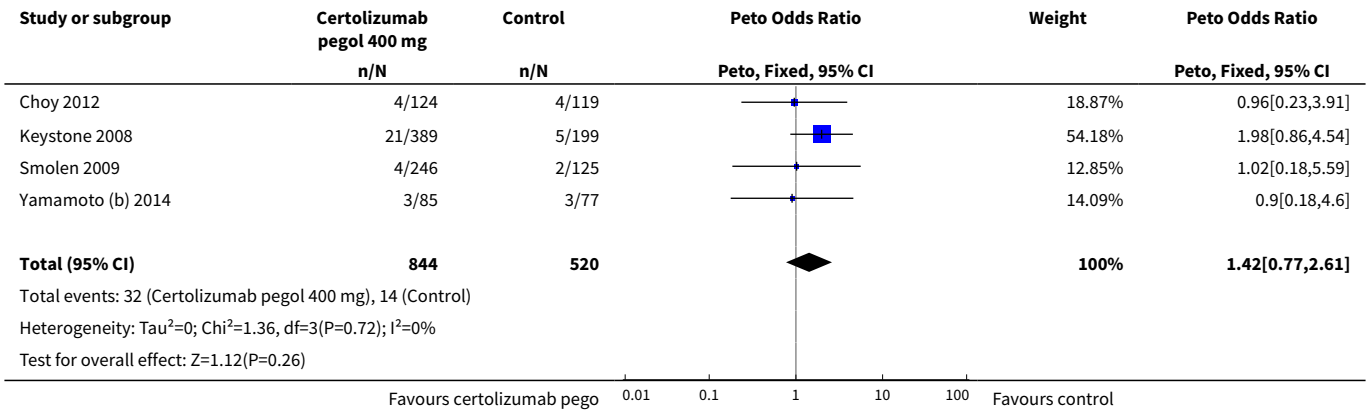


Analysis 50.34. Comparison 50 Safety, Outcome 34 Upper respiratory tract infection certolizumab 200 mg.

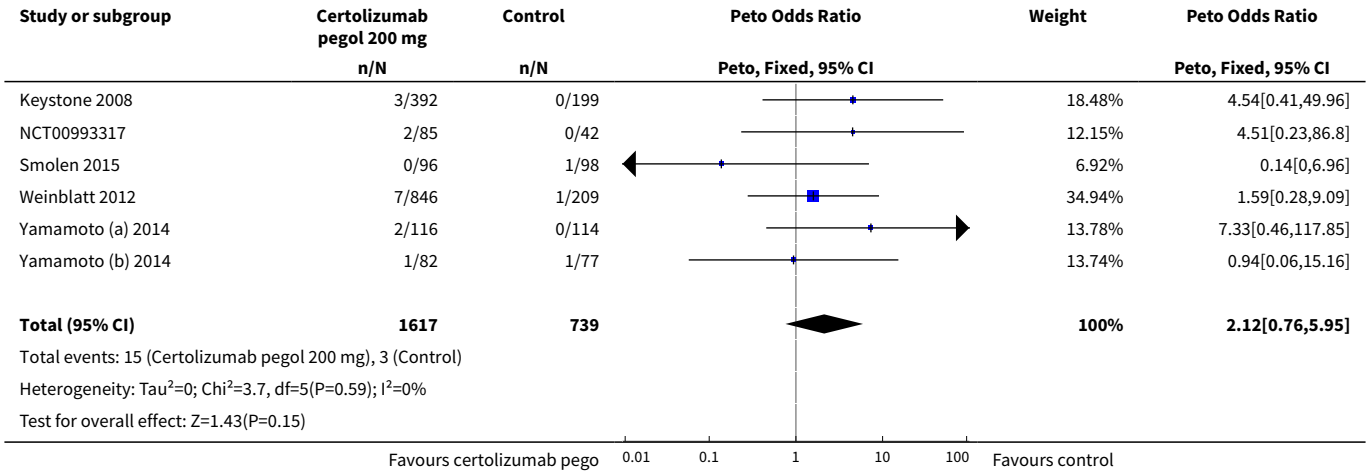
Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Emery 2015	86/660	12/219		31.29%	2.14[1.32,3.48]
Keystone 2008	24/392	5/199		11.84%	2.16[0.98,4.77]



Analysis 50.35. Comparison 50 Safety, Outcome 35 Upper respiratory tract infection certolizumab 400 mg.



Analysis 50.36. Comparison 50 Safety, Outcome 36 Lower respiratory tract infection/ lung infection certolizumab 200 mg.



Analysis 50.37. Comparison 50 Safety, Outcome 37 Lower respiratory tract infection/ lung infection certolizumab 400 mg.

Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Choy 2012	3/124	3/119		41.07%	0.96[0.19,4.83]
Keystone 2008	4/389	0/199		24.92%	4.57[0.57,36.44]
Yamamoto (b) 2014	4/85	1/77		34.01%	3.1[0.52,18.35]
Total (95% CI)	**598**	**395**		**100%**	**2.11[0.75,5.95]**
Total events: 11 (Certolizumab pegol 400 mg), 4 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.63, df=2(P=0.44); I^2=0%					
Test for overall effect: Z=1.41(P=0.16)					

Favours certolizumab pego — Favours control

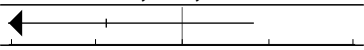
Analysis 50.38. Comparison 50 Safety, Outcome 38 Pneumonia certolizumab 200 mg.

Study or subgroup	Certolizumab 200 mg pegol n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Smolen 2015	0/96	1/98		3.51%	0.14[0,6.96]
Emery 2015	4/660	3/219		18.27%	0.38[0.07,2.12]
Atsumi 2016	7/161	8/158		50.37%	0.85[0.3,2.4]
Weinblatt 2012	7/846	1/209		17.74%	1.59[0.28,9.09]
NCT00993317	1/85	0/42		3.11%	4.46[0.07,287.18]
Yamamoto (a) 2014	2/116	0/114		6.99%	7.33[0.46,117.85]
Total (95% CI)	**1964**	**840**		**100%**	**0.94[0.45,1.97]**
Total events: 21 (Certolizumab 200 mg pegol), 13 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5, df=5(P=0.42); I^2=0%					
Test for overall effect: Z=0.16(P=0.88)					

Favours certolizumab pego — Favours control

Analysis 50.39. Comparison 50 Safety, Outcome 39 Pneumonitis certolizumab 400 mg.

Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Fleischmann 2009	0/111	1/109		0.13[0,6.7]



Favours certolizumab pego — Favours control

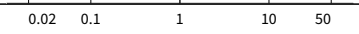
Analysis 50.40. Comparison 50 Safety, Outcome 40 Headache certolizumab 200 mg.

Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Emery 2015	66/660	11/219		40.51%	1.86[1.09,3.2]
Keystone 2008	22/392	11/199		21.46%	1.02[0.48,2.13]
Smolen 2009	9/248	1/125		6.69%	2.95[0.78,11.14]
Smolen 2015	1/96	5/98		4.5%	0.26[0.05,1.31]
Weinblatt 2012	47/846	11/209		26.83%	1.06[0.54,2.05]
Yamamoto (b) 2014	0/82	0/77			Not estimable
Total (95% CI)	**2324**	**927**		**100%**	**1.33[0.94,1.87]**
Total events: 145 (Certolizumab pegol 200 mg), 39 (Control)					
Heterogeneity: Tau^2=0; Chi^2=7.73, df=4(P=0.1); I^2=48.24%					
Test for overall effect: Z=1.61(P=0.11)					

Favours certolizumab pego — Favours control

Analysis 50.41. Comparison 50 Safety, Outcome 41 Headache certolizumab 400 mg.

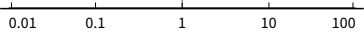
Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Choy 2012	12/124	9/119		35.13%	1.31[0.53,3.19]
Keystone 2008	18/389	11/199		45.12%	0.83[0.38,1.82]
Smolen 2009	8/246	1/125		14.36%	2.81[0.69,11.36]
Yamamoto (b) 2014	3/85	0/77		5.39%	6.89[0.7,67.36]
Total (95% CI)	**844**	**520**		**100%**	**1.3[0.76,2.2]**
Total events: 41 (Certolizumab pegol 400 mg), 21 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.5, df=3(P=0.21); I^2=33.3%					
Test for overall effect: Z=0.96(P=0.34)					



Favours certolizumab pego — Favours control

Analysis 50.42. Comparison 50 Safety, Outcome 42 Bacteriuria certolizumab 200 mg.

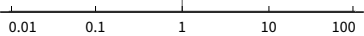
Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Smolen 2009	8/248	4/125		1.01[0.3,3.4]



Favours certolizumab pego — Favours control

Analysis 50.43. Comparison 50 Safety, Outcome 43 Bacteriuria certolizumab 400 mg.

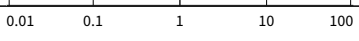
Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Smolen 2009	6/246	4/125		0.75[0.2,2.82]



Favours certolizumab pego — Favours control

Analysis 50.44. Comparison 50 Safety, Outcome 44 Nasopharyngitis/Pharyngitis certolizumab 200 mg.

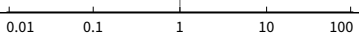
Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Emery 2015	60/660	17/219		30.64%	1.18[0.69,2.03]
Keystone 2008	21/392	3/199		12%	2.68[1.13,6.36]
NCT00993317	10/85	4/42		6.47%	1.25[0.39,4.06]
Smolen 2009	8/248	1/125		4.57%	2.79[0.69,11.32]
Smolen 2015	10/96	11/98		10.96%	0.92[0.37,2.27]
Yamamoto (a) 2014	26/116	21/114		21.86%	1.28[0.67,2.42]
Yamamoto (b) 2014	16/82	12/77		13.5%	1.31[0.58,2.95]
Total (95% CI)	**1679**	**874**		**100%**	**1.37[1.01,1.84]**
Total events: 151 (Certolizumab pegol 200 mg), 69 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.44, df=6(P=0.62); I^2=0%					
Test for overall effect: Z=2.04(P=0.04)					



Favours certolizumab pego — Favours control

Analysis 50.45. Comparison 50 Safety, Outcome 45 Nasopharyngitis/Pharyngitis certolizumab 400 mg.

Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Choy 2012	15/124	8/119		27.56%	1.87[0.79,4.4]
Keystone 2008	30/389	3/199		36.84%	3.22[1.53,6.76]
Smolen 2009	4/246	1/125		5.83%	1.86[0.29,11.99]
Yamamoto (b) 2014	15/85	12/77		29.78%	1.16[0.51,2.64]
Total (95% CI)	**844**	**520**		**100%**	**1.98[1.26,3.11]**
Total events: 64 (Certolizumab pegol 400 mg), 24 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.29, df=3(P=0.35); I^2=8.89%					
Test for overall effect: Z=2.97(P=0)					



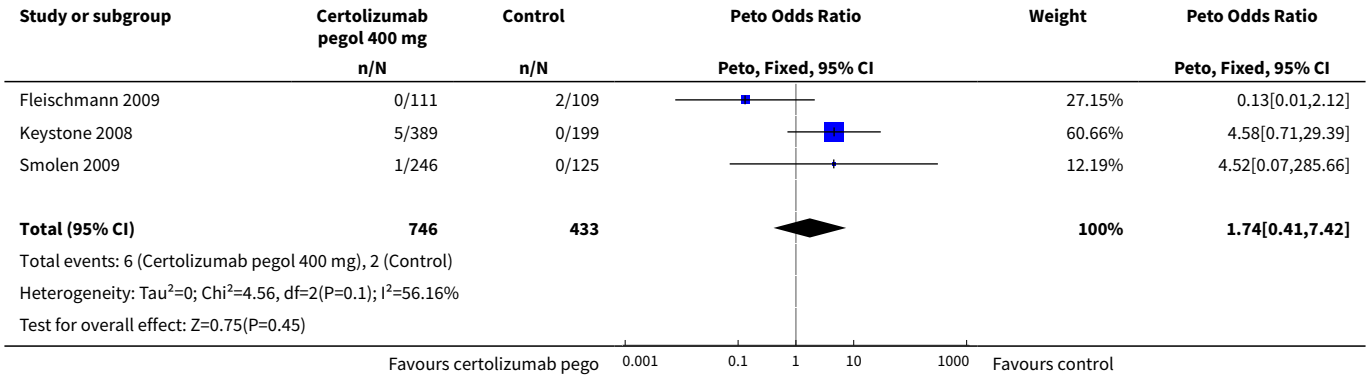
Favours certolizumab pego — Favours control

Analysis 50.46. Comparison 50 Safety, Outcome 46 Injection site pain certolizumab 200 mg.

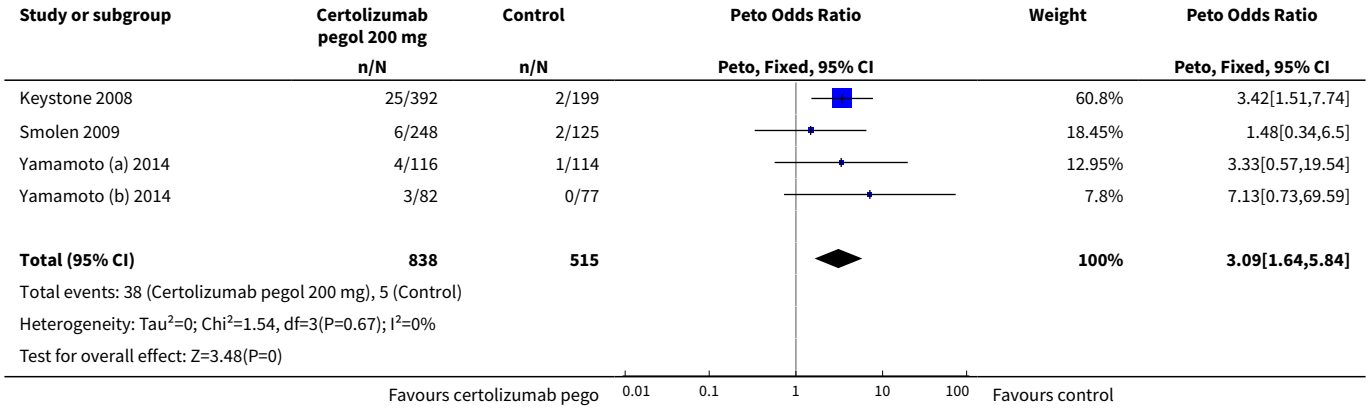
Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Keystone 2008	8/392	0/199		80.08%	4.6[1.05,20.1]
NCT00993317	0/85	2/42		19.92%	0.05[0,0.91]
Smolen 2009	0/248	0/125			Not estimable
Total (95% CI)	**725**	**366**		**100%**	**1.85[0.49,6.92]**
Total events: 8 (Certolizumab pegol 200 mg), 2 (Control)					
Heterogeneity: Tau^2=0; Chi^2=7.36, df=1(P=0.01); I^2=86.41%					
Test for overall effect: Z=0.91(P=0.36)					

Favours certolizumab pego — Favours control

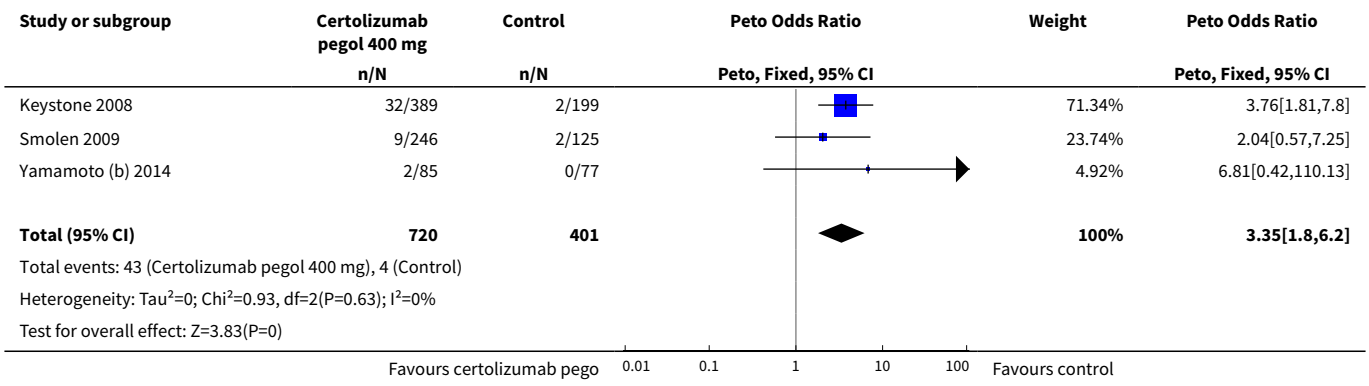
Analysis 50.47. Comparison 50 Safety, Outcome 47 Injection site pain certolizumab 400 mg.



Analysis 50.48. Comparison 50 Safety, Outcome 48 Hypertension certolizumab 200 mg.

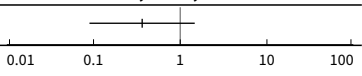


Analysis 50.49. Comparison 50 Safety, Outcome 49 Hypertension certolizumab 400 mg.



Analysis 50.50. Comparison 50 Safety, Outcome 50 Hematuria certolizumab 200 mg.

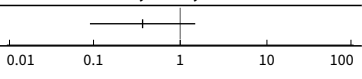
Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Smolen 2009	4/248	5/125		0.36[0.09,1.47]



Favours certolizumab pego — Favours control

Analysis 50.51. Comparison 50 Safety, Outcome 51 Haematuria certolizumab 400 mg.

Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Smolen 2009	4/246	5/125		0.37[0.09,1.49]



Favours certolizumab pego — Favours control

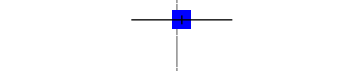
Analysis 50.52. Comparison 50 Safety, Outcome 52 Hepatic enzyme increased certolizumab 200 mg.

Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Atsumi 2016	68/161	70/158		85.92%	0.92[0.59,1.43]
Smolen 2009	3/248	4/125		6.72%	0.34[0.07,1.66]
Yamamoto (b) 2014	3/82	4/77		7.36%	0.7[0.15,3.15]
Total (95% CI)	**491**	**360**		**100%**	**0.84[0.56,1.27]**
Total events: 74 (Certolizumab pegol 200 mg), 78 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.47, df=2(P=0.48); I^2=0%					
Test for overall effect: Z=0.82(P=0.41)					

Favours certolizumab pego — Favours control

Analysis 50.53. Comparison 50 Safety, Outcome 53 Hepatic enzyme increased certolizumab 400 mg.

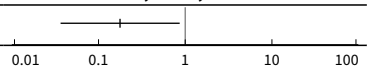
Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Smolen 2009	3/246	4/125		41.9%	0.34[0.07,1.67]
Yamamoto (b) 2014	5/85	4/77		58.1%	1.14[0.3,4.36]
Total (95% CI)	**331**	**202**		**100%**	**0.69[0.25,1.92]**
Total events: 8 (Certolizumab pegol 400 mg), 8 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.28, df=1(P=0.26); I^2=21.94%					
Test for overall effect: Z=0.71(P=0.48)					



Favours certolizumab pego — Favours control

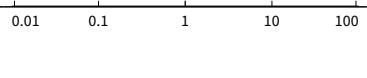
Analysis 50.54. Comparison 50 Safety, Outcome 54 AST increased certolizumab 200 mg.

Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Smolen 2009	2/248	5/125		0.18[0.04,0.86]



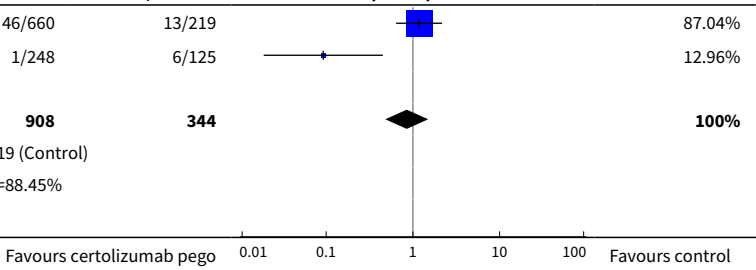
Analysis 50.55. Comparison 50 Safety, Outcome 55 AST increased certolizumab 400 mg.

Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Smolen 2009	6/246	5/125		0.58[0.16,2.07]



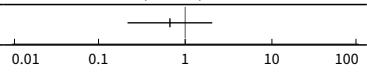
Analysis 50.56. Comparison 50 Safety, Outcome 56 ALT increased certolizumab 200 mg.

Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Emery 2015	46/660	13/219		87.04%	1.18[0.64,2.17]
Smolen 2009	1/248	6/125		12.96%	0.09[0.02,0.45]
Total (95% CI)	**908**	**344**		**100%**	**0.85[0.48,1.5]**
Total events: 47 (Certolizumab pegol 200 mg), 19 (Control)					
Heterogeneity: Tau^2=0; Chi^2=8.66, df=1(P=0); I^2=88.45%					
Test for overall effect: Z=0.57(P=0.57)					



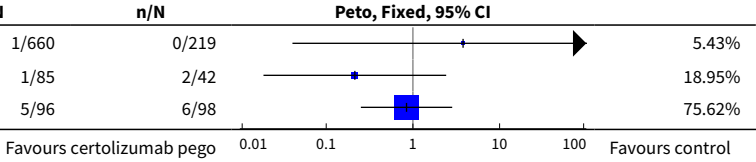
Analysis 50.57. Comparison 50 Safety, Outcome 57 ALT increased certolizumab 400 mg.

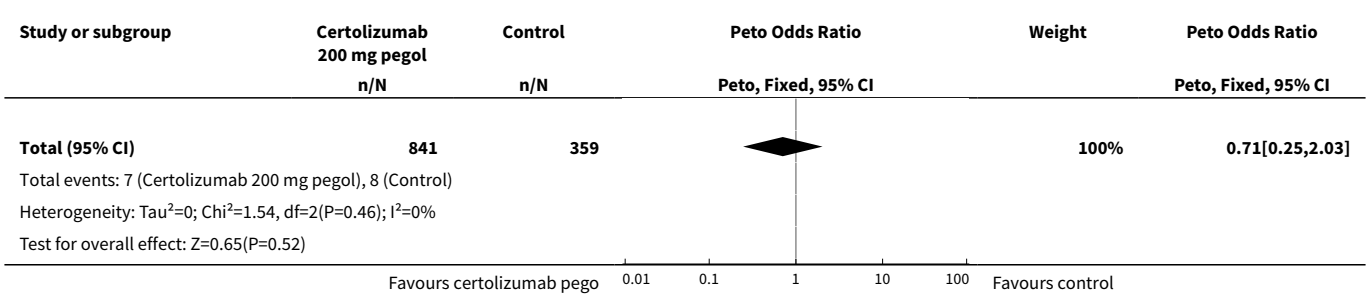
Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Smolen 2009	8/246	6/127		0.67[0.22,2.05]



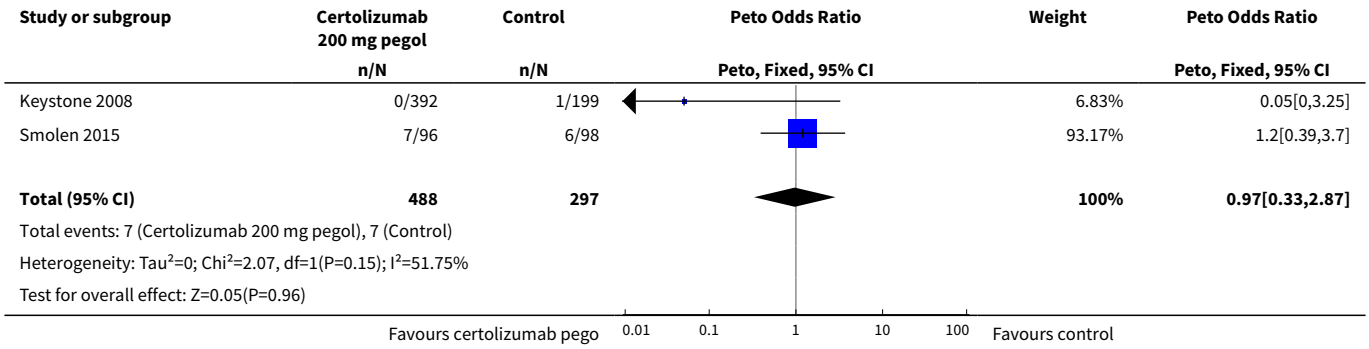
Analysis 50.58. Comparison 50 Safety, Outcome 58 Diarrhoea certolizumab 200 mg.

Study or subgroup	Certolizumab 200 mg pegol n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Emery 2015	1/660	0/219		5.43%	3.79[0.04,351.89]
NCT00993317	1/85	2/42		18.95%	0.21[0.02,2.42]
Smolen 2015	5/96	6/98		75.62%	0.84[0.25,2.84]

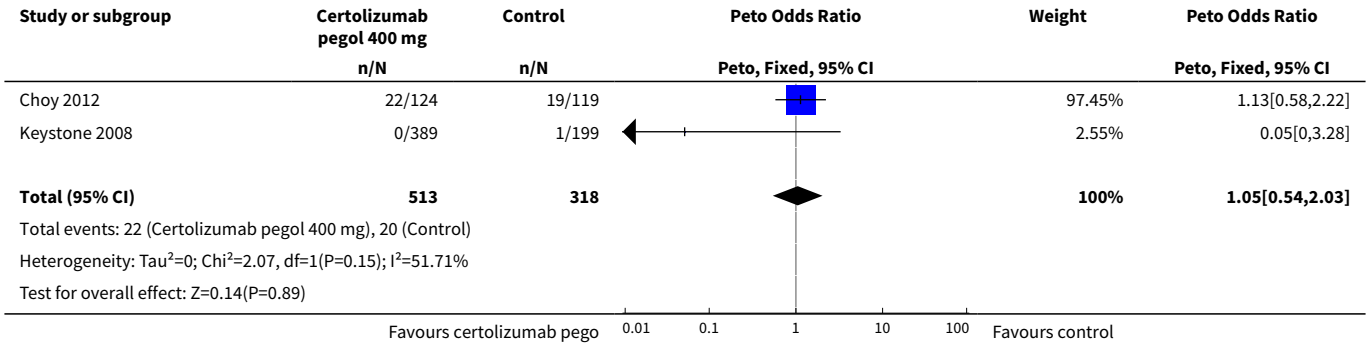




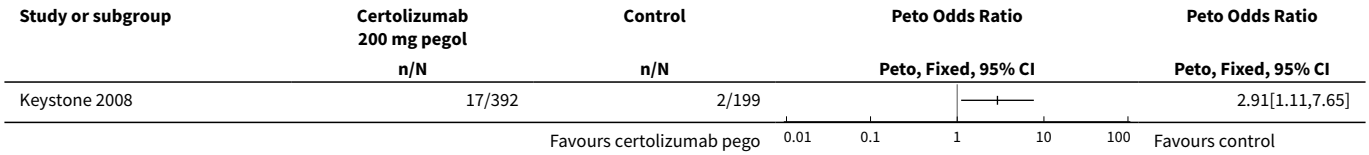
Analysis 50.59. Comparison 50 Safety, Outcome 59 Gastroenteritis certolizumab 200 mg.



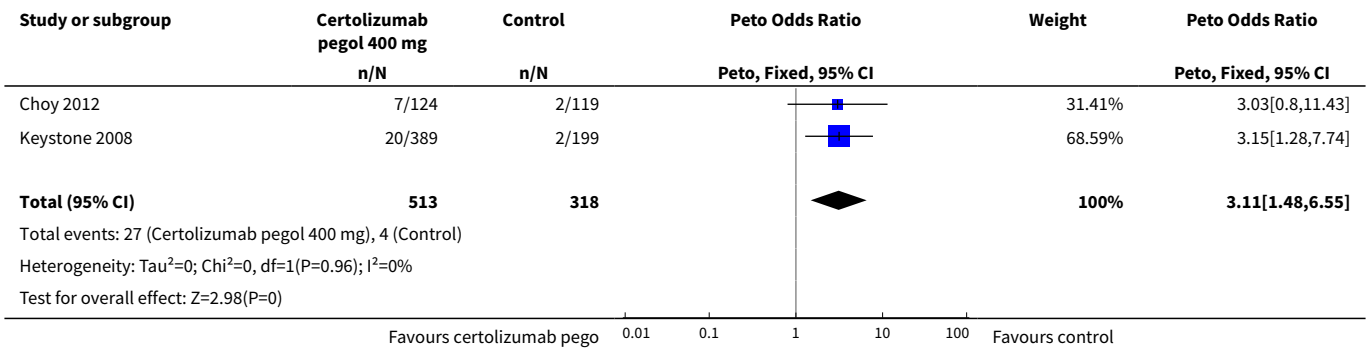
Analysis 50.60. Comparison 50 Safety, Outcome 60 Gastrointestinal disorders certolizumab 400 mg.



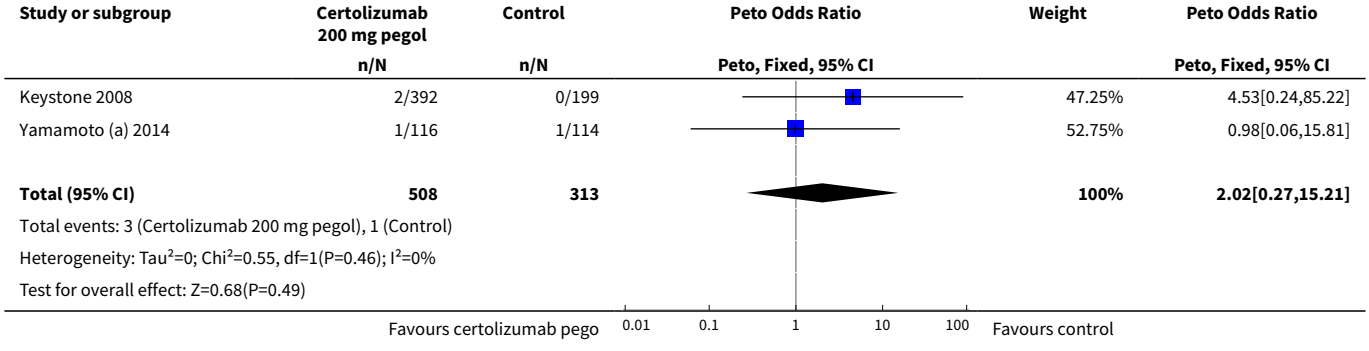
Analysis 50.61. Comparison 50 Safety, Outcome 61 Back pain certolizumab 200 mg.



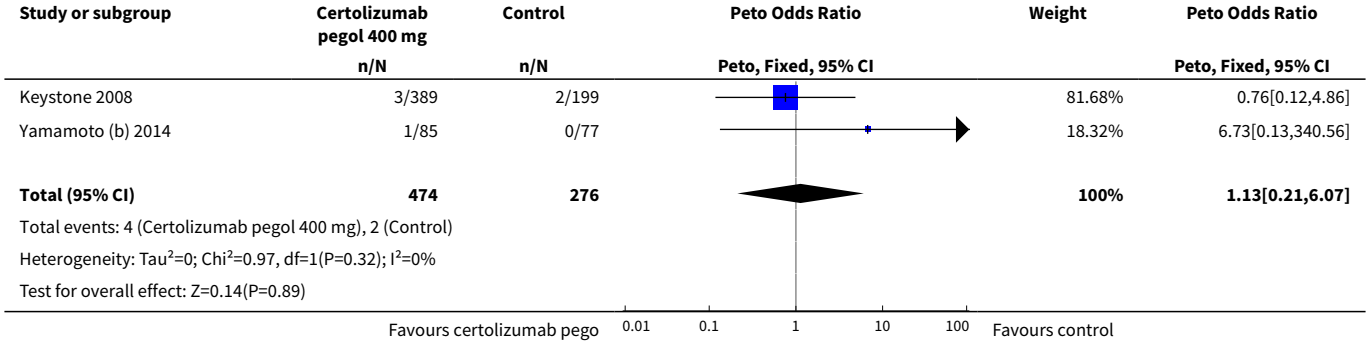
Analysis 50.62. Comparison 50 Safety, Outcome 62 Back pain certolizumab 400 mg.



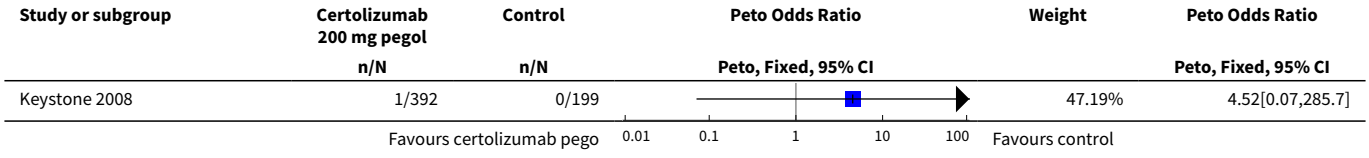
Analysis 50.63. Comparison 50 Safety, Outcome 63 Hematologic abnormalities certolizumab 200 mg.

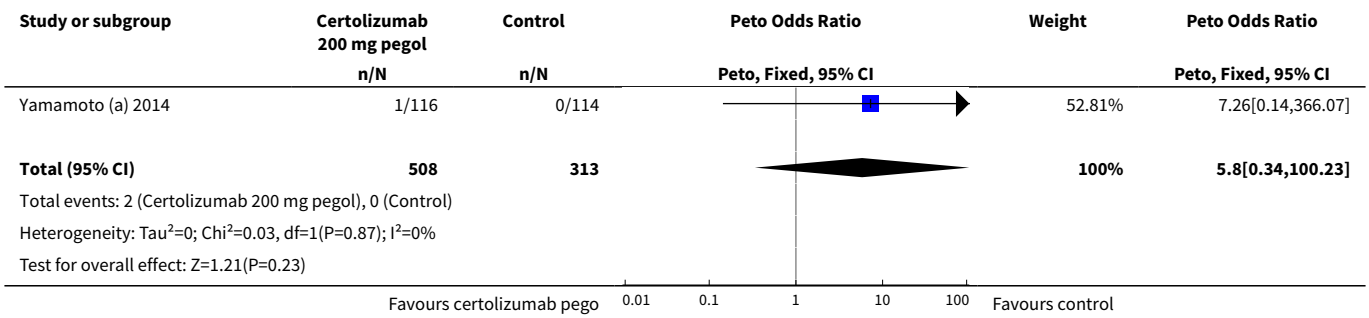


Analysis 50.64. Comparison 50 Safety, Outcome 64 Haematologic abnormalities certolizumab 400 mg.

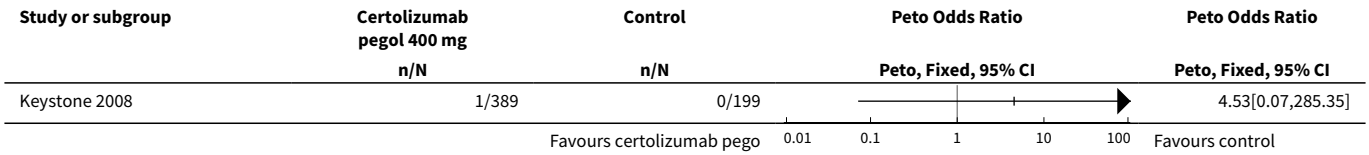


Analysis 50.65. Comparison 50 Safety, Outcome 65 Herpes viral infection certolizumab 200 mg.

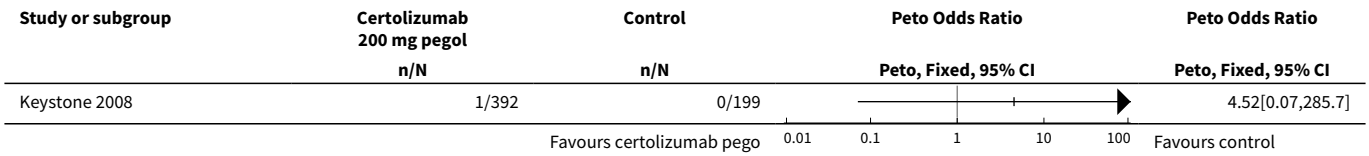




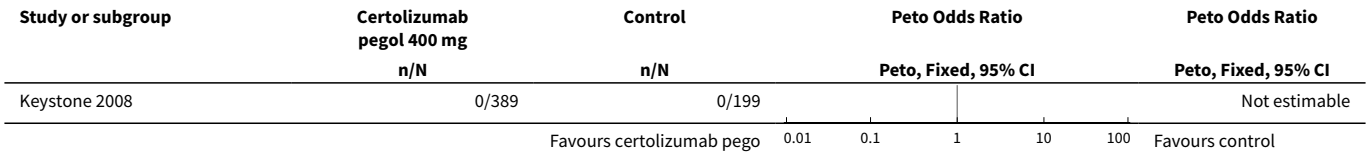
Analysis 50.66. Comparison 50 Safety, Outcome 66 Herpes viral infection certolizumab 400 mg.



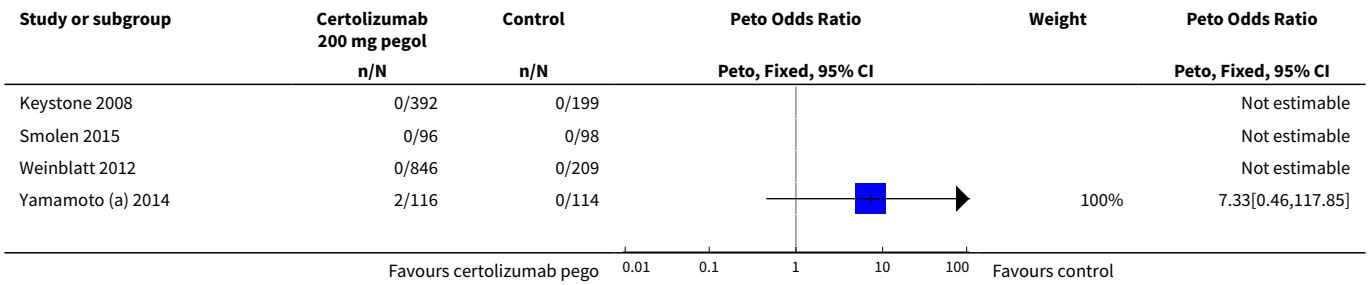
Analysis 50.67. Comparison 50 Safety, Outcome 67 Bacterial peritonitis certolizumab 200 mg.

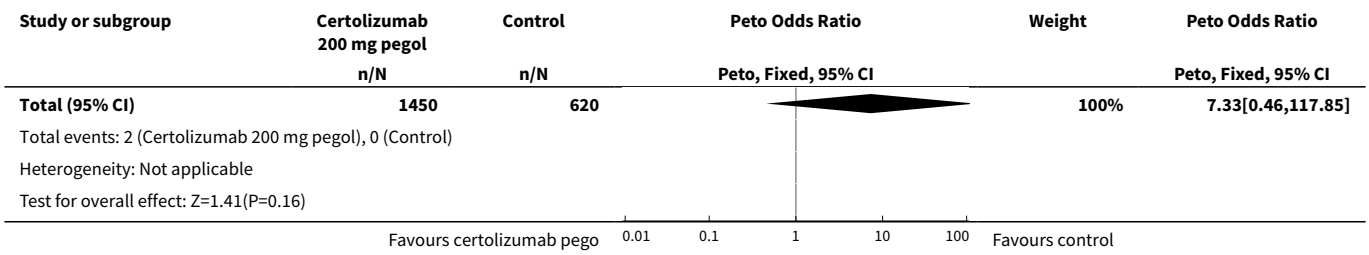


Analysis 50.68. Comparison 50 Safety, Outcome 68 Bacterial peritonitis certolizumab 400 mg.

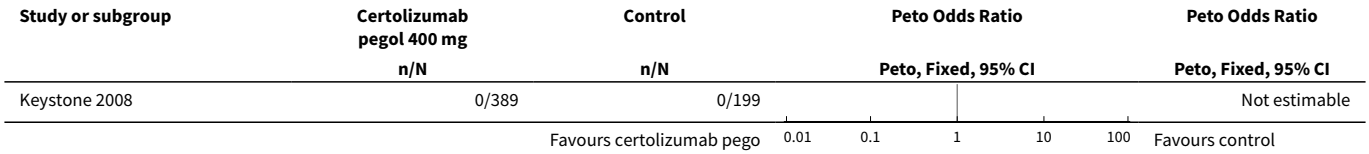


Analysis 50.69. Comparison 50 Safety, Outcome 69 Opportunistic infections certolizumab 200 mg.

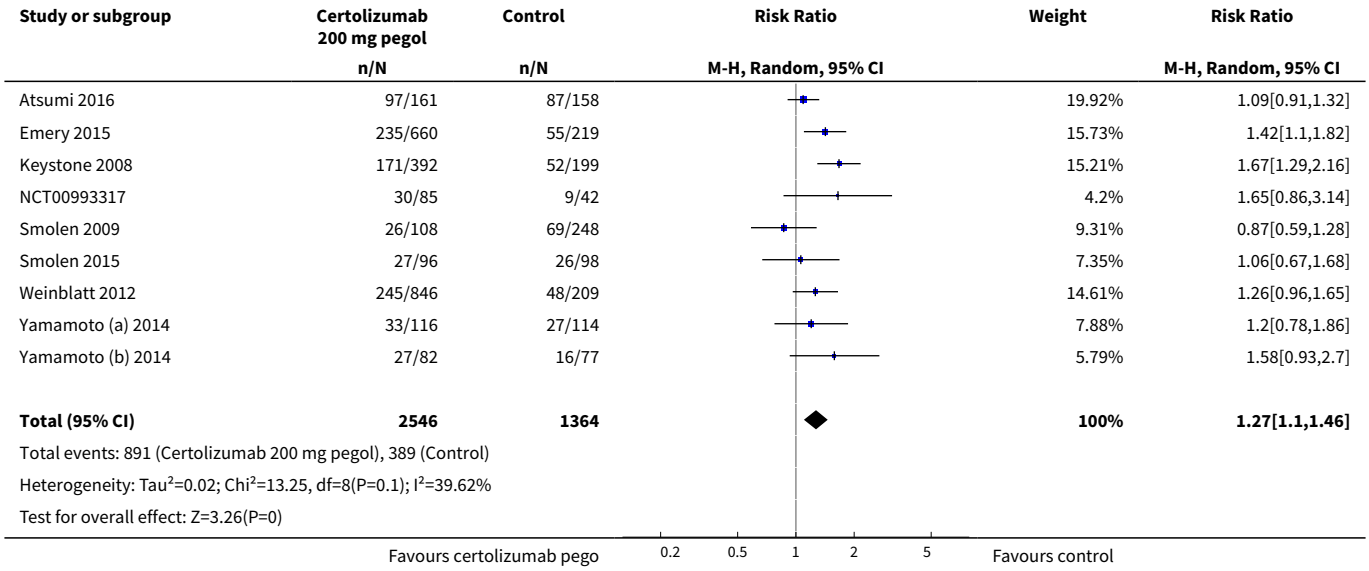




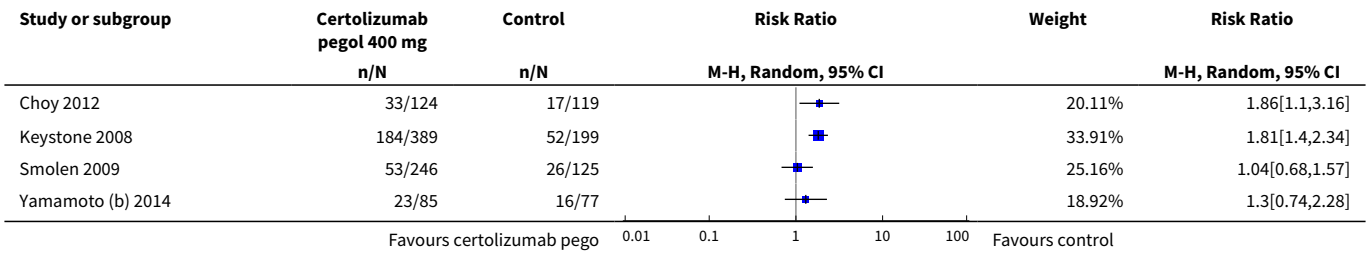
Analysis 50.70. Comparison 50 Safety, Outcome 70 Opportunistic infections certolizumab 400 mg.

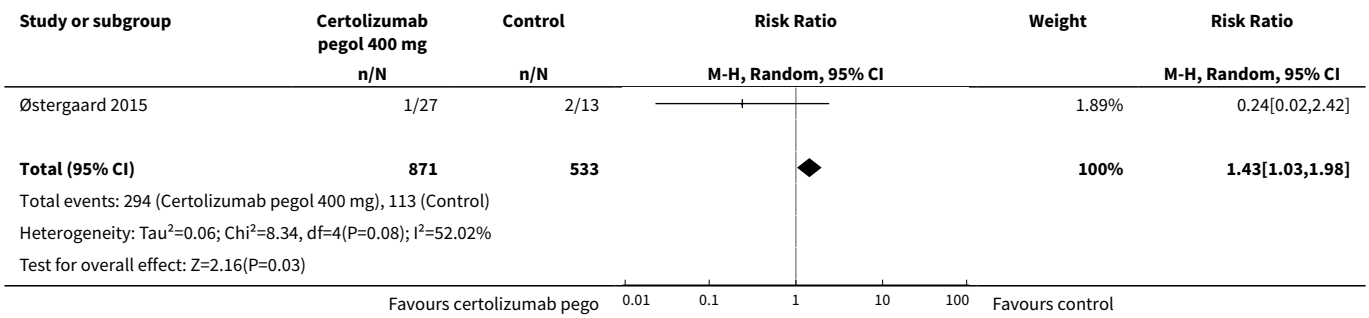


Analysis 50.71. Comparison 50 Safety, Outcome 71 Infections and infestations certolizumab 200 mg.

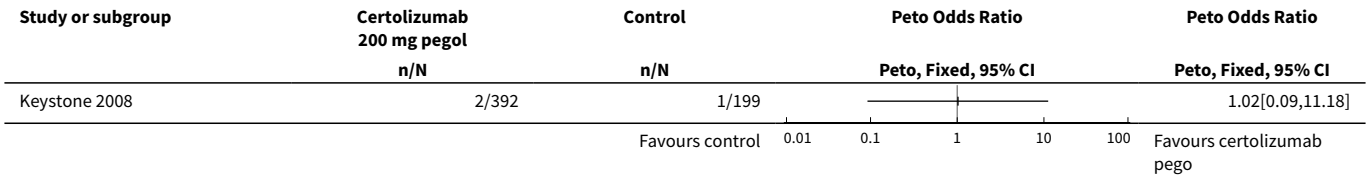


Analysis 50.72. Comparison 50 Safety, Outcome 72 Infections and infestations certolizumab 400 mg.

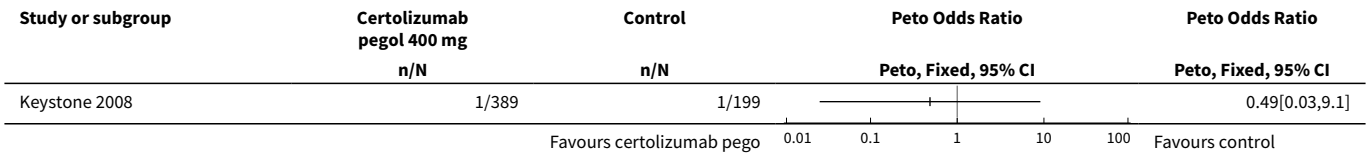




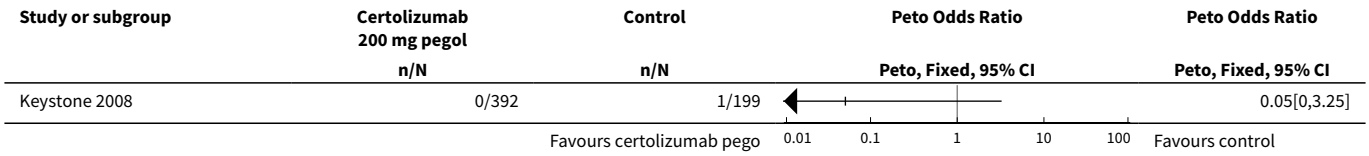
Analysis 50.73. Comparison 50 Safety, Outcome 73 Decreased haemoglobin certolizumab 200 mg.



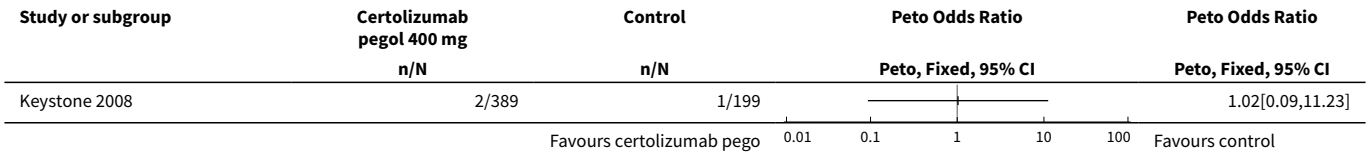
Analysis 50.74. Comparison 50 Safety, Outcome 74 Decreased haemoglobin certolizumab 400 mg.



Analysis 50.75. Comparison 50 Safety, Outcome 75 Increased platelet count certolizumab 200 mg.

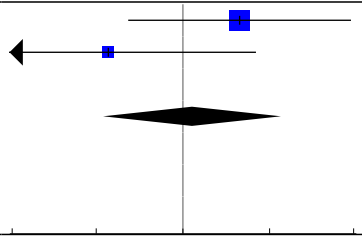


Analysis 50.76. Comparison 50 Safety, Outcome 76 Increased platelet count certolizumab 400 mg.



Analysis 50.77. Comparison 50 Safety, Outcome 77 Cerebral haemorrhage including subarachnoid certolizumab 200 mg.

Study or subgroup	Certolizumab 200 mg pegol n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
NCT00993317	2/85	0/42		63.73%	4.51[0.23,86.8]
Smolen 2015	0/96	1/98		36.27%	0.14[0,6.96]
Total (95% CI)	**181**	**140**		**100%**	**1.27[0.12,13.5]**
Total events: 2 (Certolizumab 200 mg pegol), 1 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.94, df=1(P=0.16); I^2=48.33%					
Test for overall effect: Z=0.2(P=0.84)					



Favours certolizumab pego — Favours control

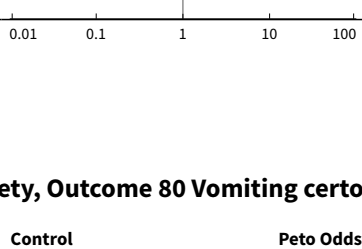
Analysis 50.78. Comparison 50 Safety, Outcome 78 Ischaemic stroke certolizumab 400 mg.

Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Fleischmann 2009	1/111	0/109		7.26[0.14,365.79]

Favours certolizumab pego — Favours control

Analysis 50.79. Comparison 50 Safety, Outcome 79 Nausea/vomiting certolizumab 200 mg.

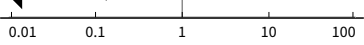
Study or subgroup	Certolizumab 200 mg pegol n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Atsumi 2016	39/161	32/158		33.09%	1.26[0.74,2.13]
Emery 2015	83/660	22/219		41.4%	1.27[0.79,2.04]
Smolen 2015	5/96	5/98		5.7%	1.02[0.29,3.64]
Weinblatt 2012	42/846	13/209		19.82%	0.78[0.39,1.53]
Total (95% CI)	**1763**	**684**		**100%**	**1.13[0.84,1.54]**
Total events: 169 (Certolizumab 200 mg pegol), 72 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.59, df=3(P=0.66); I^2=0%					
Test for overall effect: Z=0.82(P=0.41)					



Favours certolizumab pego — Favours control

Analysis 50.80. Comparison 50 Safety, Outcome 80 Vomiting certolizumab 400 mg.

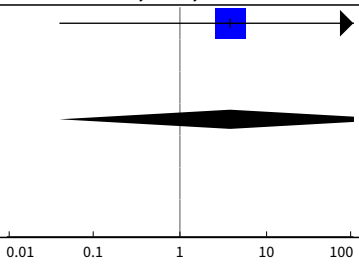
Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Fleischmann 2009	0/111	1/109		0.13[0,6.7]



Favours certolizumab pego — Favours control

Analysis 50.81. Comparison 50 Safety, Outcome 81 Acute miocardial infarction certolizumab 200 mg.

Study or subgroup	Certolizumab 200 mg pegol n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Emery 2015	1/660	0/219		100%	3.79[0.04,351.89]
Smolen 2015	0/96	0/98			Not estimable
Total (95% CI)	**756**	**317**		**100%**	**3.79[0.04,351.89]**
Total events: 1 (Certolizumab 200 mg pegol), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.58(P=0.56)					



Favours certolizumab pego — Favours control

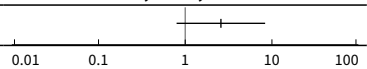
Analysis 50.82. Comparison 50 Safety, Outcome 82 Acute myocardial infarction certolizumab 400 mg.

Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Yamamoto (b) 2014	1/85	0/77		6.73[0.13,340.56]

Favours certolizumab pego — Favours control

Analysis 50.83. Comparison 50 Safety, Outcome 83 Abdominal pain/discomfort/dyspepsia certolizumab 200 mg.

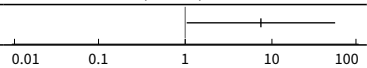
Study or subgroup	Certolizumab 200 mg pegol n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
NCT00993317	12/85	2/42		2.58[0.8,8.35]



Favours certolizumab pego — Favours control

Analysis 50.84. Comparison 50 Safety, Outcome 84 Constipation certolizumab 200 mg.

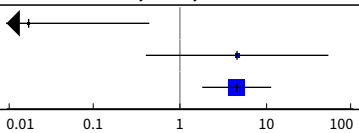
Study or subgroup	Certolizumab 200 mg pegol n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Yamamoto (a) 2014	4/116	0/114		7.46[1.04,53.63]



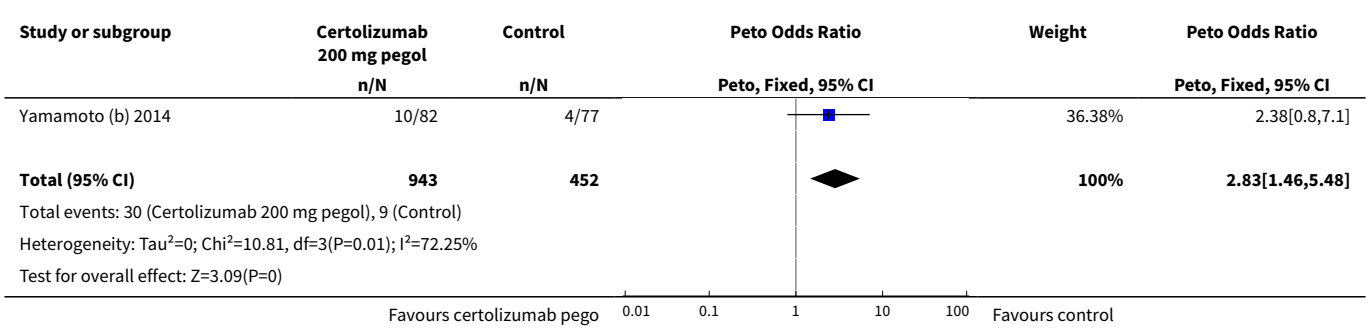
Favours certolizumab pego — Favours control

Analysis 50.85. Comparison 50 Safety, Outcome 85 Skin and subcutaneous tissue disorders certolizumab 200 mg.

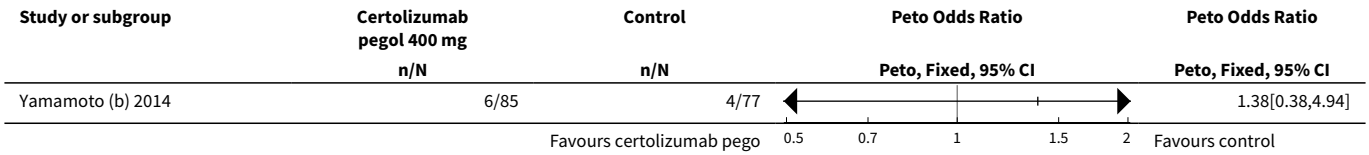
Study or subgroup	Certolizumab 200 mg pegol n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Emery 2015	0/660	2/219		4.24%	0.02[0,0.44]
NCT00993317	3/85	0/42		7.41%	4.56[0.4,51.56]
Yamamoto (a) 2014	17/116	3/114		51.98%	4.52[1.81,11.28]



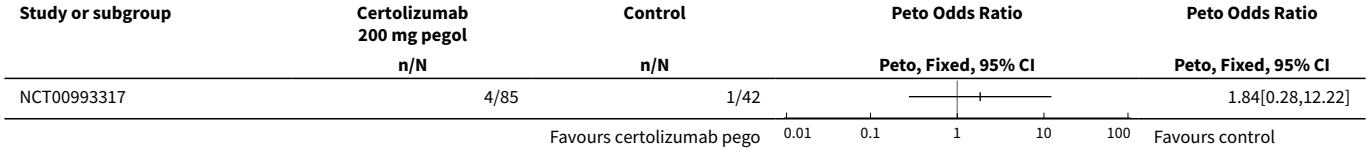
Favours certolizumab pego — Favours control



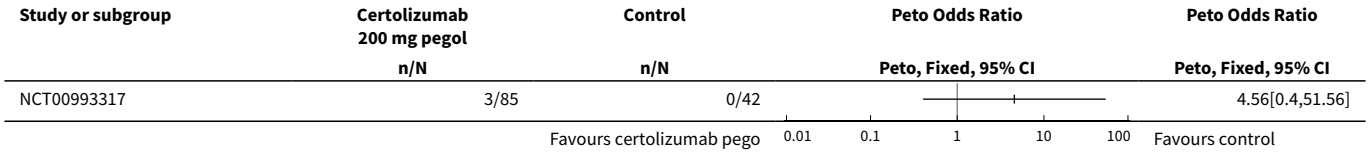
Analysis 50.86. Comparison 50 Safety, Outcome 86 Skin and subcutaneous tissue disorders certolizumab 400 mg.



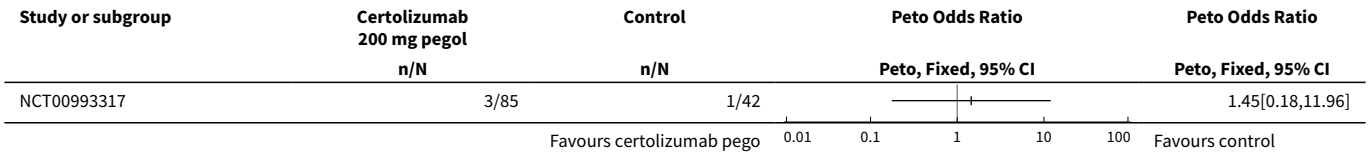
Analysis 50.87. Comparison 50 Safety, Outcome 87 Cough certolizumab 200 mg.



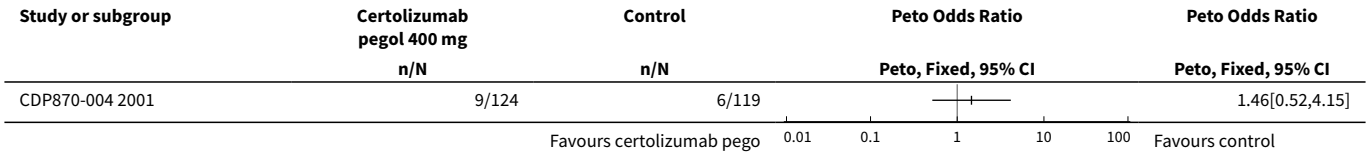
Analysis 50.88. Comparison 50 Safety, Outcome 88 Pruritus certolizumab 200 mg.



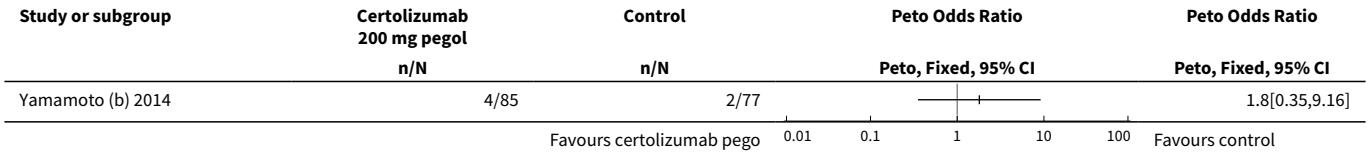
Analysis 50.89. Comparison 50 Safety, Outcome 89 Fatigue certolizumab 200 mg.



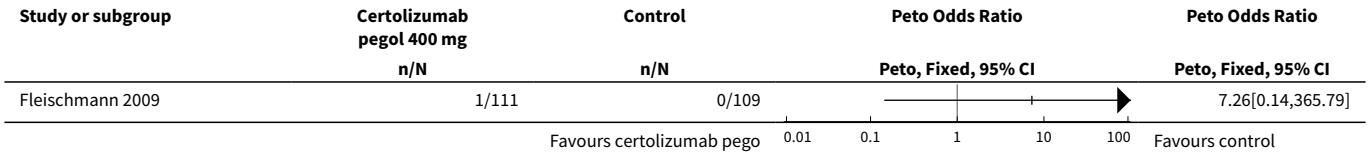
Analysis 50.90. Comparison 50 Safety, Outcome 90 Fatigue certolizumab 400 mg.



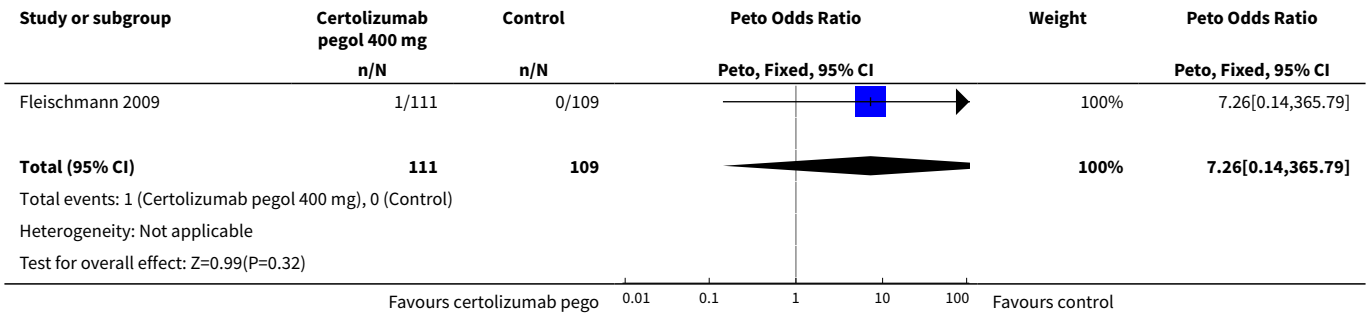
Analysis 50.91. Comparison 50 Safety, Outcome 91 Periodontitis certolizumab 200 mg.



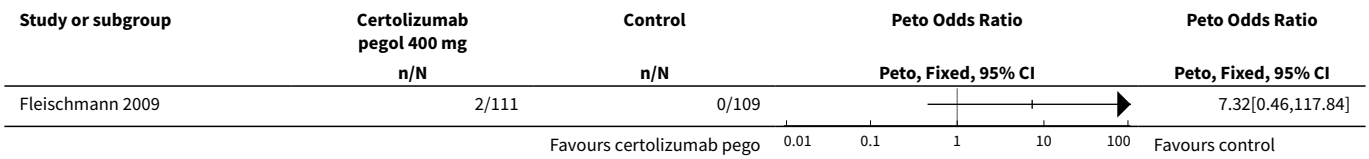
Analysis 50.92. Comparison 50 Safety, Outcome 92 Arthritis bacterial certolizumab 400 mg.



Analysis 50.93. Comparison 50 Safety, Outcome 93 Mastitis certolizumab 400 mg.

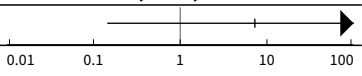


Analysis 50.94. Comparison 50 Safety, Outcome 94 Benign tumour certolizumab 400 mg.



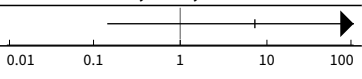
Analysis 50.95. Comparison 50 Safety, Outcome 95 Dizziness postural certolizumab 400 mg.

Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Fleischmann 2009	1/111	0/109		7.26[0.14,365.79]



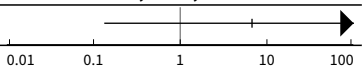
Analysis 50.96. Comparison 50 Safety, Outcome 96 Menorrhagia certolizumab 400 mg.

Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Fleischmann 2009	1/111	0/109		7.26[0.14,365.79]



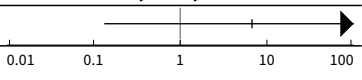
Analysis 50.97. Comparison 50 Safety, Outcome 97 Corneal perforation certolizumab 400 mg.

Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Yamamoto (b) 2014	1/85	0/77		6.73[0.13,340.56]



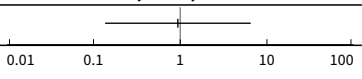
Analysis 50.98. Comparison 50 Safety, Outcome 98 Conjunctivitis allergic certolizumab 400 mg.

Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Yamamoto (b) 2014	1/85	0/77		6.73[0.13,340.56]



Analysis 50.99. Comparison 50 Safety, Outcome 99 Periodontitis certolizumab 400 mg.

Study or subgroup	Certolizumab pegol 400 mg n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Yamamoto (b) 2014	2/82	2/77		0.94[0.14,6.5]



Comparison 51. Participant's assessment of arthritis pain (VAS score 0 to 100 mm)

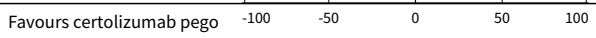
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean change at 24 weeks certolizumab pegol 200 mg	2	965	Mean Difference (IV, Random, 95% CI)	-20.49 [-23.43, -17.55]
2 Mean change at 24 weeks certolizumab pegol 400 mg	3	1182	Mean Difference (IV, Random, 95% CI)	-22.69 [-25.53, -19.84]
3 Mean change at 52 weeks certolizumab pegol 200 mg	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 Mean change at 52 weeks certolizumab pegol 400 mg	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 51.1. Comparison 51 Participant's assessment of arthritis pain (VAS score 0 to 100 mm), Outcome 1 Mean change at 24 weeks certolizumab pegol 200 mg.

Study or subgroup	Certolizumab pegol 200 mg N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Keystone 2008	393	-29.6 (21.8)	199	-8.1 (22.6)		59.66%	-21.5[-25.31,-17.69]
Smolen 2009	246	-23.7 (22)	127	-4.7 (21.4)		40.34%	-19[-23.63,-14.37]
Total ***	**639**		**326**			**100%**	**-20.49[-23.43,-17.55]**
Heterogeneity: Tau^2=0; Chi^2=0.67, df=1(P=0.41); I^2=0%							
Test for overall effect: Z=13.66(P<0.0001)							

Analysis 51.2. Comparison 51 Participant's assessment of arthritis pain (VAS score 0 to 100 mm), Outcome 2 Mean change at 24 weeks certolizumab pegol 400 mg.

Study or subgroup	Certolizumab pegol 400 mg N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Fleischmann 2009	111	-20.6 (42)	109	1.7 (42)		6.55%	-22.3[-33.4,-11.2]
Keystone 2008	390	-31.7 (21.7)	199	-8.1 (22.6)		55.76%	-23.6[-27.41,-19.79]
Smolen 2009	246	-26.1 (22)	127	-4.7 (21.4)		37.69%	-21.4[-26.03,-16.77]
Total ***	**747**		**435**			**100%**	**-22.69[-25.53,-19.84]**
Heterogeneity: Tau^2=0; Chi^2=0.52, df=2(P=0.77); I^2=0%							
Test for overall effect: Z=15.65(P<0.0001)							



Analysis 51.3. Comparison 51 Participant's assessment of arthritis pain (VAS score 0 to 100 mm), Outcome 3 Mean change at 52 weeks certolizumab pegol 200 mg.

Study or subgroup	Certolizumab pegol		Control		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Keystone 2008	393	-31 (22.6)	199	-8.8 (23.8)	+	-22.2[-26.19,-18.21]

Favours certolizumab pego -100 -50 0 50 100 Favours control

Analysis 51.4. Comparison 51 Participant's assessment of arthritis pain (VAS score 0 to 100 mm), Outcome 4 Mean change at 52 weeks certolizumab pegol 400 mg.

Study or subgroup	Certolizumab		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Keystone 2008	390	-33.5 (23.7)	199	-8.8 (22.6)	+	-24.7[-28.62,-20.78]

Favours certolizumab -100 -50 0 50 100 Favours control

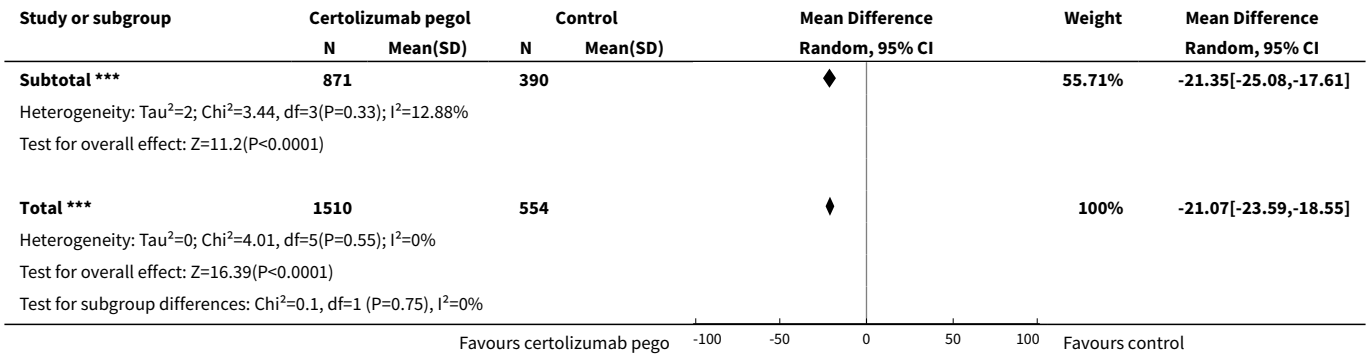
Comparison 52. Participant's assessment of arthritis pain (VAS score 0 to 100 mm) at 24 weeks, any dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline	4	2064	Mean Difference (IV, Random, 95% CI)	-21.07 [-23.59, -18.55]
1.1 certolizumab pegol 200 mg sc	2	803	Mean Difference (IV, Random, 95% CI)	-20.48 [-24.26, -16.69]
1.2 certolizumab pegol 400 mg sc	4	1261	Mean Difference (IV, Random, 95% CI)	-21.35 [-25.08, -17.61]

Analysis 52.1. Comparison 52 Participant'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 pegol		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
52.1.1 certolizumab pegol 200 mg sc							
Keystone 2008	393	-29.6 (21.8)	100	-8.1 (22.6)		26.2%	-21.5[-26.42,-16.58]
Smolen 2009	246	-23.7 (22)	64	-4.7 (21.4)		18.09%	-19[-24.92,-13.08]
Subtotal ***	**639**		**164**			**44.29%**	**-20.48[-24.26,-16.69]**
Heterogeneity: Tau^2=0; Chi^2=0.4, df=1(P=0.52); I^2=0%							
Test for overall effect: Z=10.6(P<0.0001)							
52.1.2 certolizumab pegol 400 mg sc							
Choy 2012	124	-21.8 (51.4)	119	-8.5 (19.9)		6.7%	-13.3[-23.03,-3.57]
Fleischmann 2009	111	-20.6 (42)	109	1.7 (42)		5.15%	-22.3[-33.4,-11.2]
Keystone 2008	390	-31.7 (21.7)	99	-8.1 (22.6)		25.99%	-23.6[-28.54,-18.66]
Smolen 2009	246	-26.1 (22)	63	-4.7 (21.4)		17.87%	-21.4[-27.36,-15.44]

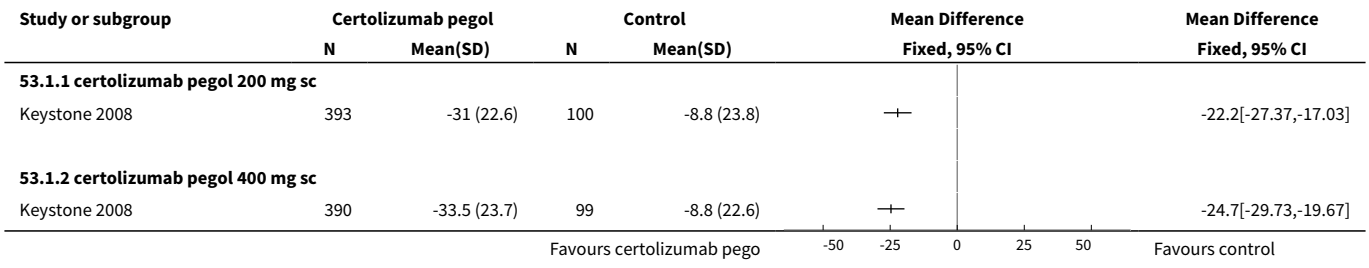
Favours certolizumab pego -100 -50 0 50 100 Favours control



Comparison 53. Participant'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		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 certolizumab pegol 200 mg sc	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 certolizumab pegol 400 mg sc	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

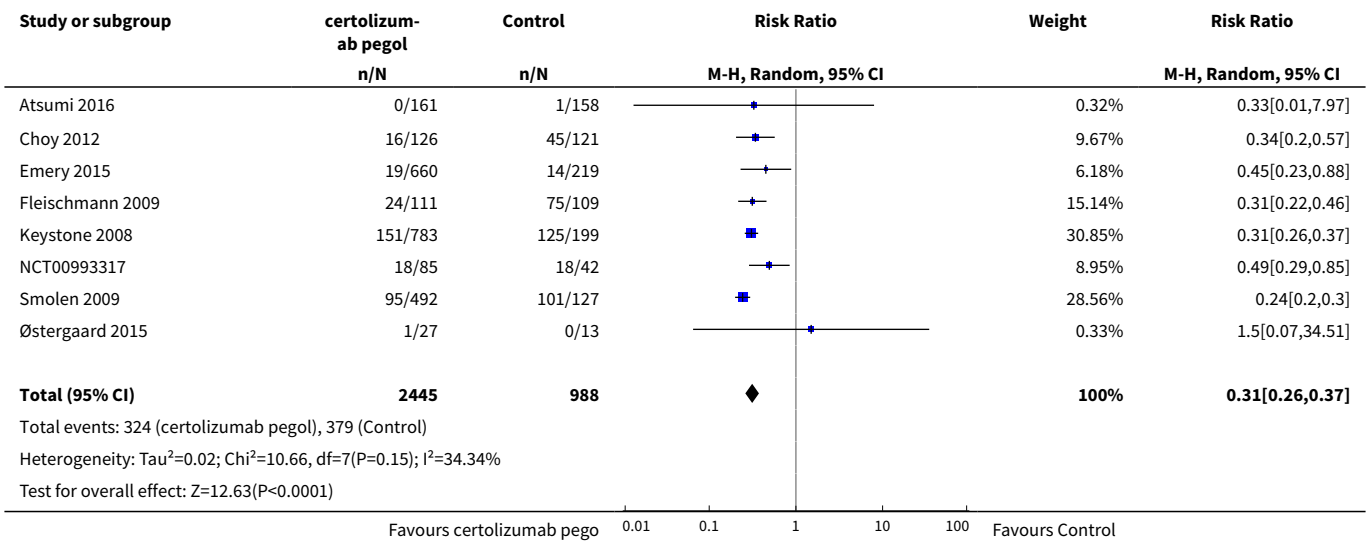
Analysis 53.1. Comparison 53 Participant's assessment of arthritis pain (VAS score 0 to 100 mm) at 52 weeks, any dose, Outcome 1 Change from baseline.



Comparison 54. Withdrawals Withdrawn due to lack of efficacy: any doses any follow-up

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Withdrawn due to lack of efficacy: any doses any follow-up	8	3433	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.26, 0.37]

Analysis 54.1. Comparison 54 Withdrawals Withdrawn due to lack of efficacy: any doses any follow-up, Outcome 1 Withdrawn due to lack of efficacy: any doses any follow-up.



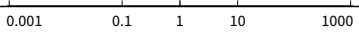
Comparison 55. Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR 50 200 mg certolizumab 24 weeks	5	1445	Risk Ratio (M-H, Random, 95% CI)	3.80 [2.42, 5.95]
2 HAQ change from baseline 200 mg certolizumab 24 weeks	4	1268	Mean Difference (IV, Random, 95% CI)	-0.35 [-0.43, -0.26]
3 Serious adverse events certolizumab 200 mg sc	9	3927	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.47 [1.13, 1.91]
4 Proportion of participants achieving remission 24 weeks certolizumab 200 mg	4	1381	Risk Ratio (M-H, Random, 95% CI)	8.47 [4.15, 17.28]
5 Radiological changes: Erosion Scores (ES) certolizumab 200 mg sc	2	859	Mean Difference (IV, Random, 95% CI)	-0.67 [-0.96, -0.38]
5.1 certolizumab 200 mg sc 24 weeks	2	859	Mean Difference (IV, Random, 95% CI)	-0.67 [-0.96, -0.38]
6 All Withdrawals:	10	3962	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.36, 0.50]
7 Withdrawals due to adverse events	9	3998	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.66 [1.15, 2.37]
8 Deaths	10	4745	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.63 [0.78, 8.91]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Certolizumab pegol 200 mg	7	3266	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.10 [0.44, 10.08]
8.2 Certolizumab pegol 400 mg	5	1349	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.53 [0.40, 31.39]
8.3 Other doses	2	130	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.48 [0.07, 286.49]
9 Tuberculosis	7	4074	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.91 [0.61, 5.96]
9.1 Certolizumab pegol 200 mg	6	3058	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.53 [0.40, 5.77]
9.2 Certolizumab pegol 400 mg	3	1016	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.52 [0.40, 31.33]
10 Upper respiratory tract infections	8	3692	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.17 [0.86, 1.59]
10.1 Certolizumab pegol 200 mg	7	2528	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.28 [0.91, 1.80]
10.2 Certolizumab pegol 400 mg	4	1164	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.81 [0.41, 1.61]
11 Lower respiratory tract infections	7	3073	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.66 [0.77, 3.58]
11.1 Certolizumab pegol 200 mg	6	2218	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.81 [0.62, 5.26]
11.2 Certolizumab pegol 400 mg	3	855	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.52 [0.50, 4.59]
12 Malignancies including lymphoma	7	3749	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.90 [0.39, 2.08]
12.1 Certolizumab pegol 200 mg	6	2570	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.79 [0.29, 2.12]
12.2 Certolizumab pegol 400 mg	3	1179	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.26 [0.26, 6.08]

Analysis 55.1. Comparison 55 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 pegol 200 mg n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Keystone 2008	144/393	15/199		25.28%	4.86[2.94,8.04]
NCT00993317	35/85	8/42		20.23%	2.16[1.1,4.24]
Smolen 2009	80/246	4/127		13.4%	10.33[3.87,27.54]
Smolen 2015	20/96	7/98		16.74%	2.92[1.29,6.58]
Yamamoto (b) 2014	45/82	13/77		24.36%	3.25[1.91,5.54]
Total (95% CI)	**902**	**543**		**100%**	**3.8[2.42,5.95]**
Total events: 324 (Certolizumab pegol 200 mg), 47 (Placebo)					
Heterogeneity: Tau^2=0.14; Chi^2=9.05, df=4(P=0.06); I^2=55.79%					
Test for overall effect: Z=5.82(P<0.0001)					



Favours control — Favours certolizumab pego

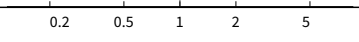
Analysis 55.2. Comparison 55 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX), Outcome 2 HAQ change from baseline 200 mg certolizumab 24 weeks.

Study or subgroup	Certolizumab pegol N	Mean(SD)	Control N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Keystone 2008	393	-0.6 (0.6)	199	-0.2 (0.6)		33.94%	-0.41[-0.51,-0.31]
NCT00993317	81	-0.5 (0.5)	40	-0.2 (0.7)		9.56%	-0.37[-0.61,-0.13]
Smolen 2009	246	-0.5 (0.5)	127	-0.1 (0.5)		33.73%	-0.36[-0.46,-0.26]
Smolen 2015	91	-0.2 (0.5)	91	-0 (0.5)		22.77%	-0.22[-0.36,-0.08]
Total ***	**811**		**457**			**100%**	**-0.35[-0.43,-0.26]**
Heterogeneity: Tau^2=0; Chi^2=4.92, df=3(P=0.18); I^2=39.05%							
Test for overall effect: Z=8.32(P<0.0001)							

Favours certolizumab pego — Favours control

Analysis 55.3. Comparison 55 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 pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Smolen 2015	5/96	7/98		5.02%	0.72[0.22,2.3]
Atsumi 2016	13/161	14/158		11.01%	0.9[0.41,1.99]
Weinblatt 2012	52/846	12/209		16.98%	1.07[0.57,2.02]
Emery 2015	70/660	20/219		26.87%	1.17[0.71,1.94]
Keystone 2008	45/392	11/199		20.14%	2[1.12,3.58]
Smolen 2009	18/248	4/125		8.21%	2.07[0.83,5.16]
Yamamoto (b) 2014	4/82	1/77		2.16%	3.21[0.54,19]
Yamamoto (a) 2014	13/116	3/114		6.64%	3.74[1.36,10.31]
NCT00993317	8/85	0/42		2.97%	4.86[1.07,22.14]
Total (95% CI)	**2686**	**1241**		**100%**	**1.47[1.13,1.91]**



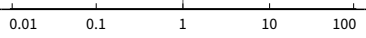
Favours certolizumab pego — Favours control

Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Total events: 228 (Certolizumab pegol 200 mg), 72 (Control)					
Heterogeneity: Tau²=0; Chi²=12.65, df=8(P=0.12); I²=36.76%					
Test for overall effect: Z=2.9(P=0)					

Favours certolizumab pego | Favours control

Analysis 55.4. Comparison 55 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX), Outcome 4 Proportion of participants achieving remission 24 weeks certolizumab 200 mg.

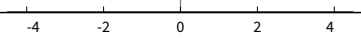
Study or subgroup	Certolizumab pegol 200 mg n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Keystone 2008	45/391	3/196		38.09%	7.52[2.37,23.89]
Smolen 2009	23/245	1/125		12.85%	11.73[1.6,85.89]
Smolen 2015	19/96	3/98		36.27%	6.47[1.98,21.14]
Yamamoto (a) 2014	19/116	1/114		12.8%	18.67[2.54,137.17]
Total (95% CI)	**848**	**533**		**100%**	**8.47[4.15,17.28]**
Total events: 106 (Certolizumab pegol 200 mg), 8 (Control)					
Heterogeneity: Tau²=0; Chi²=0.97, df=3(P=0.81); I²=0%					
Test for overall effect: Z=5.87(P<0.0001)					



Favours control | Favours certolizumab pego

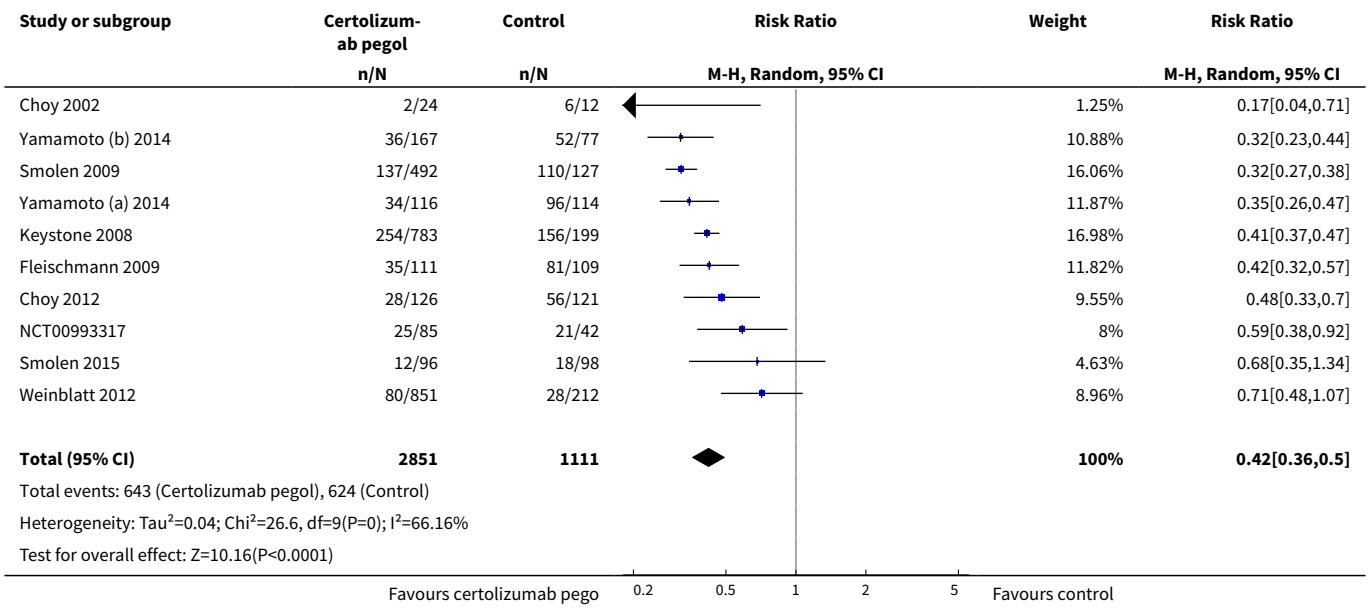
Analysis 55.5. Comparison 55 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX), Outcome 5 Radiological changes: Erosion Scores (ES) certolizumab 200 mg sc.

Study or subgroup	Certolizumab pegol N	Certolizumab pegol Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
55.5.1 certolizumab 200 mg sc 24 weeks							
Keystone 2008	353	0 (1.5)	180	0.7 (2.1)		71.91%	-0.7[-1.04,-0.36]
Smolen 2009	214	0.1 (2)	112	0.7 (2.6)		28.09%	-0.6[-1.15,-0.05]
Subtotal ***	**567**		**292**			**100%**	**-0.67[-0.96,-0.38]**
Heterogeneity: Tau²=0; Chi²=0.09, df=1(P=0.76); I²=0%							
Test for overall effect: Z=4.51(P<0.0001)							
Total ***	**567**		**292**			**100%**	**-0.67[-0.96,-0.38]**
Heterogeneity: Tau²=0; Chi²=0.09, df=1(P=0.76); I²=0%							
Test for overall effect: Z=4.51(P<0.0001)							

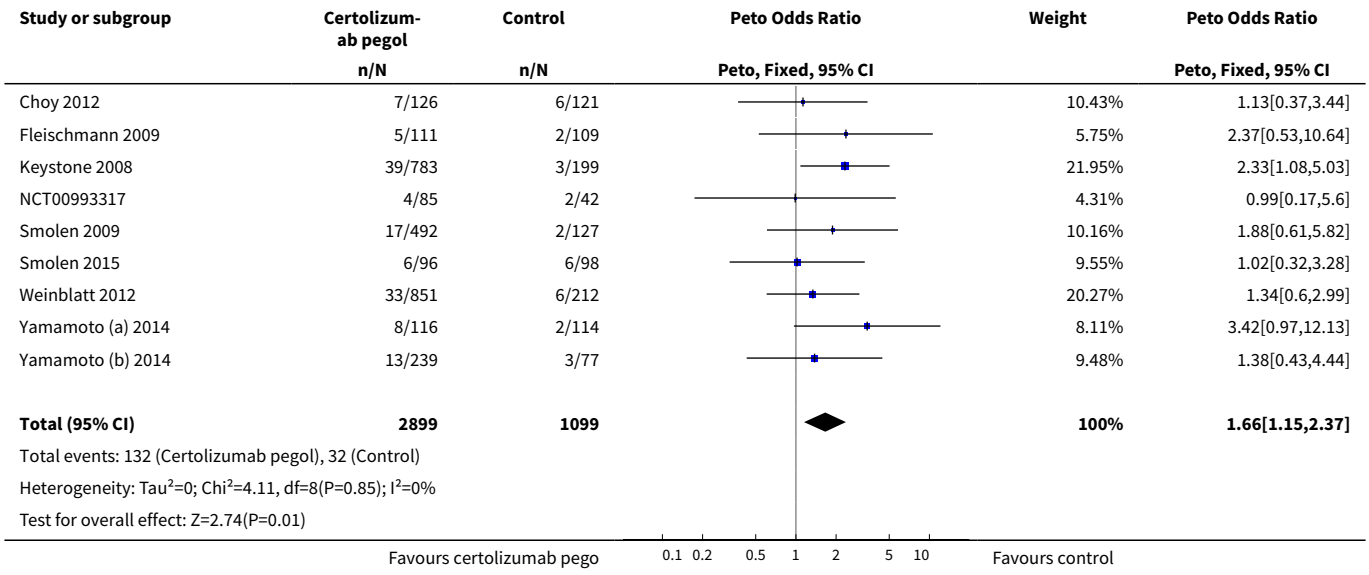


Favours certolizumab pego | Favours control

Analysis 55.6. Comparison 55 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX), Outcome 6 All Withdrawals:.

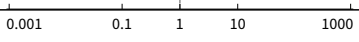


Analysis 55.7. Comparison 55 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX), Outcome 7 Withdrawals due to adverse events.



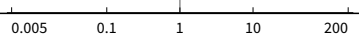
Analysis 55.8. Comparison 55 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX), Outcome 8 Deaths.

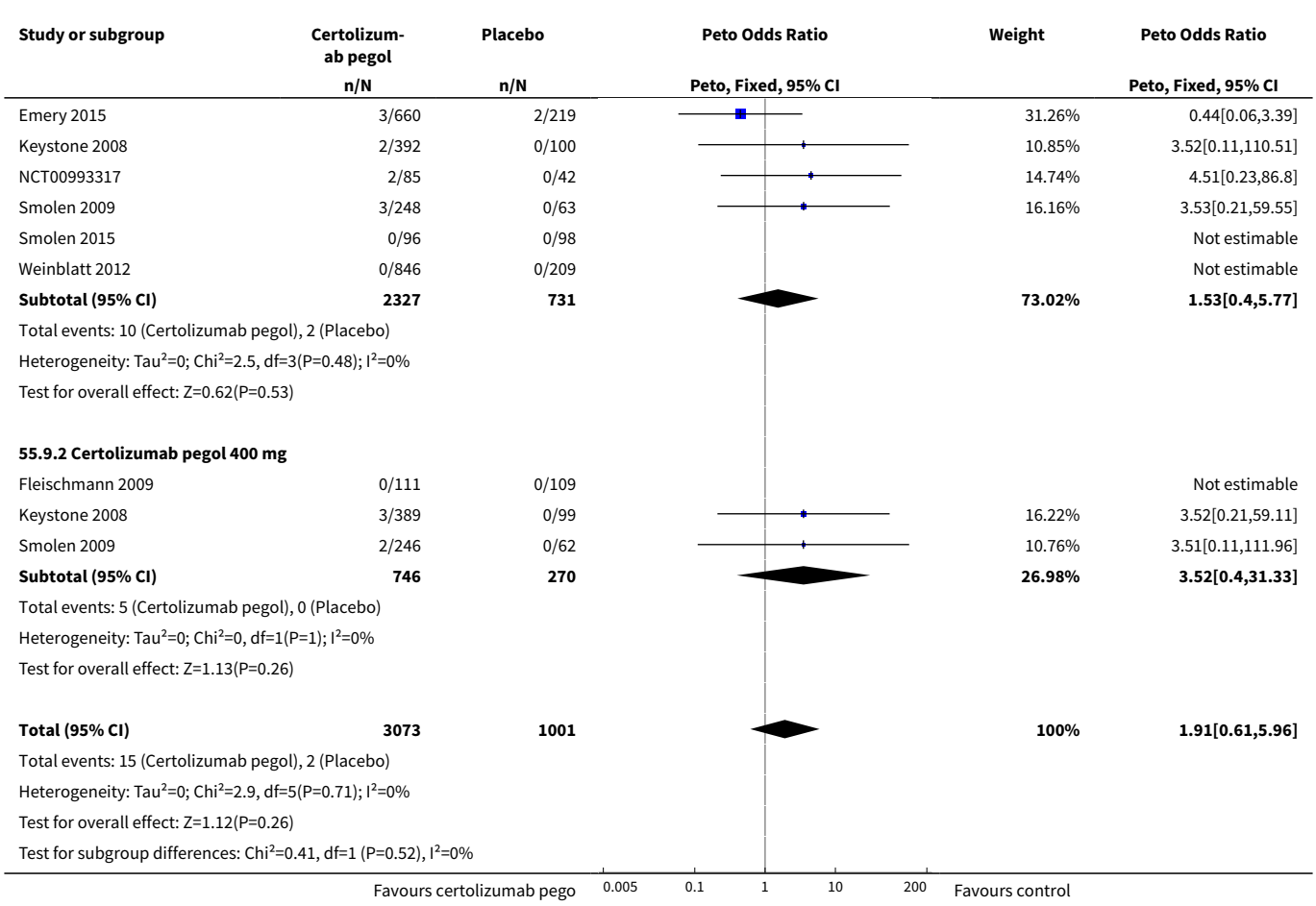
Study or subgroup	Certolizumab pegol n/N	Placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
55.8.1 Certolizumab pegol 200 mg					
Emery 2015	1/660	0/219		7.23%	3.79[0.04,351.89]
Keystone 2008	3/392	1/100		24.89%	0.75[0.07,8.6]
Smolen 2009	1/246	0/63		6.28%	3.51[0.03,455.29]
Smolen 2015	0/96	0/98			Not estimable
Weinblatt 2012	2/846	0/209		12.27%	3.48[0.11,112.96]
Yamamoto (a) 2014	1/116	0/114		9.66%	7.26[0.14,366.07]
Yamamoto (b) 2014	0/82	0/25			Not estimable
Subtotal (95% CI)	**2438**	**828**		**60.34%**	**2.1[0.44,10.08]**
Total events: 8 (Certolizumab pegol), 1 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.26, df=4(P=0.87); I^2=0%					
Test for overall effect: Z=0.93(P=0.35)					
55.8.2 Certolizumab pegol 400 mg					
Choy 2012	0/124	0/119			Not estimable
Fleischmann 2009	0/111	0/109			Not estimable
Keystone 2008	4/389	0/99		24.86%	3.53[0.31,40.72]
Smolen 2009	1/246	0/62		6.22%	3.5[0.03,464.09]
Yamamoto (b) 2014	0/65	0/25			Not estimable
Subtotal (95% CI)	**935**	**414**		**31.07%**	**3.53[0.4,31.39]**
Total events: 5 (Certolizumab pegol), 0 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=1); I^2=0%					
Test for overall effect: Z=1.13(P=0.26)					
55.8.3 Other doses					
Choy 2002	1/24	0/12		8.59%	4.48[0.07,286.49]
Yamamoto (b) 2014	0/72	0/22			Not estimable
Subtotal (95% CI)	**96**	**34**		**8.59%**	**4.48[0.07,286.49]**
Total events: 1 (Certolizumab pegol), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.71(P=0.48)					
Total (95% CI)	**3469**	**1276**		**100%**	**2.63[0.78,8.91]**
Total events: 14 (Certolizumab pegol), 1 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.47, df=7(P=0.98); I^2=0%					
Test for overall effect: Z=1.56(P=0.12)					
Test for subgroup differences: Chi^2=0.21, df=1 (P=0.9), I^2=0%					



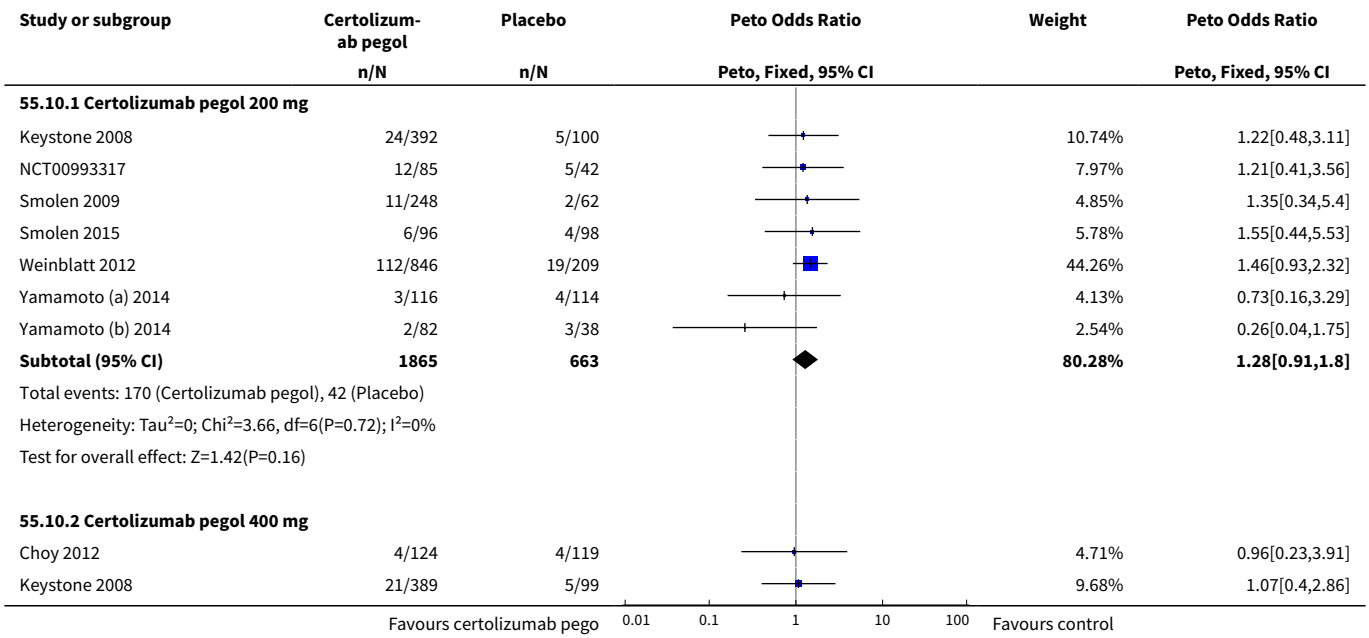
Analysis 55.9. Comparison 55 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX), Outcome 9 Tuberculosis.

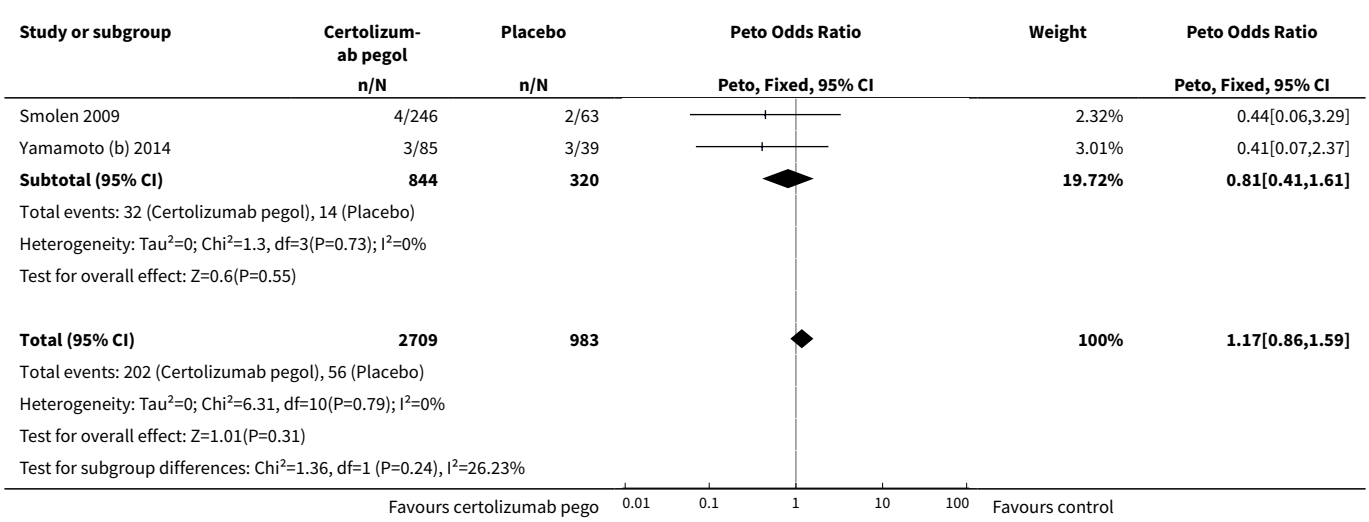
Study or subgroup	Certolizumab pegol n/N	Placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
55.9.1 Certolizumab pegol 200 mg					



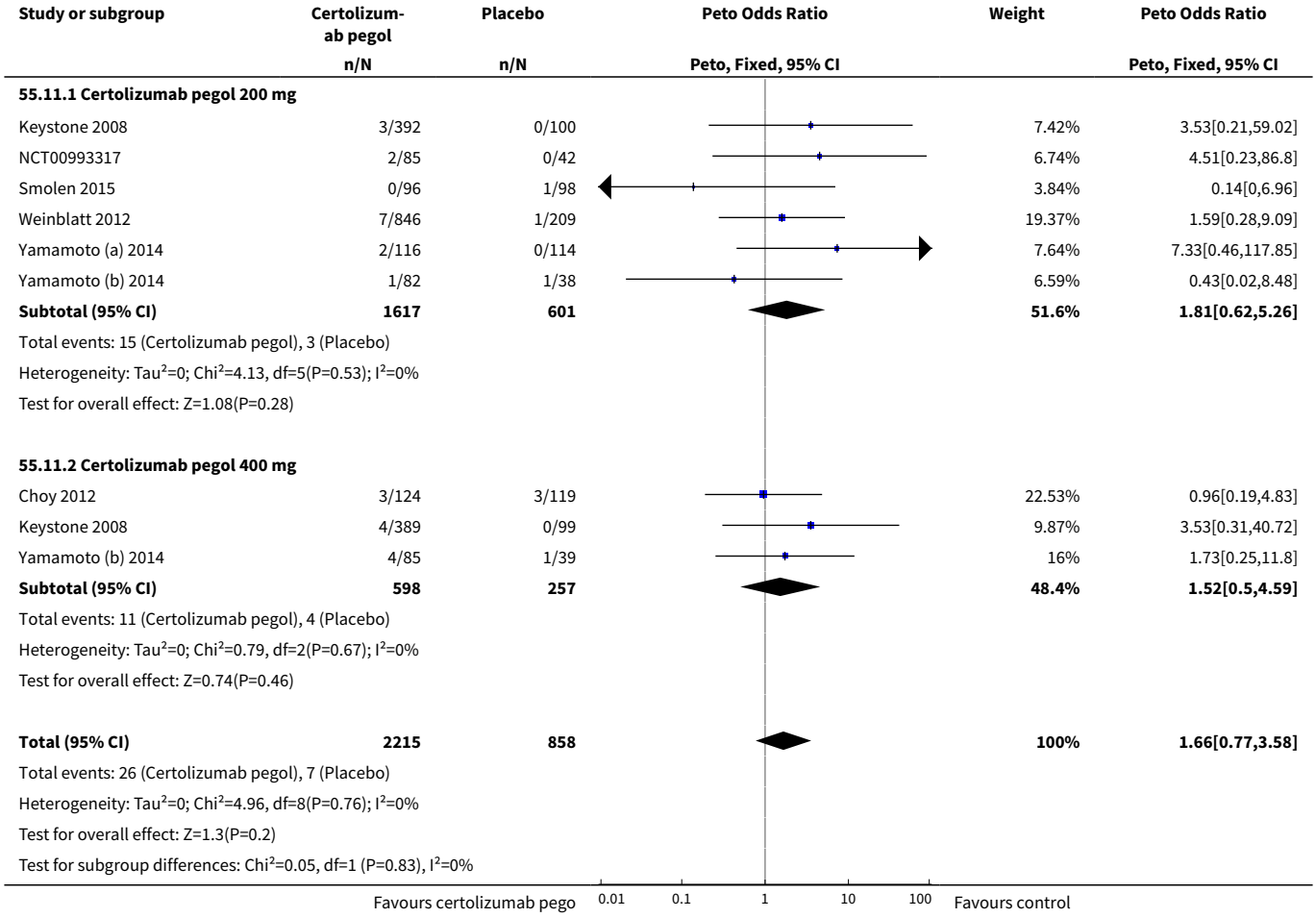


Analysis 55.10. Comparison 55 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX), Outcome 10 Upper respiratory tract infections.



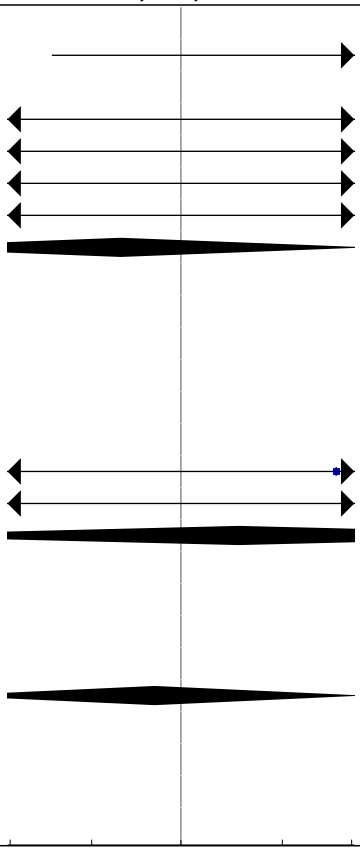


Analysis 55.11. Comparison 55 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX), Outcome 11 Lower respiratory tract infections.



Analysis 55.12. Comparison 55 Summary of findings: certolizumab (with or without MTX) versus placebo (with or without MTX), Outcome 12 Malignancies including lymphoma.

Study or subgroup	Certolizumab pegol n/N	Placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
55.12.1 Certolizumab pegol 200 mg					
Keystone 2008	7/392	1/199		32.32%	2.61[0.6,11.41]
NCT00993317	0/85	0/42			Not estimable
Smolen 2009	1/248	1/125		8.13%	0.48[0.03,9.01]
Smolen 2015	0/96	2/98		9.1%	0.14[0.01,2.2]
Weinblatt 2012	4/846	2/209		17.36%	0.43[0.06,3.18]
Yamamoto (a) 2014	0/116	1/114		4.58%	0.13[0,6.7]
Subtotal (95% CI)	**1783**	**787**		**71.49%**	**0.79[0.29,2.12]**
Total events: 12 (Certolizumab pegol), 7 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=5.32, df=4(P=0.26); I^2=24.86%					
Test for overall effect: Z=0.48(P=0.63)					
55.12.2 Certolizumab pegol 400 mg					
Fleischmann 2009	0/111	0/109			Not estimable
Keystone 2008	4/389	1/199		20.35%	1.86[0.29,11.96]
Smolen 2009	1/246	1/125		8.16%	0.48[0.03,9.06]
Subtotal (95% CI)	**746**	**433**		**28.51%**	**1.26[0.26,6.08]**
Total events: 5 (Certolizumab pegol), 2 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.58, df=1(P=0.44); I^2=0%					
Test for overall effect: Z=0.29(P=0.77)					
Total (95% CI)	**2529**	**1220**		**100%**	**0.9[0.39,2.08]**
Total events: 17 (Certolizumab pegol), 9 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=6.16, df=6(P=0.41); I^2=2.59%					
Test for overall effect: Z=0.25(P=0.81)					
Test for subgroup differences: Chi^2=0.25, df=1 (P=0.62), I^2=0%					



Comparison 56. Analysis of sensitivity ACR50 24 weeks

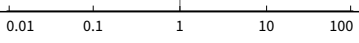
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Doses	8	3768	Risk Ratio (M-H, Random, 95% CI)	2.89 [2.38, 3.51]
1.1 certolizumab 100 mg sc	1	98	Risk Ratio (M-H, Random, 95% CI)	2.89 [1.13, 7.38]
1.2 certolizumab 200 mg sc	6	2295	Risk Ratio (M-H, Random, 95% CI)	2.73 [2.13, 3.51]
1.3 certolizumab 400 mg sc	5	1375	Risk Ratio (M-H, Random, 95% CI)	3.18 [2.29, 4.41]
2 Size	8	3768	Risk Ratio (M-H, Random, 95% CI)	2.89 [2.38, 3.51]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 certolizumab < 200 patients	2	321	Risk Ratio (M-H, Random, 95% CI)	2.44 [1.45, 4.10]
2.2 certolizumab > 200 patients	6	3447	Risk Ratio (M-H, Random, 95% CI)	2.97 [2.41, 3.67]
3 Use of MTX	8	3768	Risk Ratio (M-H, Random, 95% CI)	2.89 [2.38, 3.51]
3.1 With MTX	5	3038	Risk Ratio (M-H, Random, 95% CI)	2.77 [2.21, 3.46]
3.2 Without MTX	3	730	Risk Ratio (M-H, Random, 95% CI)	3.32 [2.23, 4.95]
4 Population	8	3768	Risk Ratio (M-H, Random, 95% CI)	2.89 [2.38, 3.51]
4.1 Asian trials	2	443	Risk Ratio (M-H, Random, 95% CI)	2.66 [1.77, 4.00]
4.2 Other trials	6	3325	Risk Ratio (M-H, Random, 95% CI)	2.96 [2.37, 3.70]
5 Duration of previous disease	6	3258	Risk Ratio (M-H, Random, 95% CI)	2.87 [2.31, 3.57]
5.1 Long previous disease duration (9 years or more)	2	467	Risk Ratio (M-H, Random, 95% CI)	4.02 [2.02, 7.98]
5.2 Short previous disease duration (less than 7 years)	4	2791	Risk Ratio (M-H, Random, 95% CI)	2.75 [2.18, 3.47]
6 Published vs unpublished studies	8	3768	Risk Ratio (M-H, Random, 95% CI)	2.89 [2.38, 3.51]
6.1 Published studies	5	3131	Risk Ratio (M-H, Random, 95% CI)	2.97 [2.36, 3.73]
6.2 Unpublished studies	3	637	Risk Ratio (M-H, Random, 95% CI)	2.71 [1.89, 3.90]
7 Imputing to ACR50 200 mg from 24 missing values with same proportion as reported outcomes	5	1445	Risk Ratio (M-H, Fixed, 95% CI)	3.34 [2.68, 4.17]
7.1 Imputing missing values with same proportion as reported outcomes	5	1445	Risk Ratio (M-H, Fixed, 95% CI)	3.34 [2.68, 4.17]
8 Imputing to ACR50 200 mg from 24 weeks 50 % of missing outcomes	5	1445	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [1.04, 1.32]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Imputing the 50 % of missing outcomes	5	1445	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [1.04, 1.32]
9 Imputing to ACR50 200 mg from 24 weeks: the worst case	5	1445	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.43, 0.52]
9.1 Analysis in the worst case. All missing values did not reach ACR50 in certolizumab group and did in placebo group	5	1445	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.43, 0.52]

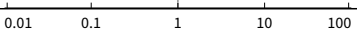
Analysis 56.1. Comparison 56 Analysis of sensitivity ACR50 24 weeks, Outcome 1 Doses.

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
56.1.1 certolizumab 100 mg sc					
Yamamoto (b) 2014	32/72	4/26		4.31%	2.89[1.13,7.38]
Subtotal (95% CI)	**72**	**26**		**4.31%**	**2.89[1.13,7.38]**
Total events: 32 (Certolizumab pegol), 4 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.22(P=0.03)					
56.1.2 certolizumab 200 mg sc					
Keystone 2008	144/393	15/100		16.16%	2.44[1.5,3.96]
NCT00993317	35/85	8/42		8.36%	2.16[1.1,4.24]
Smolen 2009	80/246	4/64		4.06%	5.2[1.98,13.67]
Smolen 2015	20/96	7/98		5.73%	2.92[1.29,6.58]
Weinblatt 2012	226/851	21/212		21.38%	2.68[1.76,4.08]
Yamamoto (b) 2014	45/82	4/26		4.45%	3.57[1.42,8.97]
Subtotal (95% CI)	**1753**	**542**		**60.14%**	**2.73[2.13,3.51]**
Total events: 550 (Certolizumab pegol), 59 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.79, df=5(P=0.73); I^2=0%					
Test for overall effect: Z=7.85(P<0.0001)					
56.1.3 certolizumab 400 mg sc					
Choy 2012	22/126	7/121		5.73%	3.02[1.34,6.81]
Fleischmann 2009	25/111	4/109		3.63%	6.14[2.21,17.05]
Keystone 2008	155/390	15/99		16.32%	2.62[1.62,4.25]
Smolen 2009	81/246	4/63		4.07%	5.19[1.98,13.61]
Yamamoto (b) 2014	46/85	5/25		5.8%	2.71[1.21,6.07]
Subtotal (95% CI)	**958**	**417**		**35.55%**	**3.18[2.29,4.41]**
Total events: 329 (Certolizumab pegol), 35 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.42, df=4(P=0.49); I^2=0%					
Test for overall effect: Z=6.94(P<0.0001)					
Total (95% CI)	**2783**	**985**		**100%**	**2.89[2.38,3.51]**
Total events: 911 (Certolizumab pegol), 98 (Control)					
Heterogeneity: Tau^2=0; Chi^2=6.73, df=11(P=0.82); I^2=0%					



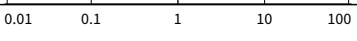
Favours control — Favours certolizumab pego

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=10.69(P<0.0001)					
Test for subgroup differences: Chi²=0.52, df=1 (P=0.77), I²=0%					



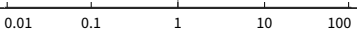
Analysis 56.2. Comparison 56 Analysis of sensitivity ACR50 24 weeks, Outcome 2 Size.

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
56.2.1 certolizumab < 200 patients					
NCT00993317	35/85	8/42		8.36%	2.16[1.1,4.24]
Smolen 2015	20/96	7/98		5.73%	2.92[1.29,6.58]
Subtotal (95% CI)	**181**	**140**		**14.09%**	**2.44[1.45,4.1]**
Total events: 55 (Certolizumab pegol), 15 (Control)					
Heterogeneity: Tau²=0; Chi²=0.31, df=1(P=0.58); I²=0%					
Test for overall effect: Z=3.37(P=0)					
56.2.2 certolizumab > 200 patients					
Choy 2012	22/126	7/121		5.73%	3.02[1.34,6.81]
Fleischmann 2009	25/111	4/109		3.63%	6.14[2.21,17.05]
Keystone 2008	155/390	15/99		16.32%	2.62[1.62,4.25]
Keystone 2008	144/393	15/100		16.16%	2.44[1.5,3.96]
Smolen 2009	80/246	4/64		4.06%	5.2[1.98,13.67]
Smolen 2009	81/246	4/63		4.07%	5.19[1.98,13.61]
Weinblatt 2012	226/851	21/212		21.38%	2.68[1.76,4.08]
Yamamoto (b) 2014	46/85	5/25		5.8%	2.71[1.21,6.07]
Yamamoto (b) 2014	45/82	4/26		4.45%	3.57[1.42,8.97]
Yamamoto (b) 2014	32/72	4/26		4.31%	2.89[1.13,7.38]
Subtotal (95% CI)	**2602**	**845**		**85.91%**	**2.97[2.41,3.67]**
Total events: 856 (Certolizumab pegol), 83 (Control)					
Heterogeneity: Tau²=0; Chi²=5.91, df=9(P=0.75); I²=0%					
Test for overall effect: Z=10.16(P<0.0001)					
Total (95% CI)	**2783**	**985**		**100%**	**2.89[2.38,3.51]**
Total events: 911 (Certolizumab pegol), 98 (Control)					
Heterogeneity: Tau²=0; Chi²=6.73, df=11(P=0.82); I²=0%					
Test for overall effect: Z=10.69(P<0.0001)					
Test for subgroup differences: Chi²=0.47, df=1 (P=0.49), I²=0%					



Analysis 56.3. Comparison 56 Analysis of sensitivity ACR50 24 weeks, Outcome 3 Use of MTX.

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
56.3.1 With MTX					



Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Choy 2012	22/126	7/121		5.73%	3.02[1.34,6.81]
Keystone 2008	144/393	15/100		16.16%	2.44[1.5,3.96]
Keystone 2008	155/390	15/99		16.32%	2.62[1.62,4.25]
NCT00993317	35/85	8/42		8.36%	2.16[1.1,4.24]
Smolen 2009	80/246	4/64		4.06%	5.2[1.98,13.67]
Smolen 2009	81/246	4/63		4.07%	5.19[1.98,13.61]
Weinblatt 2012	226/851	21/212		21.38%	2.68[1.76,4.08]
Subtotal (95% CI)	**2337**	**701**		**76.08%**	**2.77[2.21,3.46]**
Total events: 743 (Certolizumab pegol), 74 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.27, df=6(P=0.64); I^2=0%					
Test for overall effect: Z=8.94(P<0.0001)					
56.3.2 Without MTX					
Fleischmann 2009	25/111	4/109		3.63%	6.14[2.21,17.05]
Smolen 2015	20/96	7/98		5.73%	2.92[1.29,6.58]
Yamamoto (b) 2014	46/85	5/25		5.8%	2.71[1.21,6.07]
Yamamoto (b) 2014	45/82	4/26		4.45%	3.57[1.42,8.97]
Yamamoto (b) 2014	32/72	4/26		4.31%	2.89[1.13,7.38]
Subtotal (95% CI)	**446**	**284**		**23.92%**	**3.32[2.23,4.95]**
Total events: 168 (Certolizumab pegol), 24 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.86, df=4(P=0.76); I^2=0%					
Test for overall effect: Z=5.91(P<0.0001)					
Total (95% CI)	**2783**	**985**		**100%**	**2.89[2.38,3.51]**
Total events: 911 (Certolizumab pegol), 98 (Control)					
Heterogeneity: Tau^2=0; Chi^2=6.73, df=11(P=0.82); I^2=0%					
Test for overall effect: Z=10.69(P<0.0001)					
Test for subgroup differences: Chi^2=0.62, df=1 (P=0.43), I^2=0%					

Favours control 0.01 0.1 1 10 100 Favours certolizumab pego

Analysis 56.4. Comparison 56 Analysis of sensitivity ACR50 24 weeks, Outcome 4 Population.

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
56.4.1 Asian trials					
NCT00993317	35/85	8/42		8.36%	2.16[1.1,4.24]
Yamamoto (b) 2014	46/85	5/25		5.8%	2.71[1.21,6.07]
Yamamoto (b) 2014	32/72	4/26		4.31%	2.89[1.13,7.38]
Yamamoto (b) 2014	45/82	4/26		4.45%	3.57[1.42,8.97]
Subtotal (95% CI)	**324**	**119**		**22.93%**	**2.66[1.77,4]**
Total events: 158 (Certolizumab pegol), 21 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.8, df=3(P=0.85); I^2=0%					
Test for overall effect: Z=4.72(P<0.0001)					
56.4.2 Other trials					
Choy 2012	22/126	7/121		5.73%	3.02[1.34,6.81]
Fleischmann 2009	25/111	4/109		3.63%	6.14[2.21,17.05]
Keystone 2008	155/390	15/99		16.32%	2.62[1.62,4.25]

Favours control 0.01 0.1 1 10 100 Favours certolizumab pego

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Keystone 2008	144/393	15/100		16.16%	2.44[1.5,3.96]
Smolen 2009	81/246	4/63		4.07%	5.19[1.98,13.61]
Smolen 2009	80/246	4/64		4.06%	5.2[1.98,13.67]
Smolen 2015	20/96	7/98		5.73%	2.92[1.29,6.58]
Weinblatt 2012	226/851	21/212		21.38%	2.68[1.76,4.08]
Subtotal (95% CI)	**2459**	**866**		**77.07%**	**2.96[2.37,3.7]**
Total events: 753 (Certolizumab pegol), 77 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.71, df=7(P=0.57); I^2=0%					
Test for overall effect: Z=9.6(P<0.0001)					
Total (95% CI)	**2783**	**985**		**100%**	**2.89[2.38,3.51]**
Total events: 911 (Certolizumab pegol), 98 (Control)					
Heterogeneity: Tau^2=0; Chi^2=6.73, df=11(P=0.82); I^2=0%					
Test for overall effect: Z=10.69(P<0.0001)					
Test for subgroup differences: Chi^2=0.2, df=1 (P=0.65), I^2=0%					

Favours control 0.01 0.1 1 10 100 Favours certolizumab pego

Analysis 56.5. Comparison 56 Analysis of sensitivity ACR50 24 weeks, Outcome 5 Duration of previous disease.

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
56.5.1 Long previous disease duration (9 years or more)					
Choy 2012	22/126	7/121		7.19%	3.02[1.34,6.81]
Fleischmann 2009	25/111	4/109		4.55%	6.14[2.21,17.05]
Subtotal (95% CI)	**237**	**230**		**11.75%**	**4.02[2.02,7.98]**
Total events: 47 (Certolizumab pegol), 11 (Control)					
Heterogeneity: Tau^2=0.03; Chi^2=1.15, df=1(P=0.28); I^2=13.16%					
Test for overall effect: Z=3.97(P<0.0001)					
56.5.2 Short previous disease duration (less than 7 years)					
Keystone 2008	144/393	15/100		20.27%	2.44[1.5,3.96]
Keystone 2008	155/390	15/99		20.47%	2.62[1.62,4.25]
NCT00993317	35/85	8/42		10.49%	2.16[1.1,4.24]
Smolen 2009	80/246	4/64		5.1%	5.2[1.98,13.67]
Smolen 2009	81/246	4/63		5.11%	5.19[1.98,13.61]
Weinblatt 2012	226/851	21/212		26.82%	2.68[1.76,4.08]
Subtotal (95% CI)	**2211**	**580**		**88.25%**	**2.75[2.18,3.47]**
Total events: 721 (Certolizumab pegol), 67 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.23, df=5(P=0.52); I^2=0%					
Test for overall effect: Z=8.53(P<0.0001)					
Total (95% CI)	**2448**	**810**		**100%**	**2.87[2.31,3.57]**
Total events: 768 (Certolizumab pegol), 78 (Control)					
Heterogeneity: Tau^2=0; Chi^2=6.52, df=7(P=0.48); I^2=0%					
Test for overall effect: Z=9.47(P<0.0001)					
Test for subgroup differences: Chi^2=1.05, df=1 (P=0.3), I^2=4.99%					

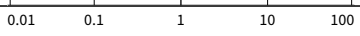
Favours control 0.01 0.1 1 10 100 Favours certolizumab pego

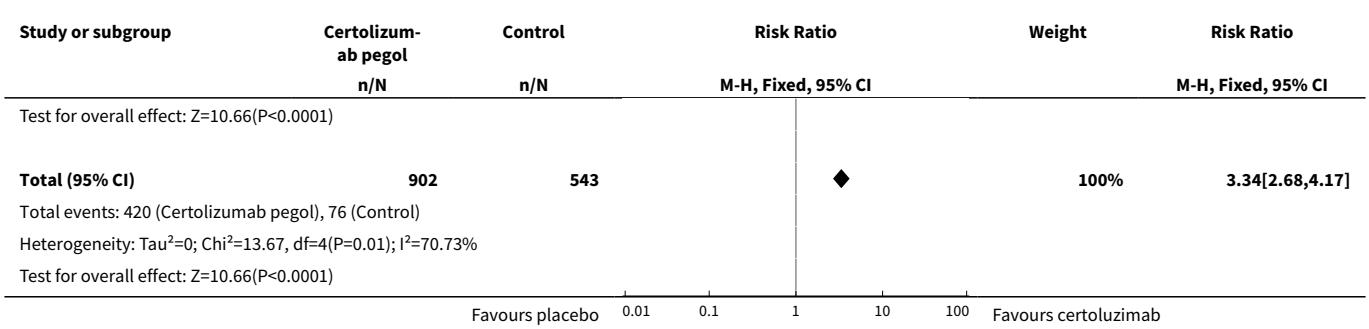
Analysis 56.6. Comparison 56 Analysis of sensitivity ACR50 24 weeks, Outcome 6 Published vs unpublished studies.

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
56.6.1 Published studies					
Choy 2012	22/126	7/121		5.73%	3.02[1.34,6.81]
Fleischmann 2009	25/111	4/109		3.63%	6.14[2.21,17.05]
Keystone 2008	155/390	15/99		16.32%	2.62[1.62,4.25]
Keystone 2008	144/393	15/100		16.16%	2.44[1.5,3.96]
Smolen 2009	81/246	4/63		4.07%	5.19[1.98,13.61]
Smolen 2009	80/246	4/64		4.06%	5.2[1.98,13.67]
Weinblatt 2012	226/851	21/212		21.38%	2.68[1.76,4.08]
Subtotal (95% CI)	**2363**	**768**		**71.34%**	**2.97[2.36,3.73]**
Total events: 733 (Certolizumab pegol), 70 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.71, df=6(P=0.46); I^2=0%					
Test for overall effect: Z=9.25(P<0.0001)					
56.6.2 Unpublished studies					
NCT00993317	35/85	8/42		8.36%	2.16[1.1,4.24]
Smolen 2015	20/96	7/98		5.73%	2.92[1.29,6.58]
Yamamoto (b) 2014	46/85	5/25		5.8%	2.71[1.21,6.07]
Yamamoto (b) 2014	45/82	4/26		4.45%	3.57[1.42,8.97]
Yamamoto (b) 2014	32/72	4/26		4.31%	2.89[1.13,7.38]
Subtotal (95% CI)	**420**	**217**		**28.66%**	**2.71[1.89,3.9]**
Total events: 178 (Certolizumab pegol), 28 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.83, df=4(P=0.93); I^2=0%					
Test for overall effect: Z=5.38(P<0.0001)					
Total (95% CI)	**2783**	**985**		**100%**	**2.89[2.38,3.51]**
Total events: 911 (Certolizumab pegol), 98 (Control)					
Heterogeneity: Tau^2=0; Chi^2=6.73, df=11(P=0.82); I^2=0%					
Test for overall effect: Z=10.69(P<0.0001)					
Test for subgroup differences: Chi^2=0.17, df=1 (P=0.68), I^2=0%					

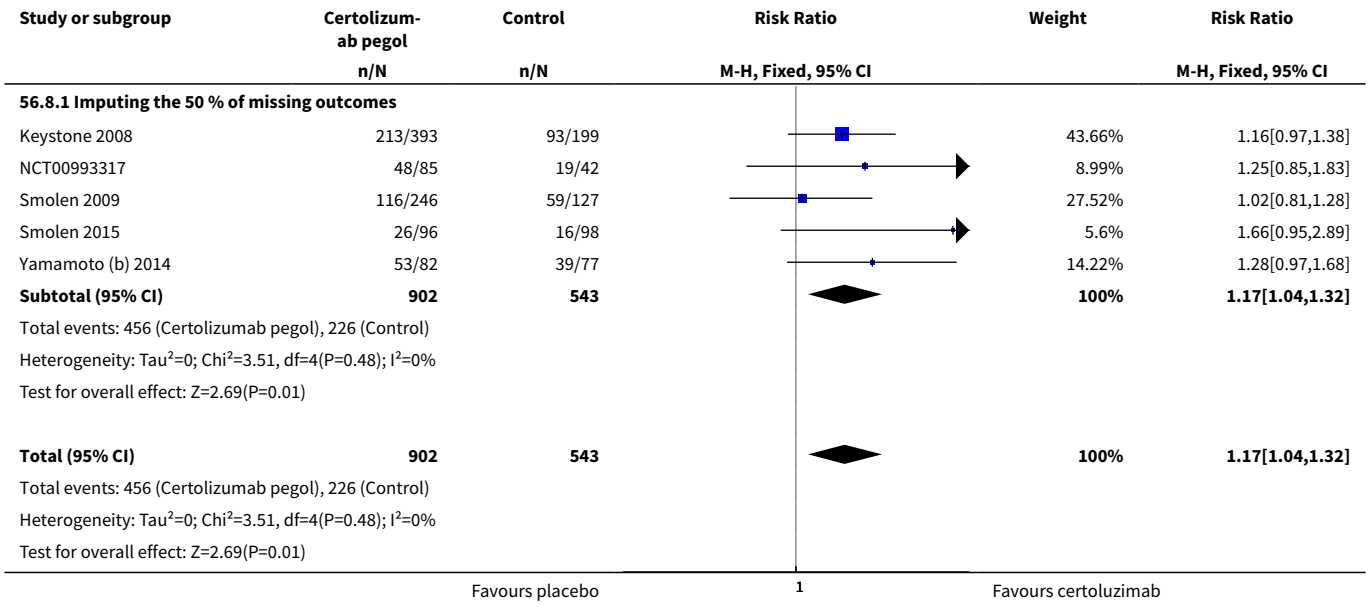
Analysis 56.7. Comparison 56 Analysis of sensitivity ACR50 24 weeks, Outcome 7 Imputing to ACR50 200 mg from 24 missing values with same proportion as reported outcomes.

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
56.7.1 Imputing missing values with same proportion as reported outcomes					
Keystone 2008	195/393	27/199		39.07%	3.66[2.54,5.27]
NCT00993317	45/85	12/42		17.51%	1.85[1.1,3.11]
Smolen 2009	103/246	7/127		10.06%	7.6[3.64,15.84]
Smolen 2015	23/96	8/98		8.63%	2.93[1.38,6.24]
Yamamoto (b) 2014	54/82	22/77		24.73%	2.3[1.57,3.39]
Subtotal (95% CI)	**902**	**543**		**100%**	**3.34[2.68,4.17]**
Total events: 420 (Certolizumab pegol), 76 (Control)					
Heterogeneity: Tau^2=0; Chi^2=13.67, df=4(P=0.01); I^2=70.73%					

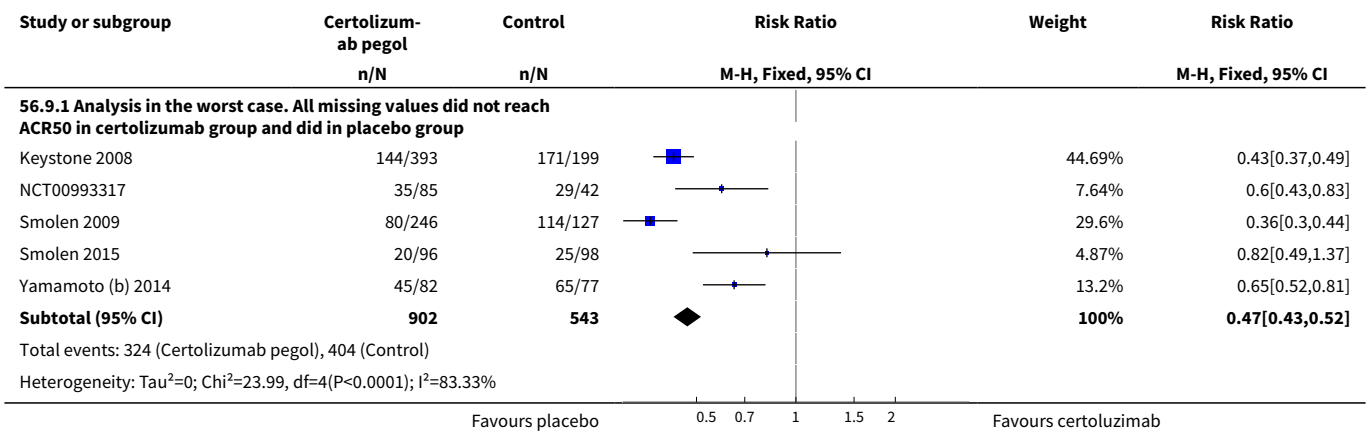


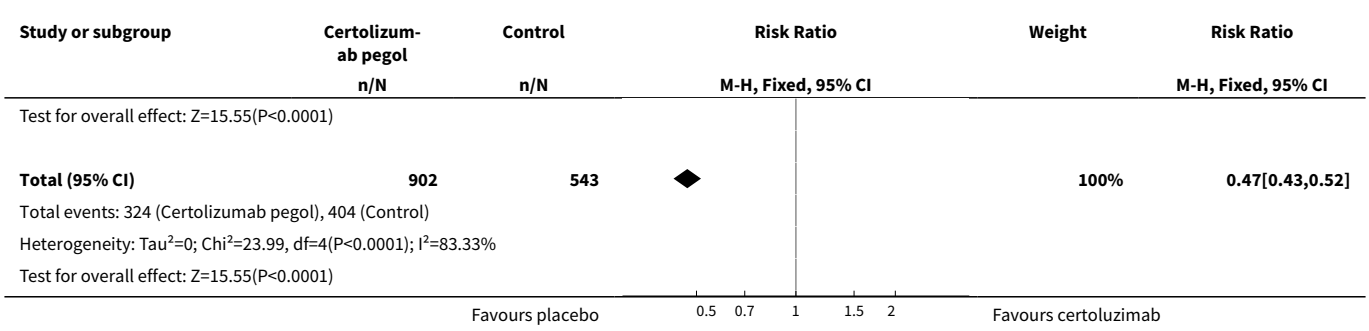


Analysis 56.8. Comparison 56 Analysis of sensitivity ACR50 24 weeks, Outcome 8 Imputing to ACR50 200 mg from 24 weeks 50 % of missing outcomes.



Analysis 56.9. Comparison 56 Analysis of sensitivity ACR50 24 weeks, Outcome 9 Imputing to ACR50 200 mg from 24 weeks: the worst case.



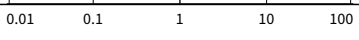


Comparison 57. Analysis of sensitivity ACR50 52 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Doses	3	2180	Risk Ratio (M-H, Random, 95% CI)	1.69 [1.22, 2.33]
1.1 certolizumab 200 mg sc	3	1691	Risk Ratio (M-H, Random, 95% CI)	1.48 [1.11, 1.96]
1.2 certolizumab 400 mg sc	1	489	Risk Ratio (M-H, Random, 95% CI)	2.62 [1.62, 4.25]
2 Size	3	2180	Risk Ratio (M-H, Random, 95% CI)	1.69 [1.22, 2.33]
2.1 certolizumab <200 patients	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 certolizumab >200 patients	3	2180	Risk Ratio (M-H, Random, 95% CI)	1.69 [1.22, 2.33]
3 Use of MTX	3	2180	Risk Ratio (M-H, Random, 95% CI)	1.69 [1.22, 2.33]
3.1 Use of MTX	3	2180	Risk Ratio (M-H, Random, 95% CI)	1.69 [1.22, 2.33]
3.2 Without MTX	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Population	3	2180	Risk Ratio (M-H, Random, 95% CI)	1.69 [1.22, 2.33]
4.1 Asian trials	1	319	Risk Ratio (M-H, Random, 95% CI)	1.41 [1.17, 1.68]
4.2 Other trials	2	1861	Risk Ratio (M-H, Random, 95% CI)	1.94 [1.01, 3.72]
5 Duration of previous disease	3	2180	Risk Ratio (M-H, Random, 95% CI)	1.69 [1.22, 2.33]
5.1 Long previous disease duration (6 years or more)	1	982	Risk Ratio (M-H, Random, 95% CI)	2.58 [1.83, 3.62]
5.2 Short previous disease duration (less than 1 year)	2	1198	Risk Ratio (M-H, Random, 95% CI)	1.29 [1.10, 1.50]

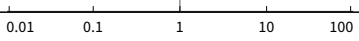
Analysis 57.1. Comparison 57 Analysis of sensitivity ACR50 52 weeks, Outcome 1 Doses.

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
57.1.1 certolizumab 200 mg sc					
Atsumi 2016	116/161	81/158		30.31%	1.41[1.17,1.68]
Emery 2015	405/660	112/219		31.4%	1.2[1.04,1.38]
Keystone 2008	149/393	15/100		19.12%	2.53[1.56,4.1]
Subtotal (95% CI)	**1214**	**477**		**80.83%**	**1.48[1.11,1.96]**
Total events: 670 (Certolizumab pegol), 208 (Control)					
Heterogeneity: Tau^2=0.05; Chi^2=9.68, df=2(P=0.01); I^2=79.34%					
Test for overall effect: Z=2.7(P=0.01)					
57.1.2 certolizumab 400 mg sc					
Keystone 2008	155/390	15/99		19.17%	2.62[1.62,4.25]
Subtotal (95% CI)	**390**	**99**		**19.17%**	**2.62[1.62,4.25]**
Total events: 155 (Certolizumab pegol), 15 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.92(P<0.0001)					
Total (95% CI)	**1604**	**576**		**100%**	**1.69[1.22,2.33]**
Total events: 825 (Certolizumab pegol), 223 (Control)					
Heterogeneity: Tau^2=0.08; Chi^2=18.63, df=3(P=0); I^2=83.89%					
Test for overall effect: Z=3.17(P=0)					
Test for subgroup differences: Chi^2=4.04, df=1 (P=0.04), I^2=75.26%					

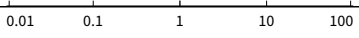


Analysis 57.2. Comparison 57 Analysis of sensitivity ACR50 52 weeks, Outcome 2 Size.

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
57.2.1 certolizumab <200 patients					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Certolizumab pegol), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
57.2.2 certolizumab >200 patients					
Atsumi 2016	116/161	81/158		30.31%	1.41[1.17,1.68]
Emery 2015	405/660	112/219		31.4%	1.2[1.04,1.38]
Keystone 2008	149/393	15/100		19.12%	2.53[1.56,4.1]
Keystone 2008	155/390	15/99		19.17%	2.62[1.62,4.25]
Subtotal (95% CI)	**1604**	**576**		**100%**	**1.69[1.22,2.33]**
Total events: 825 (Certolizumab pegol), 223 (Control)					
Heterogeneity: Tau^2=0.08; Chi^2=18.63, df=3(P=0); I^2=83.89%					
Test for overall effect: Z=3.17(P=0)					
Total (95% CI)	**1604**	**576**		**100%**	**1.69[1.22,2.33]**
Total events: 825 (Certolizumab pegol), 223 (Control)					



Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0.08; Chi²=18.63, df=3(P=0); I²=83.89%					
Test for overall effect: Z=3.17(P=0)					
Test for subgroup differences: Not applicable					

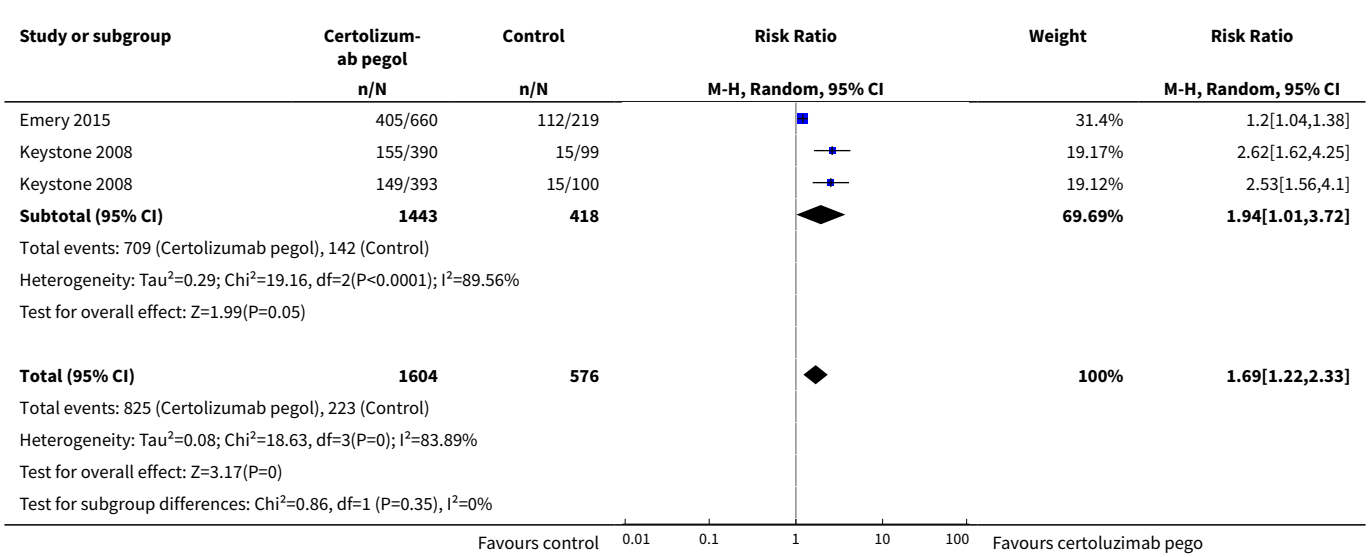


Analysis 57.3. Comparison 57 Analysis of sensitivity ACR50 52 weeks, Outcome 3 Use of MTX.

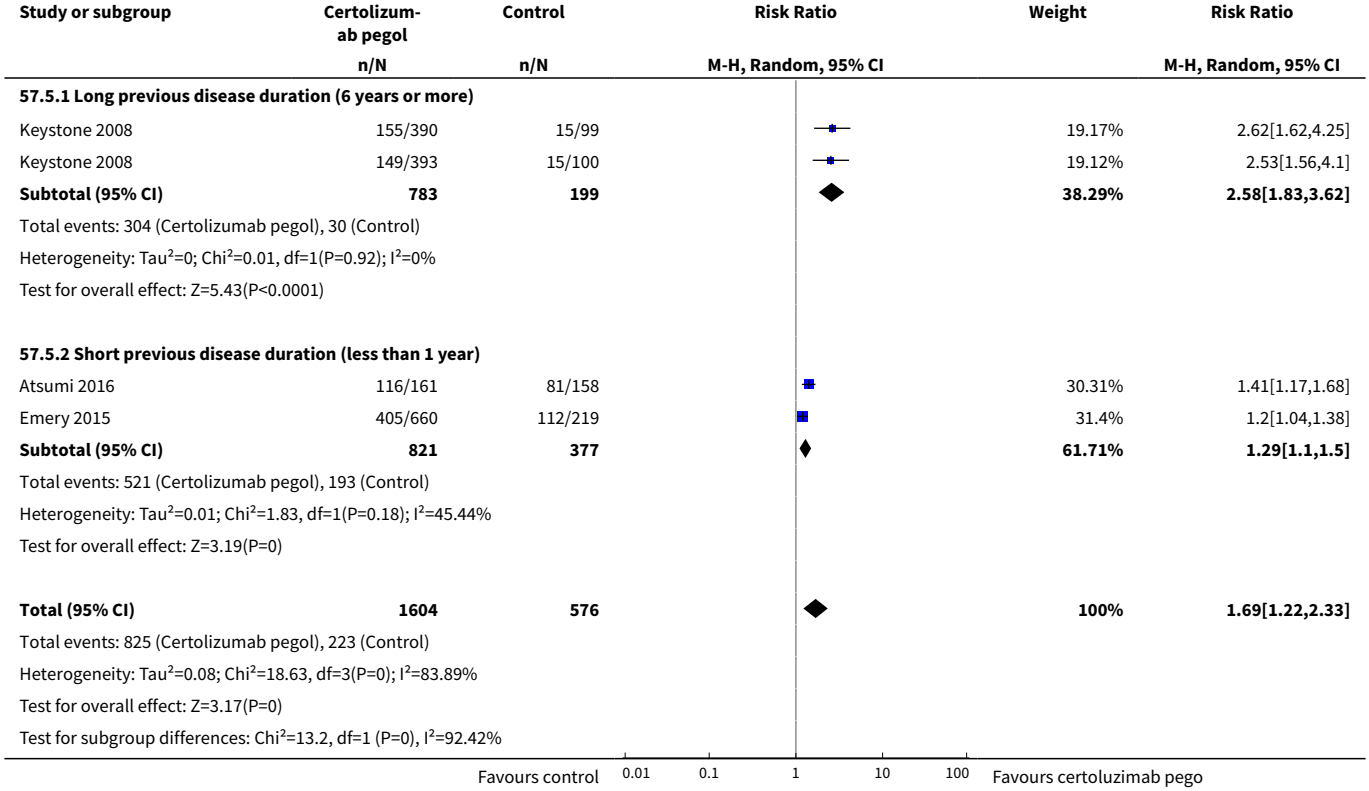
Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
57.3.1 Use of MTX					
Atsumi 2016	116/161	81/158		30.31%	1.41[1.17,1.68]
Emery 2015	405/660	112/219		31.4%	1.2[1.04,1.38]
Keystone 2008	155/390	15/99		19.17%	2.62[1.62,4.25]
Keystone 2008	149/393	15/100		19.12%	2.53[1.56,4.1]
Subtotal (95% CI)	**1604**	**576**		**100%**	**1.69[1.22,2.33]**
Total events: 825 (Certolizumab pegol), 223 (Control)					
Heterogeneity: Tau²=0.08; Chi²=18.63, df=3(P=0); I²=83.89%					
Test for overall effect: Z=3.17(P=0)					
57.3.2 Without MTX					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Certolizumab pegol), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**1604**	**576**		**100%**	**1.69[1.22,2.33]**
Total events: 825 (Certolizumab pegol), 223 (Control)					
Heterogeneity: Tau²=0.08; Chi²=18.63, df=3(P=0); I²=83.89%					
Test for overall effect: Z=3.17(P=0)					
Test for subgroup differences: Not applicable					

Analysis 57.4. Comparison 57 Analysis of sensitivity ACR50 52 weeks, Outcome 4 Population.

Study or subgroup	Certolizumab pegol n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
57.4.1 Asian trials					
Atsumi 2016	116/161	81/158		30.31%	1.41[1.17,1.68]
Subtotal (95% CI)	**161**	**158**		**30.31%**	**1.41[1.17,1.68]**
Total events: 116 (Certolizumab pegol), 81 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.71(P=0)					
57.4.2 Other trials					



Analysis 57.5. Comparison 57 Analysis of sensitivity ACR50 52 weeks, Outcome 5 Duration of previous disease.



ADDITIONAL TABLES

Table 1. Contribution of trials

	Update 2014		Update 2016	
	Benefit (B)	**Harm (H)**	**Benefit (B)**	**Harm (H)**
Atsumi 2016	-	-	B	H
CDP870-004 2001	B	H	B	-
Choy 2002	-	H	-	H
Choy 2012	B	H	B	H
Emery 2015	-	-	B	H
Fleischmann 2009	B	H	B	H
Keystone 2008	B	H	B	H
NCT00993317	B	H	B	H
Smolen 2009	B	H	B	H
Smolen 2015	B	H	B	H
Weinblatt 2012	B	H	B	H
Yamamoto (a) 2014	B	H	B	H
Yamamoto (b) 2014	B	H	B	H
Østergaard 2015	-	-	-	H
Total trials	**10**	**11**	**12**	**14**
Total pooled	**9**	**9**	**11**	**13**

The data from the two phase II studies (CDP870-004 2001; Choy 2002) were not pooled with the rest of the studies due to the different follow-ups and doses used.

Table 2. Demographic and disease characteristics of the included Phase III trials

Study	Atsumi 2016 n = 319	Choy 2012n = 247	Emery 2015 n = 879	Fleis-chmann 2009n = 220	Keystone 2008n = 982	NCT00993317 n = 127	Smolen 2009 n = 619	Smolen 2015n = 194	Wein-blatt 2012n = 1063	Ya-mamo-to (a) 2014n = 230	Ya-mamo-to (b) 2014n = 316	Øster-gaard 2015n = 41
Age (years) Mean ± (SD)	CZP 200 mg plus MTX 49.4 (10.6) Placebo plus MTX <49.0(10.3)	CZP 400 mg plus MTX 53 (12.0) Place-bo plus MTX 55.6 (11.7)	CZP 200mg plus MTX 50.4(13.6) Placebo plus MTX 51.2(13)	53.8 (12.2) CZP 400 mg 52.7 (12.7) Place-bo 54.0 (11.6)	52.0 (11.6) CZP 200 mg plus MTX 51.4 (11.6) CZP 400 mg plus MTX 52.4 (11.7) Placebo plus MTX 52.2 (11.2)	CZP 200 mg plus MTX 18 - 65 years = 72; > 65 years = 13 Place-bo plus MTX 18 - 65 years = 38; > 65 years = 4	51.9 (11.5) CZP 200 mg plus MTX 52.2 (11.1) CZP 400 mg plus MTX 51.9 (11.8) Placebo plus MTX 51.5 (11.8)	CZP 200 mg 53.6 (11.9) Place-bo 54.0 (12.4)	55.1 (12.49) CZP 200 mg 55.4 (12.4) Place-bo 53.9 (12.7)	55.7 (10.0) CZP 200 mg 56.0 (10.2) Placebo 55.4 (9.8)	Total 53.0 (11.0) CZP 100 mg plus MTX 54.3 (10.6) CZP 200 mg plus MTX 50.6 (11.4) CZP 400 mg plus MTX 55.4 (10.3) Place-bo plus MTX51.9 (11.1)	CZP 400 mg 51.3(12.6) Place-bo 48.3 (14.4)
Fol-low-up	24 and 52 weeks	24 weeks	52 weeks	24 weeks	52 weeks	24 weeks	24 weeks	24 weeks	12 weeks	12 and 24 weeks	12 and 24 weeks	2 weeks
Women n (%)	CZP 200 mg plus MTX 129 (81.1%) Place-bo plus MTX 127 (80.9%)	CZP 400mg plus MTX 72% Placebo plus MTX 66.1%	CZP 200 mg plus MTX 497 (75.9%) Placebo plus MTX 170 (79.8%)	184 (83.6%)	817 (83.2%) CZP 200 mg 324 (82.4%) CZP 400 mg 326 (83.6%) Place-bo 167 (83.9%)	112 (88.2%) CZP 200 mg 75 (59.1%) Place-bo 37 (29.13%)	505 (81.6%) CZP 200 mg 206 (83.7%) CZP 400 mg 192 (78%) Place-bo 107 (84.3%)	156 (80.4%) CZP 200 mg 81 (41.8%) Place-bo 75 (38.7%)	829 (78%) CZP 200 mg 660 (62.1%) Place-bo 169 (15.9%)	171 (74.3%) CZP 200 mg 83 (36.1%) Place-bo 88 (38.3%)	CZP 100 mg plus MTX58 (18.4%) CZP 200 mg plus MTX69 (21.8%) CZP 400 mg plus MTX69 (21.8%)	CZP 400 mg 81.5% Placebo 76.9%

Table 2. Demographic and disease characteristics of the included Phase III trials *(Continued)*

											Place-bo plus MTX66 (20.9%)	
Disease duration (years) Mean (SD)	Months CZP 200 mg plus MTX 4 ± 2.9 Placebo plus MTX 4.3 ± 2.8	CZP plus MTX 9.4 (7.5) Placebo plus MTX 9.9 (7.8)	Months CZP 200 mg plus MTX 2.9 (4.6) Placebo plus MTX 2.9 (2.9)	9.5 (NC)CZP 400 mg 8.7 (8.2) Placebo 10.4 (9.6)	6.1 (4.3) CZP 200 mg 6.1 (4.2) CZP 400 mg 6.2 (4.4) Placebo 6.2 (4.4)	CZP 200 mg 6.4 (4.2) Placebo 6 (5.1)	6.2 (4.2) CZP 200 mg 6.1 (4.1) CZP 400 mg 6.5 (4.3) Placebo 5.6 (3.9)	-	6.2 (4.2) CZP 200 mg 8.6 (8.8) Placebo 8.9 (9.1)	-	-	CZP 400 mg 4.8 (3.8) Placebo 5.9 (5.1)
RF positive (^{3} 14 IU/ml) (%)	CZP 200 mg plus MTX 153 (96.2%) Placebo plus MTX 146 (93%)	78%	CZP 200 mg plus MTX 634 (96.8) Placebo plus MTX 206 (96.7)	100% CZP 400 mg 110 (99.9%) Place-bo 109 (100%)	81.8% CZP 200 mg 312 (79.6%) CZP 400 mg 326 (83.6%) Place-bo 164 (82.8%)	-	76.9% CZP 200 mg 186 (77.5%) CZP 400 mg 179 (75.5%) Placebo 97 (78.2%)	-	CZP 200 mg 555 (73.9%) Place-bo 137 (78.2%)	-	-	-
MTX concomitant dose (mg/week) Mean(SD)	CZP 200 mg plus MTX 11.6 (3) Placebo plus MTX 11.6 (2.7)	CZP plus MTX 16.9 (3.9) Placebo plus MTX 16.6 (3.6)	-	N/A	13.6 CZP 200mg 13.6 (4.3) CZP 400 mg 13.6 (4) Place-bo 13.4 (4.2)	CZP 200 mg 13.4 (2.5) Placebo 13.6 (2.8)	12.5 CZP 200 mg 12.5 (3.6) CZP 400 mg 12.6 (3.7) Placebo 12.2 (3.3)	N/A	CZP 200 mg 17.2 (5.7) Placebo 16.3 (5.3)	N/A	N/A	Only percentage of concomitant use CZP 400 mg 85.2% Placebo 92.3%
Number of previous DMARDS Mean (SD)	MTX-naïve CZP 200 mg plus MTX 31 (19.5%)	1.3	DMARDS-naïve	2.0 CZP 400 mg 2.0 (1.2) Placebo 2.0 (1.3)	1.3 CZP 200 mg 1.3 (1.3) CZP 400 mg 1.3 (1.3)	1.2 CZP 200 mg 3.3 (1.3) Placebo 3.2 (1.5)	1.2 CZP 200 mg 1.2 (1.3) CZP 400 mg 1.3 (1.2)	-	-	-	-	-

Table 2. Demographic and disease characteristics of the included Phase III trials *(Continued)*

	Placebo plus MTX 19 (18.5%)				Placebo 1.4 (1.4)		Placebo 1.2 (1.2)					
Tender Joint count Mean (0 - 66) (SD)	CZP 200 mg plus MTX 8.4 ± 6.1 Placebo plus MTX 8.9 ± 6.5	CZP plus MTX 29 (11.6) Placebo plus MTX 31 (12.9)	CZP 200 mg plus MTX 15.6 (6.5) Placebo plus MTX 16.2 (6.5)	29.0 (13.13)	30.7 (12.9)	CZP 200 mg 25.04 (14.94) Placebo 25.05 (14.61)	30.2 (14.0)		CZP 200 mg 14.7 (6.6) Placebo 14.7 (6.6)			CZP 400 mg 13 (7.8) Placebo 13.8 (7.4)
Swollen Joint Count Mean (0 - 66) (SD)	-	CZP plus MTX 22.8 (9.4) Placebo plus MTX 22.2 (9.6)	CZP 200 mg plus MTX 12.4 (5.5) Placebo plus MTX 13 (5.6)	20.5 (9.67)	21.5 (9.8)	CZP 200 mg 15.96 (8.86) Placebo 17.31 (11.18)	21.0 (9.8)	-	CZP 200 mg 11.8 (5.6) Placebo 11.1 (5.2)	-	-	CZP 400 mg 10 (6.4) Placebo 9.9 (6.3)
HAQ-DI mean (SD)	CZP 200 mg plus MTX 1.0 ± 0.6 Placebo plus MTX 1.1 ± 0.7	CZP plus MTX 1.4 (0.6) Placebo plus MTX 1.5 (0.7)	CZP 200 mg plus MTX 1.6 (0.6) Placebo plus MTX 1.7 (0.7)	1.5 (0.64)	1.7 (0.60)	CZP 200 mg 1.43 (0.67) Placebo 1.53 (0.74)	1.6 (0.59)	-	CZP 200 mg 1.5 (0.6) Placebo 1.6 (0.6)	-	-	CZP 400 mg 1.2 (0.6) Placebo 1.4 (0.5)
CRP (mg/L) Geometric mean (CV)	-	CZP plus MTX 11.9 Placebo plus MTX 13.1	Median (min, max) CZP 200 mg plus MTX 11.1 (0.2, 231.1) Placebo plus MTX 10.5 (0.3, 243.2)	11.5 (NC)	14.7 (144.2)	-	13.6 (180.9)	-	CZP 200 mg 9 Placebo 10	-	-	CZP 400mg3.8 (171) Placebo 6.2 (247.5)
DAS-28 (ESR) Mean (SD)	-	6.2 (0.99)	CZP 200 mg plus MTX 6.7 (0.9) Placebo plus MTX 6.8 (0.9)	6.3 (1.00)	6.9 (0.8)	-	6.8 (0.83)	-	CZP 200 mg 6.4 (0.9) Placebo 6.4 (0.9)	-	-	CZP 400mg 5.1 (1.1) Placebo 5.3(1.2)

Notes: All randomised participants; the actual numbers vary slightly across parameters
CZP: certolizumab pegol
CV: coefficient of variation
DAS: disease activity score
DMARD: disease-modifying anti-rheumatic drug
ESR: erythrocyte sedimentation rate
IU: international units
L: litre
mg: milligrams
mL: millilitres
N/A: not applicable
NC: not calculated
RF: rheumatoid factor
SD: standard deviation
Y: years

Table 3. Flow of participants in the included Phase III trials

Study	Placebo	Certolizumab pegol 100 mg	Certolizumab pegol 200 mg	Certolizumab pegol 400 mg
Atsumi 2016	ITT n = 158Safety n = 157	-	ITT n = 161Safety n = 159	-
	Discontinued n = 15 (%) Consent withdrawn = 3 (2%) Lack of efficacy = 1 (0.06%) Adverse event = 6 (4%)Other reasons = 5 (3%) **Moved to rescue = 70 (44%)**	-	Discontinued n = 12 (7,45%) Consent withdrawn = 2 (1%) Lack of efficacy = 0 Adverse event = 9 (5%) Other reasons = 1 (0,5%) **Moved to rescue = 36 (22%)**	-
	Completed n= 73 (46.20%)	-	Completedn = 111(69%)	-
Choy 2012	ITT n = 121[a] Safety n = 119	-	-	ITT n = 126 Safety n = 124
	All withdrawn n = 56 (46.3%) Lack of efficacy = 45 (37.2%) Adverse event = 6 (5%) Other reasons = 5 (4.1%)	-	-	All withdrawn n = 28 (22.2%) Lack of efficacy = 16 (12.7%) Adverse event = 7 (5.6%) Other reasons = 5 (4%)
	Completed n = 65 (53.7%)	-	-	Completed n = 98 (77.8%)
	ITT n = 121[a] Safety n = 119	-	ITT n = 126[a] Safety n = 124	
Emery 2015	ITT n = 219 Safety n = 217	-	ITT n = 660 Safety n = 659	-
	All withdrawn n = 76 (35%) Lack of efficacy = 14 (6%) Adverse event = 17 (8%) Protocol violation = 6 (3%) Lost to follow-up = 6 (3%) Consent withdrawn = 15 (7%) Other reasons = 18 (8%)	-	All withdrawn n = 160 (24%) Lack of efficacy = 19 (3%) Adverse event = 51 (8%) Protocol violation = 18 (3%) Lost to follow-up = 14 (2%) Consent withdrawn = 35 (5%) Other reasons = 23 (3%)	-

Table 3. Flow of participants in the included Phase III trials *(Continued)*

	Completed n = 143 (65%)	-	Completed n = 500 (76%)	-
Fleischmann 2009	ITT n = 109 Safety n = 109	-	-	ITT n = 111 Safety n = 111
	All withdrawn n = 81 (74%) Lack of efficacy = 75 (68.8%) Adverse event = 2 (1.8%) Protocol violation = 1 (0.9%) Lost to follow-up = 3 (2.8%)	-	-	All withdrawn n = 35 (31.5%) Lack of efficacy = 24 (21.6%) Adverse event = 5 (4.5%) Protocol violation = 4 (3.6%) Consent withdrawn = 2 (1.8%)
	Completed n = 28 (25.7%)	-	-	Completed n = 76 (68.5%)
Keystone 2008	ITT n = 199 Safety n = 199	-	ITT n = 393 Safety n = 392[b]	ITT n = 390 Safety n = 389[b]
	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%)
	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%)
NCT00993317	ITT n = 42 Safety n = 42	-	ITT n = 85 Safety n = 85	-
	All withdrawn n = 21 (50%) Lack of efficacy = 18 (42%) Adverse event = 2 (4.76%) Other reasons = 1 (2.38%)	-	All withdrawn n = 25 (29.41%) Lack of efficacy = 18 (21.8%) Adverse event = 4 (4.70%) Other reasons = 3 (3.52%)	-
	Completed	-	Completed	-

Table 3. Flow of participants in the included Phase III trials *(Continued)*

	n = 21 (50%)		n = 60 (70.58%)	
Smolen 2009	ITT n = 127 Safety n = 125	-	ITT n = 246 Safety n = 248[c]	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%)
Smolen 2015	ITT n = 98Safety n = 98	-	ITT n = 96Safety n = 96	-
	All withdrawnn = 18 (18.36%) Lack of efficacy = 7 (7.14%) Adverse event = 6 (6.12 %) Other reasons = 5 (5.10%)	-	All withdrawnn = 12 (12.5%) Lack of efficacy = 2 (2.08 %) Adverse event = 6 (6.25%) Other reasons = 4 (4.16%)	-
	Completed n = 80 (81.63%)	-	Completedn = 84 (87.5%)	-
Weinblatt 2012	ITT n = 212 Safety n = 209	-	ITT n = 851 Safety n = 846	-
	All withdrawn n = 28 (13.20%) Lack of efficacy = 6 (2.83%) Adverse event = 6 (2.83%) Other reasons = 16 (7.54%)	-	All withdrawn n = 80 (9.41%) Lack of efficacy = 6 (0.70%) Adverse event = 33 (3.87%) Other reasons = 41 (4.81%)	-
	Completed n = 184 (86.79%)	-	Completed n = 771 (90.59%)	-
Yamamoto (a) 2014	ITT n = 114Safety n = 114	-	ITT n = 116Safety n = 116	-
	All withdrawnn = 96 (84.2%) Lack of efficacy = 2 (1.75%) Adverse event = 2 (1.75%) Other reasons (protocol planned n = 88) = 94 (82%)	-	All withdrawnn = 34 (29.31%) Lack of efficacy = 0 (0%) Adverse event = 8 (6.9%) Other reasons (protocol planned n = 24) = 26 (22.4%)	-

Table 3. Flow of participants in the included Phase III trials *(Continued)*

	Completed n = 18 (15.8%)	-	Completedn = 82 (70.69%)	
Yamamoto (b) 2014	ITT n = 77 Safety n = 77	ITT n = 72 Safety n = 72	ITT n = 82 Safety n = 82	ITT n = 85 Safety n = 85
	All withdrawn n = 52 (67.53%) Lack of efficacy = 2 (2.98%) Adverse event = 3 (3.90%) Other reasons (Protocol planned withdrawal = 45) = 47 (61.04%)	All withdrawn n = 21 (29.17%) Lack of efficacy = 3 (4.17%) Adverse event = 0 (0%) Other reasons (Protocol planned withdrawal = 14) = 18 (25%)	All withdrawn n = 16 (19.51%) Lack of efficacy = 1 (1.22%) Adverse event = 3 (3.66%) Other reasons (Protocol planned withdrawal = 11) = 12 (14.63%)	All withdrawn n = 20 (23.53%) Lack of efficacy = 0 (0%) Adverse event = 7 (8.23%) Other reasons (Protocol planned withdrawal = 11) = 13 (15.29%)
	Completed n = 25 (32.47%)	Completed n = 51 (70.83%)	Completed n = 66 (80.49%)	Completed n = 65 (76.47%)
Østergaard 2015	ITT n = 13 Safety at 12 weeks n = 13	-	ITT n = 27 Safety at 12 weeks n = 27	-
	Only the data obtained at week 2 were usable		Only the data obtained at week 2 were usable	

[a] Manufacturers reported efficacy calculations from placebo n = 119 and certolizumab pegol n = 124.
[b] Two participants in each treatment group did not take study medication.
[c]Two participants in the placebo group received certolizumab pegol and were included for safety in the 200 mg group. (d)

Table 4. Beneficial ACR50

	Follow-up	Doses/study	Response rate certolizumab pegol	Response rate placebo	RR (CI 95%)	% RD	NNTB
ACR50							
Analysis 2.1	24 weeks	200 mg: Smolen 2015; Yamamoto (b) 2014; NCT00993317; Keystone 2008; Smolen 2009	36%	9%	3.80 (2.42 to 5.95)	27 (20 to 33)	4 (3 to 8)
Analysis 3.1	24 weeks	400 mg: Choy 2012; Fleischmann 2009; Yamamoto (b) 2014; Keystone 2008; Smolen 2009	34%	7%	4.65 (3.09 to 6.99)	27 (17 to 34)	4 (3 to 7)
Analysis 4.1	52 weeks	200 mg: Atsumi 2016; Emery 2015; Keystone 2008	55%	36%	1.54 (1.38 to 1.73)	20 (15 to 24)	5 (3 to 7)
Analysis 5.1	52 weeks	400 mg: Keystone 2008	40%	8%	5.27 (3.19 to 8.71)	32 (26 to 38)	3 (2 to 6)

Table 5. Health-related quality of life

	Follow-up	Doses/study	Mean differences
HAQ (0 - 3) (Best = 0; Worst = 3)			
Analysis 7.1	24 weeks	200 mg/ Smolen 2015; NCT00993317; Keystone 2008; Smolen 2009	-0.35 (-0.43 to -0.26)
Analysis 7.2	24 weeks	400 mg/ Choy 2012; Fleischmann 2009; Keystone 2008; Smolen 2009	-0.38 (-0.48 to -0.28)
Analysis 9.1.1	52 weeks	200 mg/ Emery 2015; Keystone 2008	-0.27 (-0.35 to -0.20)
Analysis 9.1.2	52 weeks	400 mg/ Keystone 2008	-0.45 (-0.57 to -0.33)
SF-36 PCS (0 - 100) (Worst = 0; Best = 100)			
Analysis 10.1	24 weeks	200 mg/ Smolen 2015; Keystone 2008; Smolen 2009	5.03 (3.90 to 6.16)
Analysis 10.2	24 weeks	400 mg/ Choy 2012; Keystone 2008; Smolen 2009	5.54 (4.11 to 6.97)
SF-36 MCS (0 - 100) (Worst = 0; Best = 100)			
Analysis 11.1	24 weeks	200 mg/ Keystone 2008; Smolen 2009	4.18 (2.70 to 5.66)
Analysis 11.2	24 weeks	400 mg/ Choy 2012; Keystone 2008; Smolen 2009	4.05 (2.77 to 5.34)
SF-36 PCS			
Analysis 12.1	52 weeks	200 mg/ Keystone 2008	6.06 (4.59 to 7.53)
Analysis 12.2	52 weeks	400 mg/ Keystone 2008	6.88 (5.42 to 8.34)
SF-36 MCS (0 - 100) (Worst = 0; Best = 100)			
	52 weeks	200 mg/ Keystone 2008	4.3 (2.4 to 6.2)
	52 weeks	400 mg/ Keystone 2008	4.3 (2.4 to 6.2)
Participants' VAS score (0 - 100)			
Analysis 52.1	24 weeks	200 mg/ Keystone 2008; Smolen 2009	-20.48 (-24.26 to -16.69)
		400 mg/ Fleischmann 2009; Keystone 2008; Smolen 2009	-21.35 (-25.08 to -17.61)
Analysis 53.1	52 weeks	200 mg/ Keystone 2008	-22.20 (-27.37 to -17.03)
		400 mg/ Keystone 2008	-24.70 (-29.73 to -19.67)
DAS-28 remission (< 2.6)			
Analysis 21.2	24 weeks	200 mg/ Smolen 2015; Yamamoto (a) 2014; Atsumi 2016; Emery 2015; Keystone 2008; Smolen 2009	3.79 (1.90 to 7.56)
Analysis 21.3		400 mg/ Choy 2012; Keystone 2008; Smolen 2009	7.18 (3.12 to 16.50)

Table 5. Health-related quality of life *(Continued)*

Analysis 21.4	52 weeks	200 mg/ Atsumi 2016; Emery 2015; Keystone 2008	1.83 (1.53 to 2.18)
Analysis 21.5		400 mg/ Keystone 2008	12.49 (3.99 to 39.12)

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 - 398			
Analysis 37.1	24 weeks	200 mg/ Keystone 2008; Smolen 2009	-1.06 (-1.58 to -0.55)
Analysis 37.2	24 weeks	400 mg/ Keystone 2008; Smolen 2009	-1.32 (-1.85 to -0.78)
Analysis 36.1.1	52 weeks	200 mg/ Keystone 2008; Emery 2015	-2.4 (-4.11 to -0.69)
Analysis 36.1.2	52 weeks	400 mg/ Keystone 2008	-2.6 (-4.29 to -0.91)
Erosion Score is the sum of joint scores collected for 46 joints and has a range of 0 to 230			
Analysis 29.1	24 weeks	200 mg/ Keystone 2008; Smolen 2009	-0.35 (-0.50 to -0.21)
Analysis 29.2	24 weeks	400 mg/ Keystone 2008; Smolen 2009	-0.76 (-1.14 to -0.37)
Analysis 29.3	52 weeks	200 mg/ Keystone 2008; Emery 2015	-1.14 (-1.54 to -0.74)
Analysis 29.4	52 weeks	400 mg/ Keystone 2008	-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			
Analysis 32.1	24 weeks	200 mg/ Keystone 2008; Smolen 2009	-0.45 (-0.77 to -0.13)
Analysis 32.2	24 weeks	400 mg/ Keystone 2008; Smolen 2009	-0.55 (- 0.86 to -0.24)
Analysis 32.3	52 weeks	200 mg/ Keystone 2008	-1 (-1.85 to -0.15)
Analysis 32.4	52 weeks	400 mg/ Keystone 2008	-1.2 (-1.98 to -0.42)

Table 7. Adverse events

Studies	Response rate in % (number of events) cer-tolizumab pegol	Response rate in % (number of events) placebo	RR (95% CI)	% RD	NNTH
Serious adverse events (doses)			**Peto OR**		

Table 7. Adverse events *(Continued)*

Analysis 41.1 200 mg certolizumab pegol	Smolen 2015; Yamamoto (a) 2014; Yamamoto (b) 2014; NCT00993317; Keystone 2008; Smolen 2009; Weinblatt 2012; Atsumi 2016; Emery 2015	8.4% (228)	5,8% (72)	1.47 (1.13 to 1.91)	3 (1 to 4)	33 (25o 100)
Analysis 42.1 400 mg certolizumab pegol	Choy 2012; Fleischmann 2009; Yamamoto (b) 2014; Keystone 2008; Smolen 2009; Østergaard 2015	10% (95)	4% (31)	1.98 (1.36 to 2.9)	5 (2 to 7)	28 (15 to 74)
Adverse events leading to withdrawal				**Peto OR**		
Analysis 50.15 200 mg certolizumab pegol	Emery 2015; Keystone 2008; NCT00993317; Smolen 2009; Smolen 2015; Weinblatt 2012; Yamamoto (a) 2014; Yamamoto (b) 2014	6% (147)	4% (46)	1.32 (0.95 to 1.84)	1 (0 to 3)	NS
Analysis 50.16 400 mg certolizumab pegol	Choy 2012; Fleischmann 2009; Yamamoto (b) 2014; Keystone 2008; Smolen 2009	5% (48)	2% (16)	2.01 (1.20 to 3.36)	3 (1 to 5)	52 (23 to 257)
Death				**Peto OR**		
Analysis 50.17; 200 mg certolizumab pegol	Emery 2015; Keystone 2008; Smolen 2009; Smolen 2015; Weinblatt 2012; Yamamoto (a) 2014	0.03% (8)	0.1% (1)	2.66 (0.63 to 11.16)	0 (-1 to 1)	NS
Analysis 50.18 400 mg certolizumab pegol	Choy 2012; Fleischmann 2009; Keystone 2008; Smolen 2009; Østergaard 2015	0.5% (5)	0% (1)	1.87 (0.31 to 11.34)	0 (-1 to 1)	NS
Tuberculosis				**Peto OR**		
Analysis 50.20; 200 mg certolizumab pegol	Emery 2015; Keystone 2008; NCT00993317; Smolen 2009; Smolen 2015; Weinblatt 2012	0.4% (7)	0% (0)	1.90 (0.55 to 6.58)	Not calculated	NS
Analysis 50.21 400 mg certolizumab pegol	Fleischmann 2009; Keystone 2008; Smolen 2009	0.6% (5)	0% (0)	4.55 (0.71 to 29.11)	Not calculated	NS
Malignancies (neoplasias including lymphoma)				**Peto OR**		
Analysis 50.23 200 mg certolizumab pegol	Atsumi 2016; Emery 2015; Keystone 2008; NCT00993317; Smolen 2009; Smolen 2015; Weinblatt 2012; Yamamoto (a) 2014	0.7% (19)	0.7% (9)	0.92 (0.40 to 2.11)	0 (-1 to 1)	NS

Table 7. Adverse events *(Continued)*

Analysis 50.24 400 mg certolizumab pegol	Fleischmann 2009; Keystone 2008; Smolen 2009	0.6 % (5)	0.4% (2)	1.26 (0.26 to 6.08)	0 (-1 to 1)	NS
Infections and infestations				**RR**		
Analysis 50.71 200 mg certolizumab pegol	Atsumi 2016; Emery 2015; Keystone 2008; NCT00993317; Smolen 2009; Smolen 2015; Weinblatt 2012; Yamamoto (a) 2014; Yamamoto (b) 2014	35% (891)	29% (389)	1.27 (1.10 to 1.46)	7 (1 to 13)	14 (8 to 58)
Analysis 50.72 400 mg certolizumab pegol	Choy 2012; Keystone 2008; Smolen 2009; Yamamoto (b) 2014; Østergaard 2015	34% (298)	21% (183)	1.43 (1.03 to 1.98)	10 (1 to 20)	10 (5 to 44)

APPENDICES

Appendix 1. MEDLINE search strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

1 (CDP870 or CDP 870 or "certolizumab pegol" or certolizumab or CDP-870 or cimzia).mp. (393)

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. (98824)

3 exp Arthritis, Rheumatoid/ (94528)

4 2 or 3 (126632)

5 1 and 4 (131)

6 Clinical trial.pt. (473242)

7 randomized.ab. (256728)

8 Placebo.ab. (140242)

9 dt.fs. (1573096)

10 randomly.ab. (187872)

11 trial.ab. (264547)

12 groups.ab. (1216413)

13 or/6-12 (3112539)

14 5 and 13 (114)

15 limit 14 to yr="2009 -Current" (99)

Search date: 2009 - February 12, 2013

Appendix 2. Embase search strategy

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 date: 2009 - February 12, 2013

Appendix 3. CINAHL search strategy

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

Search date: 2009 - February 12, 2013

Appendix 4. Search strategy for CDSR and CENTRAL, HTA, DARE, NHS EED

Last search in 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)

Search date: 2009 - February 12, 2013

Appendix 5. SCOPUS search strategy

Search strategy for benefits:
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

Search date: 2009 - February 12, 2013

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

Search date: 2009 - February 12, 2013

Appendix 7. Web of Knowledge

Web of Knowledge (Science Citation Index and Social Science Citation Index) 1900 – February 2013

Search terms: TS= (certolizumab OR cimzia OR or CDP870 OR cdp 870) and ("rheumatoid arthritis")

Search date: 2009-February 12, 2013

Appendix 8. Results of searches 2013

Database name and coverage	Search date	Total Retrieved
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present	2009-February 12, 2013	315
Ovid Embase Classic+Embase 1947 to 2013 January 16	2009 - February 12, 2013	1365
Wiley Cochrane Library – CENTRAL Issue 1 of 12- Jan. 2013	2009 - February 12, 2013	11
EbscoHost CINAHL 1982-January 2013	2009 - February 12, 2013	32
Toxline (TOXNET)	2007 - February 12, 2013	34
Web of Knowledge	2009 - February 12, 2013	189
SCOPUS 1966 to 2013 January	2009 - February 12, 2013	814
	Total	2760
	Total without duplicates	1300

Appendix 9. Searches updated to June 2014

Database name and coverage	Search date	Total Retrieved	Total without Duplicates
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 2013-2014	June 5, 2014	29	28
Ovid Embase Classic+Embase 2013-2014	June 5, 2014	208	192
EbscoHost CINAHL 2013-2014	June 5, 2014	1	1
Wiley Cochrane Library – CENTRAL 2013-2014	June 6, 2014	4	4

(Continued)

SCOPUS 2013-2014	June 10, 2014	233	124
Web of Knowledge 2013-2014	June 10, 2014	94	54
	Total	569	403

Appendix 10. Medline search strategy January 25, 2016

MEDLINE Total retrieved = 70

1. exp Arthritis, Rheumatoid/

2. ((Arthritis adj2 Rheumatoid) or (caplan* adj2 s?ndrome?) or (Familial and felty* and s?ndrome?) or (felty* adj2 s?ndrome?) or (Rheumatoid and arthritis and splenomegaly and neutropenia) or (rheumatoid and nodul*) or (rheumatoid and vasculiti*) or (sicca* and s?ndrome?) or (sjogren* and s?ndrome?) or (adult* and onset and still* disease?) or (ankylo* and spondylarthriti*) or (ankylo* and spondylistis) or (ankylosing and spondylorthriti*) or (spondylitis and rheumatoid) or (bechterew* and disease?) or (marie* struempell and disease?) or (rheumatoid and spondylitis) or (spondylarthriti* and ankylo*)).mp.

3. exp Spondylitis, Ankylosing/

4. exp Certolizumab Pegol/

5. (pegylated tumo?r necrosis factor alpha antibody Fab fragment or pha 738144 or (870* adj1 cdp*) or cdp?870? or certolizumab pegol* or cimzia* or pegol* adj1certolizumab).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

6. 4 or 5

7. 1 or 2 or 3

8. 6 and 7

9. limit 8 to yr="2014 -Current"

10. Clinical trial.pt. or randomized.ab. or placebo.ab. or dt.fs. or randomly.ab. or trial.ab. or groups.ab.

11. 9 and 10

Appendix 11. Embase search strategy January 25, 2016

EMBASE Total retrieved= 304

1. ((Arthritis adj2 Rheumatoid) or (caplan* adj2 s?ndrome?) or (Familial and felty* and s?ndrome?) or (felty* adj2 s?ndrome?) or (Rheumatoid and arthritis and splenomegaly and neutropenia) or (rheumatoid and nodul*) or (rheumatoid and vasculiti*) or (sicca* and s?ndrome?) or (sjogren* and s?ndrome?) or (adult* and onset and still* disease?) or (ankylo* and spondylarthriti*) or (ankylo* and spondylistis) or (ankylosing and spondylorthriti*) or (spondylitis and rheumatoid) or (bechterew* and disease?) or (marie* struempell and disease?) or (rheumatoid and spondylitis) or (spondylarthriti* and ankylo*)).mp.

2. (arthritis deformans or arthrosis deformans or (beauvais adj2 disease?) or (chronic adj2 poly?arthritis) or (chronic adj2 rheumatoid adj2 arthritis) or inflammatory arthritis or (polyarthritis adj2 primary adj2 chronic) or (progressive adj2 polyarthritis adj2 chronic) or rheumarthritis or rheumatism, chronic articular or (rheumatic adj2 arthritis) or (rheumatic adj1 polyarthritis)).mp.

3. 1 or 2

4. exp rheumatoid arthritis/

5. exp pneumoconiosis/

6. exp Felty syndrome/

7. exp rheumatoid nodule/

8. exp rheumatoid vasculitis/

9. exp Sjoegren syndrome/

10. exp adult onset Still disease/

11. exp ankylosing spondylitis/

12. or/4-11

13. 3 or 12

14. exp certolizumab pegol/

15. (pegylated tumo?r necrosis factor alpha antibody Fab fragment or pha?738144 or (870* adj1 cdp*) or cdp?870? or certolizumab pegol* or cimzia* or pegol* adj1certolizumab).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

16. 14 or 15

17. 13 and 16

18. limit 17 to yr="2014 -Current"

19. random:.tw. or clinical trial:.mp. or exp health care quality/

20. 18 and 19

Appendix 12. Central search strategy January 22, 2016

COCHRANE retrieved =36

#1 (870* next cdp*) or cdp?870? or certolizumab or cimzia*

#2 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees

#3 ((Arthritis next Rheumatoid) or (caplan* next syndrome*) or (Familial and felty* and syndrome*) or (felty* next syndrome*) or (Rheumatoid and arthritis and splenomegaly and neutropenia) or (rheumatoid and nodul*) or (rheumatoid and vasculiti*) or (sicca* and syndrome*) or (sjogren* and s*ndrome*) or (adult* and onset and still* disease*) or (ankylo* and spondylarthriti*) or (ankylo* and spondylistis) or (ankylosing and spondylorthriti*) or (spondylitis and rheumatoid) or (bechterew* and disease*) or (marie* struempell and disease*) or (rheumatoid and spondylitis) or (spondylarthriti* and ankylo*))

#4 arthritis deformans or arthrosis deformans or (beauvais next disease*) or (chronic next polyarthritis) or (chronic next rheumatoid next arthritis) or inflammatory arthritis or (polyarthritis next primary next chronic) or (progressive next polyarthritis next chronic) or rheumarthritis or rheumatism, chronic articular or (rheumatic next arthritis) or (rheumatic next polyarthritis)

#5 #2 or #3 or #4

#6 #1 and #5

#7 ((Arthritis next Rheumatoid) or (caplan* next syndrome*) or (Familial and felty* and syndrome*) or (felty* next syndrome*) or (Rheumatoid and arthritis and splenomegaly and neutropenia) or (rheumatoid and nodul*) or (rheumatoid and vasculiti*) or (sicca* and syndrome*) or (sjogren* and s*ndrome*) or (adult* and onset and still* disease*) or (ankylo* and spondylarthriti*) or (anky-

lo* and spondylistis) or (ankylosing and spondylorthriti*) or (spondylitis and rheumatoid) or (bechterew* and disease*) or (marie* struempell and disease*) or (rheumatoid and spondylitis) or (spondylarthriti* and ankylo*))

Appendix 13. WOK search strategy January 22, 2016

WOK retrieved =

Web of Knowledge (Science Citation Index and Social Science Citation Index) 1900 – January 2016

#1 Topic: ((((((((((((((((((Arthritis NEAR Rheumatoid) OR (caplan* NEAR s?ndrome?)) OR ((Familial AND felty*) AND s?ndrome?)) OR (felty* NEAR s?ndrome?)) OR (((Rheumatoid AND arthritis) AND splenomegaly) AND neutropenia)) OR (rheumatoid AND nodul*)) OR (rheumatoid AND vasculiti*)) OR (sicca* AND s?ndrome?)) OR (sjogren* AND s?ndrome?)) OR ((adult* AND onset) AND still* disease?)) OR (ankylo* AND spondylarthriti*)) OR (ankylo* AND spondylitis)) OR (ankylosing AND spondylorthriti*)) OR (spondylitis AND rheumatoid)) OR (bechterew* AND disease?)) OR (marie$struempell AND disease?)) OR ((rheumatoid AND spondylitis spondylarthriti*) AND ankylo*)) OR ((((((((((arthritis deformans OR arthrosis deformans) OR (beauvais NEAR disease?)) OR (chronic NEAR poly?arthritis)) OR ((chronic NEAR rheumatoid) NEAR arthritis)) OR inflammatory arthritis) OR ((polyarthritis NEAR primary) NEAR chronic)) OR ((progressive NEAR polyarthritis) NEAR chronic)) OR rheumarthritis) OR rheumatism, chronic articular) OR (rheumatic NEAR arthritis)) OR (rheumatic NEAR polyarthritis)))

limit=2016

#2 Topic: ((pegylated tumo?r necrosis factor alpha antibody Fab fragment or pha?738144 or (870* NEAR cdp*) or cdp?870? or certolizumab pegol* or cimzia* or (pegol* NEAR certolizumab)))

Time=2016

#3 #2 AND #1

#4 Refined by: Document (CLINICAL TRIAL)

Appendix 14. Search strategy Clinicaltrials.gov

certolizumab pegol AND Rheumatoid arthritis

Appendix 15. Searches on International Clinical Trials Registry Platform

certolizumab pegol/Intervention AND Rheumatoid arthritis/Condition | Studies updated from to 12/31/2016

Appendix 16. Results of searches updated to January 2016

Database name and coverage	Search date	Total Retrieved
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)	January 25, 2016	70

(Continued)

2014-2016		
Ovid Embase Classic+Embase 2014-2016	January 25, 2016	304
Wiley Cochrane Library – CENTRAL 2014-2016	January 25, 2016	36
Web of Knowledge 2014-2016	January 25, 2016	25
Clinicaltrials.gov 2014-2016	January 25, 2016	28
	Total	**463**

Appendix 17. Results of searches updated to September 2016

Database name and coverage	Search date	Total Retrieved
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) From 1 January 2016 to 26 September 2016	September 26, 2016	21
Ovid Embase Classic+Embase 2014-2016 Embase Classic+Embase 1947 to 2016 26 September 2016	September 26, 2016	97
Wiley Cochrane Library – CENTRAL From 1 January 2016 to 26 September 2016	September 26, 2016	4
Web of Knowledge From 1 January 2016 to 27 September 2016	September 27, 2016	2
Clinicaltrials.gov From 1 January 2016 to 27 September 2016	October 1, 2016	28
ICTRP to 31 December 2016	Decemeber 31, 2016	42
	Total	**194**

WHAT'S NEW

Date	Event	Description
26 September 2016	New citation required but conclusions have not changed	For this update, we changed the authors in the team: José Antonio Bernal is new.
26 September 2016	New search has been performed	We include 14 trials, 3 more than in the previous review. All of them have information about harm, but we have only pooled 12 trials. 12 trials gave information on benefits, but we have only pooled 11. We have more information regarding the quality of trials because UCB© gave us further data. We have used this information to update our assessment of the quality of trials. For the new trials we obtained unpublished data about the quality and results, including withdrawals and serious adverse events from clinicaltrials.gov. We checked this information with UCB©.

HISTORY

Protocol first published: Issue 1, 2009
Review first published: Issue 2, 2011

Date	Event	Description
3 April 2008	New search has been performed	CMSG ID: C001-R

CONTRIBUTIONS OF AUTHORS

Design the protocol: Juan Cabello; Vicente Ruiz; Amanda Burls
Write the Background: Paloma Vela and José Antonio Bernal
Develop the search strategy: Tamara Rader
Trial search (two people): Vicente Ruiz; Sylvia Bort
Obtain copies of the trials: Sylvia Bort
Selection of trials for inclusion (two plus one): Vicente Ruiz; Sylvia Bort. If data discrepancies were to be resolved by involvement of a third person: Amanda Burls
Retrieval of trial data on benefits (two plus one): Vicente Ruiz; Sylvia Bort. If data discrepancies were to be resolved by involvement of a third person: Amanda Burls
Data input in Review Manager 5: Sylvia Bort
Carry out analyses: Vicente Ruiz
Interpret analyses: Vicente Ruiz
Write up results: Vicente Ruiz; ; Paloma Vela; Amanda Burls; Juan Cabello; Sylvia Bort; José Antonio Bernal
Update review: Vicente Ruiz; José Antonio Bernal; Paloma Vela

DECLARATIONS OF INTEREST

UCB paid Dr Vicente Ruiz's registration for the Cochrane meeting in Madrid 2011. In 2011 and 2012 he attended the UCB Advisory Board meetings in Madrid when the sponsor explained details and preliminary results for the new trials of certolizumab pegol. He did not receive any economic or other kind of compensation for these meetings.

Burls A: none known.

Cabello JB: none known.

Vela Casasempere P: "I have participated as a member of advisory boards for Roche and Pfizer. I have also received fees for development of educational presentations for Roche, Abbvie, UCB, BMS and MSD, and travel and accommodations expenses to attend scientific meetings from Pfizer, Abbvie and Roche".

Bort-Marti S: none known.

Bernal JA: "I have received travel and accommodations expenses to attend scientific meetings from Pfizer and MSD".

SOURCES OF SUPPORT

Internal sources

- Grant from, Spain.

  Instituto de Salud Carlos III. Ministerio de Sanidad. FIS number PI08_90617 in the first previous systematic review.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Types of participants

Protocol specified adults with RA who have persistent disease activity, despite current or previous use of conventional DMARDs. We have included two studies (Atsumi 2016; Emery 2015) with MTX-naïve participants. This approach is now considered justified in early RA, as data are available showing differences in outcome when remission is obtained as soon as possible.

Types of outcomes

In the protocol we stated that we "We will review also this list of adverse 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". In the previous update and with the approval of the editors, we made serious adverse events, DAS and radiological changes of major outcomes. DAS28 is used as an indicator of RA disease activity and a response to treatment.

Searches

We did not perform the searches in CINHAL nor in SCOPUS, because although we covered these database in the original protocol they did not yield any additional information in our previous searches. Following MECIR criteria, we conducted searches on the WHO international clinical trials registry platform.

Data synthesis

We decided to perform a random-effects model analysis, despite low values of the I^2 statistic. Although the trials used the same drug, there was clear clinical heterogeneity (different doses, allowing MTX or not, different follow-up, different duration of RA, etc.).

Subgroup analysis

Subgroup analyses were planned for the duration of the illness (approximately three years evolution), participants' sex, drug dose and administration, and methodological quality; but we performed only a subgroup analysis for dosage of certolizumab pegol. All Phase III trials were conducted in participants with a long mean duration of RA (from 6.1 to 9.5 years) and we could not obtain any data categorised by sex. All Phase III trials allowed previous DMARD treatment (mean 1.2 to 2 years). We rated all the Phase III trials included in the meta-analysis as high quality and so we did not perform subgroup analysis based on methodological quality.

INDEX TERMS

Medical Subject Headings (MeSH)

Antirheumatic Agents [adverse effects] [*therapeutic use]; Arthritis, Rheumatoid [*drug therapy]; Certolizumab Pegol [adverse effects] [*therapeutic use]; Immunoglobulin Fab Fragments [*therapeutic use]; Methotrexate [therapeutic use]; Randomized Controlled Trials as Topic; Withholding Treatment [statistics & numerical data]

MeSH check words

Adult; Humans