RoActemra® (tocilizumab)
NICE STA Submission

ACHIEVING CLINICAL EXCELLENCE IN THE TREATMENT OF MODERATE TO SEVERE RHEUMATOID ARTHRITIS

Roche Submission to the
National Institute for Health and Clinical Excellence
6th February 2009

Contents

1 Description of technology under assessment

1.1 Give the brand name, approved name and, where appropriate, therapeutic class. For devices please provide details of any different versions of the same device.

Tocilizumab (RoActemra®) is a humanised IgG1 monoclonal antibody against the human interleukin-6 (IL-6) receptor. It is an immunosuppressant, interleukin inhibitor.

1.2 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, please give the date on which authorisation was received. If not, please state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Positive opinion received from the European regulators (CHMP) on 20th November. EU Commission marketing authorisation received January 20th 2009.

1.3 What are the (anticipated) indication(s) in the UK? For devices, please provide the (anticipated) CE marking, including the indication for use.

RoActemra in combination with methotrexate (MTX) is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists. In these patients, RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

1.4 To what extent is the technology currently being used in the NHS for the proposed indication? Include details of use in ongoing clinical trials. If the technology has not been launched, please supply the anticipated date of availability in the UK.

Anticipated commercial availability in the United Kingdom will be following this technology appraisal . At present 78 patients in the UK have received tocilizumab as part

of phase III clinical trials. This is made up of one phase III study with 13 patients (no further recruitment) and one phase IIIb study with 65 patients recruited to date (recruitment to conclude with 185 patients in total).

One further phase IIIb trial to commence with recruitment target of 36 UK patients. Total clinical trial population will be 234. All three trials are within the anticipated marketing authorisation

1.5 Does the technology have regulatory approval outside the UK? If so, please provide details.

Tocilizumab is licensed in Japan for the management of Castleman's disease and moderate to severe rheumatoid arthritis in patients who have had an inadequate response or are intolerant to DMARDs or anti TNFs. This is either in combination with methotrexate or as monotherapy. Tocilizumab is also licensed for use in the EU, Switzerland, Kuwait, Moldova, Brazil, India and Peru as of January 30th 2009. .

1.6 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

This technology will be submitted to and reviewed by the Scottish Medicines Consortium following the granting of its marketing authorisation.

1.7 For pharmaceuticals, what formulation(s) (for example, ampoule, vial, sustained-release tablet, strength(s) and pack size(s) will be available?

3 vial sizes will be available. The licensed dose will be 8mg/kg.

80 mg of tocilizumab in 4 ml (20 mg/ml).

200 mg of tocilizumab in 10 ml (20 mg/ml).

400 mg of tocilizumab in 20 ml (20 mg/ml)

1.8 What is the proposed course of treatment? For pharmaceuticals, list the dose, dosing frequency, length of course and anticipated frequency of repeat courses of treatment.

The recommended posology stated within the license is 8 mg/kg (but no lower than a minimum dose of 480 mg) given once every four weeks by intravenous infusion. Rheumatoid arthritis is a chronic disease so consistent with existing biologic therapy, treatment will be indefinite in those patients continuing to respond. A 4mg dose is also listed within the SmPC as a temporary treatment strategy for the management of specific adverse events and pharmacodynamic effects listed within the SmPC.

1.9 What is the acquisition cost of the technology (excluding VAT)? For devices, provide the list price and average selling price. If the unit cost of the technology is not yet known, please provide details of the anticipated unit cost, including the range of possible unit costs.

The NHS list price for tocilizumab has not been set. The provisional price which should be used for the purposes of this appraisal is £1.28 per mg or £9,295 per annum.

1.10 What is the setting for the use of the technology?

Tocilizumab will be given in infusion clinics. It is anticipated that this will primarily focus on secondary care rheumatology services. If necessary, tocilizumab can be administered within a community setting or at the patient's home.

1.11 For patients being treated with this technology, are there any other aspects that need to be taken into account? For example, are there additional tests or investigations needed for selection, or particular administration requirements, or is there a need for monitoring of patients over and above usual clinical practice for this condition? What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

Tocilizumab will be given in combination with methotrexate in the majority of patients.

In respect to monitoring, the requirements for tocilizumab, because the majority of patients will have concomitant MTX the monitoring for both tocilizumab and MTX can be combined. These are highlighted below. In the event that the patient is administered tocilizumab as monotherapy, the monitoring below would be additive as no methotrexate monitoring would be required.

1. Liver function: ALT and AST levels should be monitored every 4 to 8 weeks for the first 6 months of treatment followed by every 12 weeks thereafter.

2. Assessment of lipid parameters should be performed 4 to 8 weeks following initiation of tocilizumab therapy. Patients should be managed according to local clinical guidelines for management of hyperlipidaemia.

3. Neutrophils and platelets should be monitored 4 to 8 weeks after start of therapy and thereafter according to standard clinical practice.

2 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the Evidence Submission will address.

	Final scope issued by NICE	Decision problem addressed in the submission
Population	Adults with moderate to severe rheumatoid arthritis	1. Adults with moderate to severe active rheumatoid arthritis (RA) who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease modifying anti-rheumatic drugs (DMARDs). 2. Adults with moderate to severe active rheumatoid arthritis (RA) who have either responded inadequately to, or who were intolerant to, previous therapy with one or more tumour necrosis factor (TNFα) antagonists.
Intervention	Tocilizumab alone or in combination with methotrexate	Tocilizumab in combination with methotrexate (MTX) followed by the current treatment sequence. Tocilizumab will be additive to the assumed existing standard of care / treatment strategy. DMARD-IR Indication: i. Tocilizumab + MTX ii. TNFα inhibitor (etanercept assumed most commonly used) iii. Rituximab iv. Leflunomide v. Gold

		vi. Cyclosporine vii. Palliative care TNF-IR Indication: i. Tocilizumab + MTX ii. Rituximab iii. Leflunomide iv. Gold v. Cyclosporine vi. Palliative care
Comparator(s)	Management strategies involving DMARDs without tocilizumab, including treatment with: • conventional DMARDs • biologic agents including adalimumab, etanercept, infliximab and rituximab	**1.DMARD-IR indication** Tocilizumab is licensed in the management of moderate to severe active RA patients who have had an inadequate response or intolerance to one or more DMARDs. The current treatment sequence identified for this patient population according to current NICE guidance and therefore will form the assumed comparator sequence is: i. TNFα inhibitor (etanercept currently assumed to be most commonly used) ii. Rituximab iii. Leflunomide iv. Gold v. Ciclosporine vi. Palliative care

		2. TNF-IR indication Tocilizumab is licensed in the management of moderate to severe active RA patients who have had an inadequate response or intolerance to one or TNF inhibitors. The current treatment sequence identified for this patient population according to current NICE guidance and therefore will form the comparator sequence is: i. Rituximab ii. Leflunomide iii. Gold iv. Ciclosporine v. Palliative care
Outcomes	The outcome measures to be considered include: • disease activity • physical function • joint damage/radiographic progression • joint replacement • pain • mortality • fatigue • health-related quality of life • adverse effects of treatment	As well as the stated outcome measures, the inhibition of disease progression will be considered and evaluated in its own right. Specific outcome measures highlighted will be American College of Rheumatology (ACR) scores, Disease Activity Scores (DAS), EULAR scores, Health Assessment Questionaire (HAQ) score, Fatigue (FACIT-F) score, Short Form (SF-36) scores and the Sharp radiographic assessment scores.
Economic Analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time	Two reference cases reflecting the DMARD IR and TNF IR populations will be presented. The same economic model and structure will be utilised for both ICERs. In both analyses the cost-effectiveness of the Tocilizumab treatments will be expressed in terms of incremental cost per quality-adjusted life year.

	horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	The economic model will be an individual sampling model (ISM) similar to that used within the rituximab RA single technology appraisal. The key issues/drivers within the model that Roche anticipate forming a large part of the committee's discussions when considering previous RA appraisals relates to **long term HAQ progression.** Roche propose to utilise the actual observed HAQ data from within its phase III trials to inform this rate. After the end of the trial follow-up, an assumption will be required. This will be informed by previous NICE RA technology appraisals. Secondly Roche will re-estimate the **relationship between HAQ and utilities** through using its patient level trial data which permits the mapping of HAQ directly to the EQ-5D instrument. Previous NICE appraisals methods relied upon mapping via the HUI-3 instrument.
Subgroups to be considered	None identified	None identified
Special considerations, including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where evidence allows, subgroup analysis may be carried out in sero-positive and sero-negative patients or any other bio-markers that may define subgroups	No comment

3 Executive summary

a) Background

Tocilizumab is the first biologic to be granted a licence in both DMARD and TNF inadequate responding (IR) patients and is the first biologic to inhibit IL-6, a major cytokine in the inflammatory network and a recognised driver of autoimmunity. Tocilizumab has been assessed through the largest phase III clinical trial program of any biologic enabling an extensive evidence base upon which to evaluate both the clinical and cost effectiveness of tocilizumab.

Tocilizumab in combination with MTX can provide rapid and durable remission (DAS28<2.6) in patients with an inadequate response to DMARDs and anti TNFs. This is combined with significant and sustained improvements in ACR20, 50, 70 and HAQ over time. The safety profile of tocilizumab has been assessed using over 3,500 patient years experience.

At present around 30-40% of patients have an inadequate response to either traditional DMARDs or TNF inhibitor therapies. Tocilizumab will help address this large unmet patient need. The key information requested within the STA executive summary template is summarised in the table below.

Table 1: Tocilizumab key information

Approved Name	Tocilizumab
Brand Name	RoActemra
Marketing Status	Tocilizumab was granted marketing authorization on the 20th January 2009.
Indication	Tocilizumab's license includes two indications, DMARD IR and TNF IR. The Summary of Product characteristics states that: "RoActemra, in combination with methotrexate (MTX), is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists. In these patients, RoActemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate."
Pharmacological Action	Tocilizumab is an immunosuppressant, interleukin inhibitor. It is a recombinant humanized monoclonal antibody targeting interleukin-6 receptor (IL-6R).
Formulation	Tocilizumab is administered as an intra-veneous injection
Pack Sizes	Single-use vial containing tocilizumab one 80 mg Single-use vial containing tocilizumab one 200 mg Single-use vial containing tocilizumab one 400 mg
Acquisition Cost	Tocilizumab: £9,295 per annum (70kg patient)

	Etanercept: £9,295 per annum Adalimumab: £9,857 per annum Infliximab: £8,812 per annum* (70kg patient)
Frequency of treatment	Administration as an intravenous infusion every 4 weeks at a dose of 8mg/kg

**average over first 4 years including year 1 loading dose*

Comparators

The comparator in all phase III clinical trial programs was methotrexate with the exception of the TOWARD study, this allowed the option to administer other DMARDs in combination with tocilizumab apart form methotrexate, including Chloroquine/hydroxychloroquine, Sulfasalazine, Leflunomide, Parenteral gold and Azathioprine. Combination of tocilizumab with DMARDs other than methotrexate is not licensed.

Consistent with previous NICE technology appraisals of RA therapies, the comparator within the economic evaluation is a sequence of various therapies. This is because the NICE reference case requires a lifetime perspective. RA is a long term chronic disease for which patients are commonly treated with a series of therapeutic agents. Consistent with previous NICE technology appraisals, tocilizumab is assumed to be an additional treatment option compared to the current management of RA and not a permanent replacement for existing treatment options. Given these important assumptions, the relevant comparator treatment sequences are illustrated below.

Table 2: Comparator treatment sequences

DMARD-IR Indication		**TNF-IR indication**	
Intervention sequence	Comparator sequence	Intervention sequence	Comparator sequence
i. Tocilizumab + MTX ii. TNFα inhibitor iii. Rituximab iv. Leflunomide v. Gold vi. Cyclosporine vii. Palliative care	i. TNFα inhibitor ii. Rituximab iii. Leflunomide iv. Gold v. Cyclosporine vi. Palliative care	i. Tocilizumab + MTX ii. Rituximab iii. Leflunomide iv. Gold v. Cyclosporine vi. Palliative care	i. Rituximab ii. Leflunomide iii. Gold iv. Cyclosporine v. Palliative care

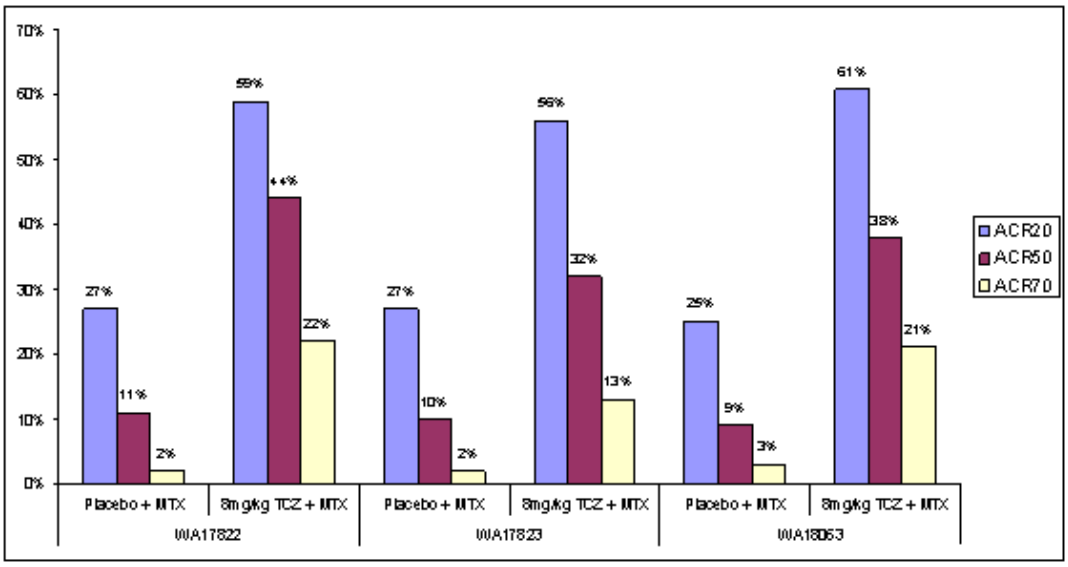
b) Clinical Effectiveness

The clinical effectiveness of Tocilizumab is based upon an extensive phase III clinical trial evidence base of 5 randomised control trials that included in excess of 3,500 RA patients.

OPTION, LITHE & TOWARD (DMARD-IR patients)

These three trials were double-blinded, placebo-controlled, multicentre studies with patients that had an inadequate response to a tDMARD. The results from the 3 trials were also pooled in order to examine the clinical and HRQL outcomes of tocilizumab in these DMARD IR patients.

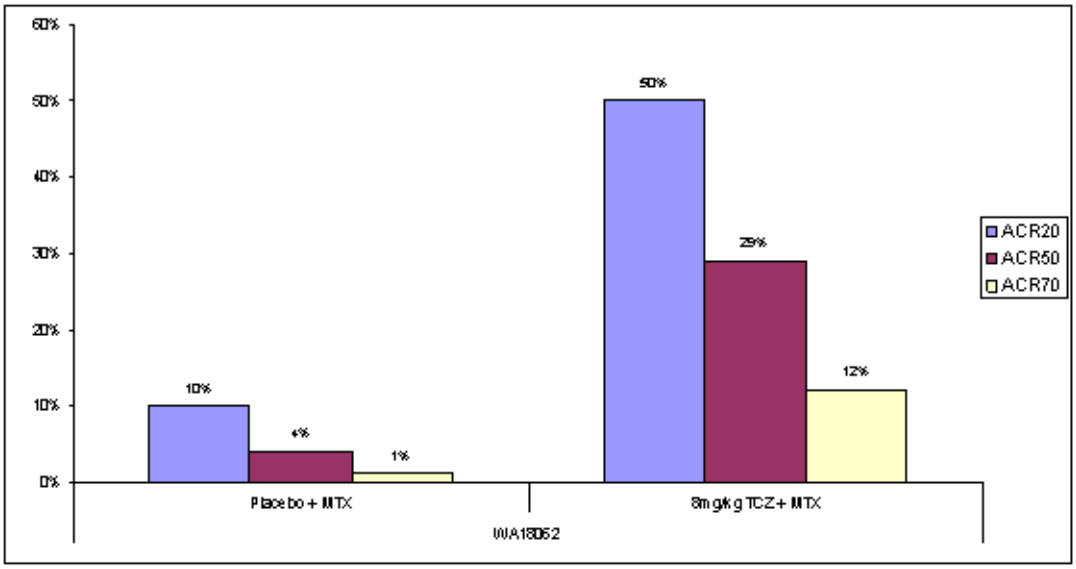
Figure 1: Tocilizumab ACR response rates for DMARD IR patients



RADIATE (TNF-IR patients)

The trial was a double-blinded, placebo-controlled, multicentre study with patients that had an inadequate response to an anti-TNF.

Figure 2: Tocilizumab ACR response rates for TNF IR patients



The AMBITION study related to patients receiving monotherapy in Methotrexate free patients. The specific population included in this trial is not licensed based upon the tocilizumab SPC and is therefore not summarised here.

Long term extension data

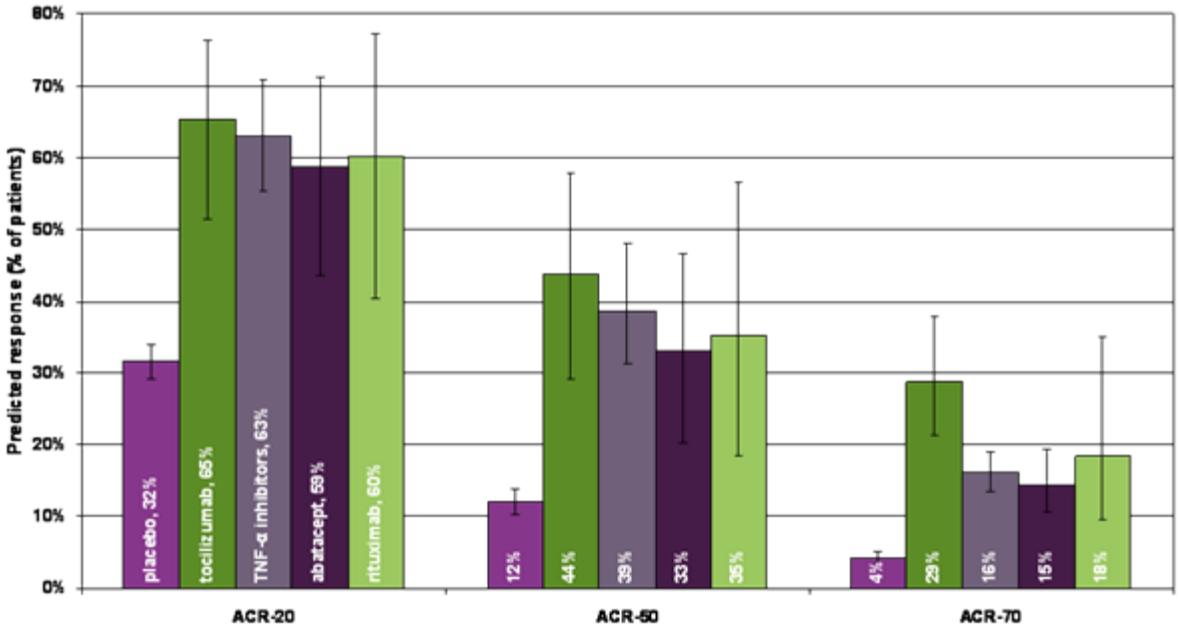
Responding patients from OPTION, TOWARD and RADIATE entered 2 open-label extension trials and their disease status continued to be monitored, confirming the longer term durability of the efficacy of tocilizumab.

Indirect Comparisons

In order to minimise any bias in the application of ACR response rates from different trials, a mixed treatment comparison (MTC) was performed, as recommended by the current NICE Guide to Methods of Technology Appraisal. The RCTs included in the analysis were assessed for similarity in patient population, research procedures and treatments and were found sufficiently similar to be included in a pooled analysis. The similarity was also tested statistically and the subsequent response rate calculations were driven by these findings (random vs. fixed effects models).

The results of the MTC for the primary endpoints of the phase II studies (ACR) can be summarised as follows:

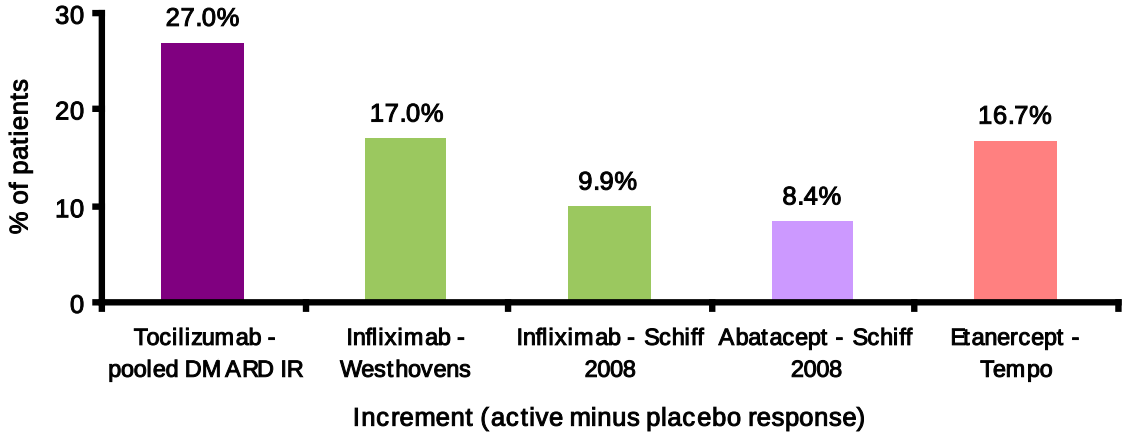
Figure 3: ACR response rates from Mixed Treatment Comparison (MTC)



Aside form ACR, an additional important endpoint in the management of RA is the DAS28 measure. Although insufficient evidence was available to perform a formal MTC, a comparison of the incremental effectiveness in achieving disease remission (a major objective of treatment in RA) across the major trials of biologic DMARDs provides an

indication of the strong relative efficacy of tocilizumab compared to existing biologic therapies.

Figure 4: Incremental remission (DAS28 < 2.6) with bDMARDs at 6 months in DMARD IR patients



c) Cost Effectiveness

The tocilizumab cost effectiveness evaluation attempts to improve the evidence base informing key parameters within the economic evaluation of biologic DMARDs in RA. This has been achieved through fully utilising the multiple tocilizumab phase III clinical trials whilst also fully understanding the strengths, weaknesses and limitations of previous economic evaluations considered by NICE. The specific analyses included within this Roche submission that improves upon the existing evidence base and can be summarised as follows:

1. Non-linear mapping of HAQ to EQ-5D, the NICE reference case instrument extracted directly from tocilizumab phase III studies based upon 1,800 patients.
2. Over 3 years follow-up data from the tocilizumab phase III data on both the HAQ and EQ-5D quality of patient reported outcomes (PRO) instruments, helping to reduce uncertainty in long term assumptions of HAQ change for responding patients.
3. A comprehensive mixed treatment comparison (MTC) utilising all published biologic DMARD trials in order to minimise any bias in evaluating the relative efficacy of DMARD therapy in RA.
4. Observing the longer term trends in EQ-5D data for patients responding to tocilizumab from within 2 tocilizumab phase III studies.

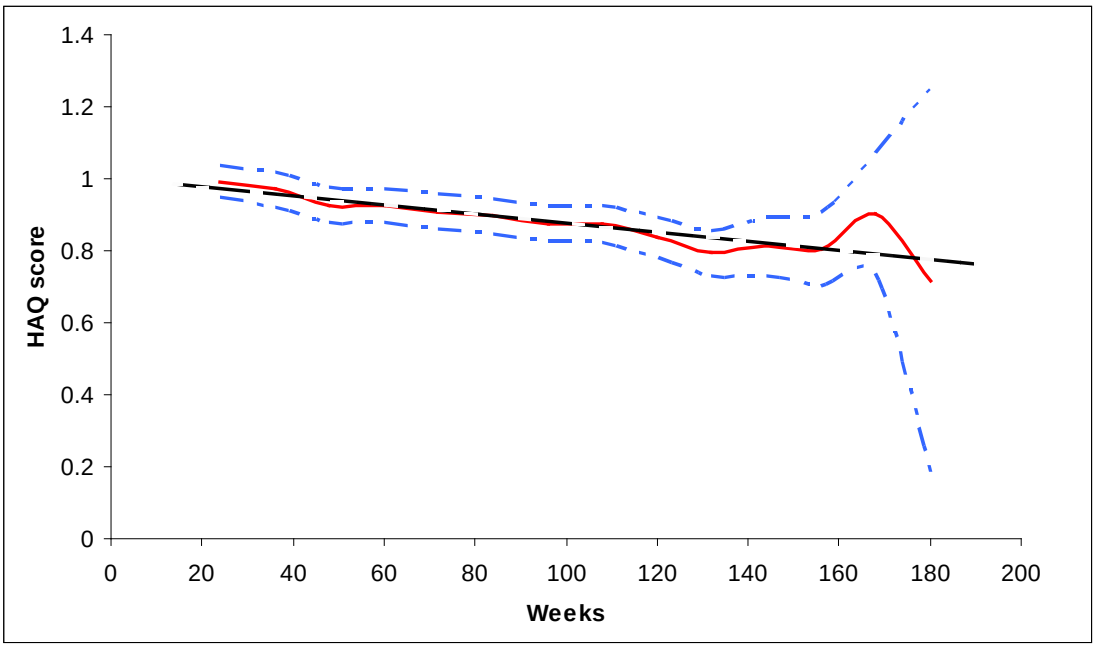
Model Design

The economic model utilised is consistent with models used in previous RA NICE appraisals. ACR response categories define the size of the initial HAQ drop, utilising the rates derived from the MTC. The 'individual simulation model' is used to track the individual characteristics of the patients and maintain a record of their HAQ change for the duration they stay within the model. In principle, to inform patient HAQ change the model attempts to utilise the tocilizumab trial data for as long as this is available. Following this, assumptions identical to those applied in the appraisal of the TNF inhibitors are applied. Total direct NHS costs, QALYs and the subsequent ICERs were estimated across for both the DMARD IR and TNF IR indications.

HAQ Change over time

A key clinical parameter that influences the final ICER for any RA therapy is the assumed long term HAQ change for a responding patient. For the purposes of this NICE evaluation, Roche utilised as long a follow-up of both the DMARD IR and TNF IR phase III studies in order to minimise uncertainty in the estimation of this key parameter. Contrary to previous NICE conclusions which were largely based upon retrospective observational data, the HAQ change over the first 3 years for patients remaining on tocilizumab illustrated a continuous improvement in physical functioning (i.e. negative HAQ slope).

Figure 5: Long term HAQ change for tocilizumab patients remaining on therapy (DMARD IR population)



Results

The mean incremental costs and QALYs gained for the tocilizumab containing therapy regimens together with the corresponding ICER for each indication are summarised in the table below.

Table 3: Cost Effectiveness results

DMARD-IR Indication		TNF-IR indication	
Incremental Costs	Incremental QALYs	Incremental Costs	Incremental QALYs
£23,253	1.17	£26,640	1.21
£19,870 per QALY		**£22,003 per QALY**	

Tocilizumab presents a cost-effective RA treatment option for NHS patients in both the DMARD-IR and TNF-IR indication. Probabilistic Sensitivity Analysis (PSA) that included all major model parameters illustrated at a willingness to pay threshold of £30,000 per QALY, tocilizumab is cost effective in 100% of scenarios in both the DMARD IR and TNF IR indications.

d) Conclusion

From a clinical perspective, tocilizumab demonstrates at least equivalence in efficacy compared to TNF inhibitors with a statistically significant improvement in ACR70 compared to TNF inhibitors. The clinical benefits have been illustrated to extend beyond the initial 6 month period characterised by an improvement in both HAQ and EQ-5D scores for the duration of trial follow-up (over 3 years). With an annual drug cost equivalent to existing TNF inhibitors, the estimated ICERs indicate tocilizumab is a cost effective treatment option in both the DMARD IR and TNF IR indications.

4 Context

Rheumatoid Arthritis is the most common systemic inflammatory chronic autoimmune disease

The overall aim of management is to ensure timely diagnosis and effective treatment to limit disease progression and maintain patients' quality of life

Despite the significant benefits of pharmacological treatment there is a significant unmet need with 30-40% of patients having an inadequate response to either non biologic DMARDs or TNF-α antagonists

Tocilizumab is an interleukin 6 receptor antagonist, the first in its class. It is licensed in combination with MTX for patients who have had an inadequate response to DMARDs or TNF-α therapies. In those patients who treatment with MTX is inappropriate tocilizumab can be given alone.

Tocilizumab is the first biologic to be licensed in both DMARD and TNF-α inadequate responders and represents a significant step forward in the management options in RA.

RA is the most common of the incurable and potentially disabling chronic systemic inflammatory autoimmune diseases. Affecting approximately 0.5-1% of the population worldwide, the onset of disease occurs in adults in their fourth and fifth decade, at a time when they are most economically active. The disease, which is 2.5-fold more prevalent in women than in men[2], is characterized by symmetric synovitis and erosive arthritis, often rapidly progressive with joint damage apparent soon after the onset of symptoms[3,4]. This feature typically leads to a progressive decline in functional status and work disability[5]. Patients with RA not only suffer chronic severe disability, but are also likely to die prematurely[6,7,8,9,10]. Anemia, a common extra-articular manifestation of RA with characteristics of anemia of chronic disease, is estimated to occur in approximately 30% of patients[11] . It reduces patients' quality of life and is associated with excess morbidity and mortality[12,13,14]. Improvement in hemoglobin is associated with reduction in systemic inflammation and decrease in disease activity[15].

Timely diagnosis and early aggressive treatment with the goal of rapidly controlling symptoms, limiting joint damage, improving function and preventing disability is essential. MTX, considered the gold standard of DMARDs based on its established efficacy and safety profile, has been and remains the mainstay of treatment in newly diagnosed patients with moderate to severe disease. Other DMARDs such as leflunomide, sulfasalazine and antimalarials are generally reserved for the approximately

80% of patients with persistently active RA who have either not responded adequately to or are intolerant of MTX. The introduction of novel biologic therapies targeting cytokine pathways and mediators in the inflammatory cascade such as the tumor necrosis factor α (TNF-α) antagonists has transformed the management of the disease. These agents have a more rapid onset of action than traditional non-biologic DMARDs and often produce sustained and clinically significant suppression of signs and symptoms, as well as inhibition of joint damage. In patients with early active RA (< 2 years duration), intervention with currently available biologics has been shown to be highly effective, providing rapid clinical improvement and inhibition of joint damage progression[16,17,18,19,20].

Despite these advances, approximately 30-40% of patients with established RA fail to respond adequately either to non-biologic DMARDs or to TNF-α antagonists and 50-60% of patients fail to achieve a major clinical response (by American College of Rheumatology [ACR] criteria) or good European League Against Rheumatism (EULAR) response. Even among responders, the majority do not achieve remission[21]. Additionally, many patients experience toxicity or lose their response within 2-3 years of starting treatment[22,23,24,25,26,27]. These limitations have prompted investigation into new targets and the development of therapies with alternative mechanisms of action. Two such examples are a selective co-stimulation modulator (abatacept) and a B cell-targeted therapy (rituximab). However, there remains a need for additional unique and mechanistically specific therapies to expand the availability of effective treatment options for this disease.

Tocilizumab, a humanized anti-IL-6 receptor antibody, which blocks the function of the pleiotropic cytokine IL-6, considered to play a central role in maintaining chronic inflammation in RA, represents one such approach[28].

4.1 What was the rationale for the development of the new technology?

IL-6 is a pleiotropic pro-inflammatory multi-functional cytokine produced by a variety of cell types including various types of lymphocyte, fibroblasts, synoviocytes, endothelial cells, neurons, adrenal glands, mast cells, keratinocytes, Langerhans cells, astrocytes and colonic epithelial cells. Elevated levels of IL-6 have been implicated in the disease pathology of several inflammatory and autoimmune disorders including RA. Instrumental in RA pathophysiology, IL-6 has been shown to be involved in processes such as T-cell activation, differentiation of B cells into immunoglobulin-secreting plasma cells, maturation of megakaryocytes leading to platelet production[29,30] and is now well recognized to stimulate the production of acute phase proteins by hepatocytes. IL-6 also induces the synthesis of the iron regulatory peptide hepcidin during inflammation. Hepcidin-induced degradation of ferroportin blocks iron absorption by gut enterocytes as well as iron export out of macrophages, accounting for the apparent iron-deficiency anemia, despite adequate body iron stores, seen in inflammatory diseases[31,32]. In

addition, IL-6 is also known to promote osteoclast differentiation in the presence of soluble IL-6R (sIL-6R), indicating a role in bone resorption and the osteopenia associated with chronic inflammation[33].

Elevated serum IL-6 levels have been reported in RA patients compared with controls and in synovial fluid compared with serum, reflecting local production of IL-6 by the synovium[34,35]**.** Overproduction of IL-6 is closely related to the pathological findings in RA and there are correlations between elevated IL-6 levels in serum and synovial fluid and clinical and laboratory indices[36,37]. Thus, the inhibition of the biological activity of IL-6 and/or its receptor represents a new approach for the treatment of IL-6-associated inflammatory diseases such as RA.

4.2 What is the principal mechanism of action of the technology?

Tocilizumab (TCZ), also sometimes referred to as myeloma receptor antibody (MRA), is a recombinant humanized anti-human monoclonal antibody of the immunoglobulin G_1 (IgG_1) sub-class directed against the **soluble** and **membrane-bound** interleukin 6 receptor (IL-6R). Elevated tissue and serum levels of IL-6 have been implicated in the disease pathology of rheumatoid arthritis (RA) (see Section 4.1 above). Thus, the inhibition of the biological activity of IL-6 and/or its receptor represents a promising new approach for the treatment of RA.

4.3 What is the suggested place for this technology with respect to treatments currently available for managing the disease/condition?

The licensed indications for TCZ are as follows;

Tocilizumab, in combination with methotrexate (MTX) is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists. In these patients, tocilizumab can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Therefore the first option is to utilise tocilizumab in patients who have failed 1 or 2 previous DMARDs, with a second option to utilise tocilizumab in patients having responded inadequately to 1 or more prior TNF inhibitors. Therefore the clinical and cost effectiveness of tocilizumab in both these positions within the treatment strategy is evaluated within this submission.

It is assumed that tocilizumab will be an additive treatment option in the life time management of RA and will not substitute for any existing treatment options in the long term. This is consistent with previous NICE appraisals of biologic treatments in RA, where the current standard of care treatment sequence is compared to an alternative

treatment sequence where the new intervention is assumed to be additive. Such a treatment sequencing approach is necessary to satisfy the NICE reference case requirements for a lifetime perspective.

4.4 Describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

One area of uncertainty that is currently under review is the suitability of TNF cycling in the event that a patient has an inadequate response due to lack of efficacy. Within this submission it is assumed that the cycling of TNF in the event of lack of efficacy is not permitted consistent with NICE TA36.

Secondly the current first TNF inhibitor of choice may vary across the NHS; however the impact of modifying the base case assumption (etanercept) upon the final cost effectiveness estimates is evaluated within the submission.

4.5 Provide details of any relevant guidelines or protocols.

BSR Clinical Guidelines: Rheumatoid Arthritis

BSR Statement on Rituximab for Refractory RA

13 November 2006

Guideline for the Management of Rheumatoid Arthritis (First 2 Years)

July 2006

Updated BSR guidelines for prescribing TNF blockers in adults with Rheumatoid Arthritis

Published in July 2004. (Update of previous guidelines of April 2001)

BSR guidelines on standards of care for persons with Rheumatoid Arthritis

Published in July 2004

BSR Statement on Adalimumab for Rheumatoid Arthritis

Originally published on 11th September 2003 and later revised and updated on 7th November 2003

RCN Guidelines on Assessing, Managing and Monitoring Biologic Therapies for Inflammatory Arthritis

Published in April 2003.

Guidelines for prescribing TNF-a blockers in adults with Rheumatoid Arthritis. April 2001

Published in April 2001. For current Guidelines see above.

National Guidelines for Monitoring Second Line Drugs

Published in July 2000

The Scottish Intercollegiate Guidelines Network (SIGN) Clinical guidelines

Management of Early Rheumatoid Arthritis SIGN Publication No. 48

Published December 2000

The National Institute of Health and Clinical Excellence

Rheumatoid arthritis: the management of rheumatoid arthritis in adults

Ongoing, anticipated February 2009

Rheumatoid arthritis (refractory) - abatacept

Rheumatoid arthritis (refractory) - rituximab

Rheumatoid arthritis - adalimumab, etanercept and infliximab

Rheumatoid arthritis - anakinra

5 Equity and equality

5.1 Identification of equity and equalities issues

Are there any issues relating to equity or equalities (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?

None

How has the analysis addressed these issues?

None

6 Clinical evidence

The 5 pivotal phase III studies have been chosen to demonstrate the efficacy and safety profile of tocilizumab in relation to the decision problem

The phase II/III Japanese studies have been excluded due to the significant variation in RA clinical management compared to the EU and the applicability of the results to the UK population as a whole

The open label extension studies give some insight into the long term efficacy of tocilizumab in the DMARD and TNF-α IR populations

The five studies reviewed can be considered reflective of UK clinical practice

One area where the UK population varies from that examined in the studies is the mean number of prior DMARDs before going onto biologic therapy, this is thought to reflect the difference between the EU/US and UK in terms of guidelines prior to biologic use and the earlier availability of biologic therapy in clinical trials versus real clinical practice.

6.1 Identification of studies

The following databases were used to identify relevant studies:

- Medline via Dialog DataStar. Medline 1993 to date (MEYY) and Medline-In process-Latest eight weeks (MEIP) were searched on 20 January 2009. Medline was searched from 1993 to the present, and also the eight weeks prior to 20 January 2009.

- Embase via Dialog DataStar. Embase 1993 to date (EMYY) and Embase latest eight weeks (EMBA) were searched on 20 January 2009. Embase was searched from 1993 to the present, and also the eight weeks prior to 20 January 2009.

- The Cochrane Library, accessed via Wiley Interscience at http://www3.interscience.wiley.com. Searched on 20 January 2009. The Cochrane Library was searched with unrestricted dates up to 20 January 2009.

- EULAR abstracts (the European League against Rheumatism) (annual meetings 2002-2008) searched via the website http://www.eular.org. Searched on 21 January 2009.

- ACR (American College of Rheumatology) abstracts searched (annual meetings 2002-2008) via the website http://www.rheumatology.org Searched on 21 January 2009

Searches used index and text words which included *tocilizumab, atlizumab* (the previous generic name for tocilizumab) and *rheumatoid arthritis* as major descriptors. The search was restricted to include only documents relating to humans and clinical trials. The search was further restricted manually according to inclusion/exclusion criteria in 6.2.2. Although there were no restrictions by language, data from clinical studies conducted in Japan by Chugai were not included, as data in this patient population was not considered sufficiently relevant to European patients.

Details of the search strategies used are provided in Appendix 2, section 9.2.

6.2 Study selection

The five pivotal phase III studies have been chosen to demonstrate the efficacy and safety profile of TCZ in relation to the decision problem

The phase II/III Japanese studies have not been included due to the significant variation in RA practice and the applicability of the results to a EU population.

6.2.1 Complete list of RCTs

Pivotal Studies

The pivotal clinical development program for TCZ consists of four 24-week Phase III studies and a 52-week interim analysis of data from an ongoing 2-year Phase III study designed to evaluate physical function and prevention of joint damage. A brief description of the five Phase III studies is provided below:

- **Study WA17822** was a Phase III, three-arm randomized, double-blind, placebo-controlled, parallel group, international, multi-center study in patients with moderate to severe active RA who had an **inadequate response to MTX**. The study was designed to assess safety and reduction in the signs and symptoms of RA after 24 weeks of TCZ therapy in combination with MTX versus MTX alone.

- **Study WA17823** was a Phase III, three-arm randomized, double-blind, placebo-controlled, parallel group international multi-center study in patients with moderate to severe RA who had an **inadequate response to MTX**. The study was designed to assess safety, reduction in signs and symptoms of RA after 24 weeks, prevention of joint damage (evaluated by radiographs) at 52 weeks (with confirmation at 104 weeks) and physical function at 52 weeks (with confirmation at 104 weeks) of TCZ therapy in combination with MTX versus MTX alone.

- **Study WA18063** was a Phase III, two-arm randomized, double-blind, placebo-controlled, parallel group international multi-center study in patients with moderate to severe active RA who had an **inadequate response to current DMARD therapy**. The study was designed to assess safety and reduction in signs and symptoms of RA after 24 weeks of TCZ therapy in combination with background DMARD therapy versus DMARD therapy alone.

- **Study WA17824** was a Phase III, two-arm randomized, double-blind, double-dummy, parallel group, international, multi-center, non-inferiority study comparing TCZ monotherapy with MTX monotherapy, in patients with active RA who were **MTX naïve or who had discontinued MTX, but not due to lack of efficacy or toxic effect.** The study was designed to assess safety and reduction in signs and symptoms of RA after 24 weeks of therapy. As an internal control for efficacy, the study also included a three-arm, 8-week sub study that included a placebo arm.

- **Study WA18062** was a Phase III, three-arm, randomized, double-blind, placebo-controlled, international, multi-center study in patients with moderate to severe active RA who had an **inadequate clinical response or were intolerant to one or more anti-TNF therapies**. The anti-TNF agent was discontinued prior to randomization. The study was designed to assess safety and reduction in signs and symptoms of RA after 24 weeks of TCZ therapy in combination with MTX versus MTX alone.

Supporting Studies

Phase II dose-finding studies:

- **Study LRO301** was a 20-week Phase II, double-blind, parallel-group, placebo-controlled, randomized, seven-arm, dose-finding study conducted in Europe, with TCZ given alone or in combination with MTX. This was the primary study used to support the doses investigated in the pivotal trials.

- **Study MRA009JP** was a 12-week Phase II, double-blind, placebo-controlled, randomized, dose-finding study conducted in Japan with TCZ given alone.

Phase III studies in Japanese patients:

- **Study MRA012JP** was a Phase III, two-arm, parallel-group, open-label, multi-center study comparing TCZ 8 mg/kg monotherapy with existing therapy in RA patients who had an inadequate response to current DMARD or immunosuppressant therapy. This study was designed to investigate the safety and efficacy (including progression of structural damage) of 52 weeks of therapy.

- **Study MRA213JP** was a Phase III, two-arm, parallel-group, double-blind, multi-center study comparing TCZ 8 mg/kg monotherapy every 4 weeks with MTX 8 mg weekly in RA patients with an inadequate response to MTX. The study was designed to assess safety and signs and symptoms of RA after 24 weeks of TCZ therapy.

Long-Term Extension Studies

Patients who completed the 6-month pivotal studies (WA17822, WA18063, WA18062 and WA17824) were allowed to transition into one of two open-label, long-term extension studies (a brief summary is provided below).

- **Study WA18695** is an open-label extension study to assess the long-term safety of TCZ 8 mg/kg + MTX in patients completing treatment in WA17822.

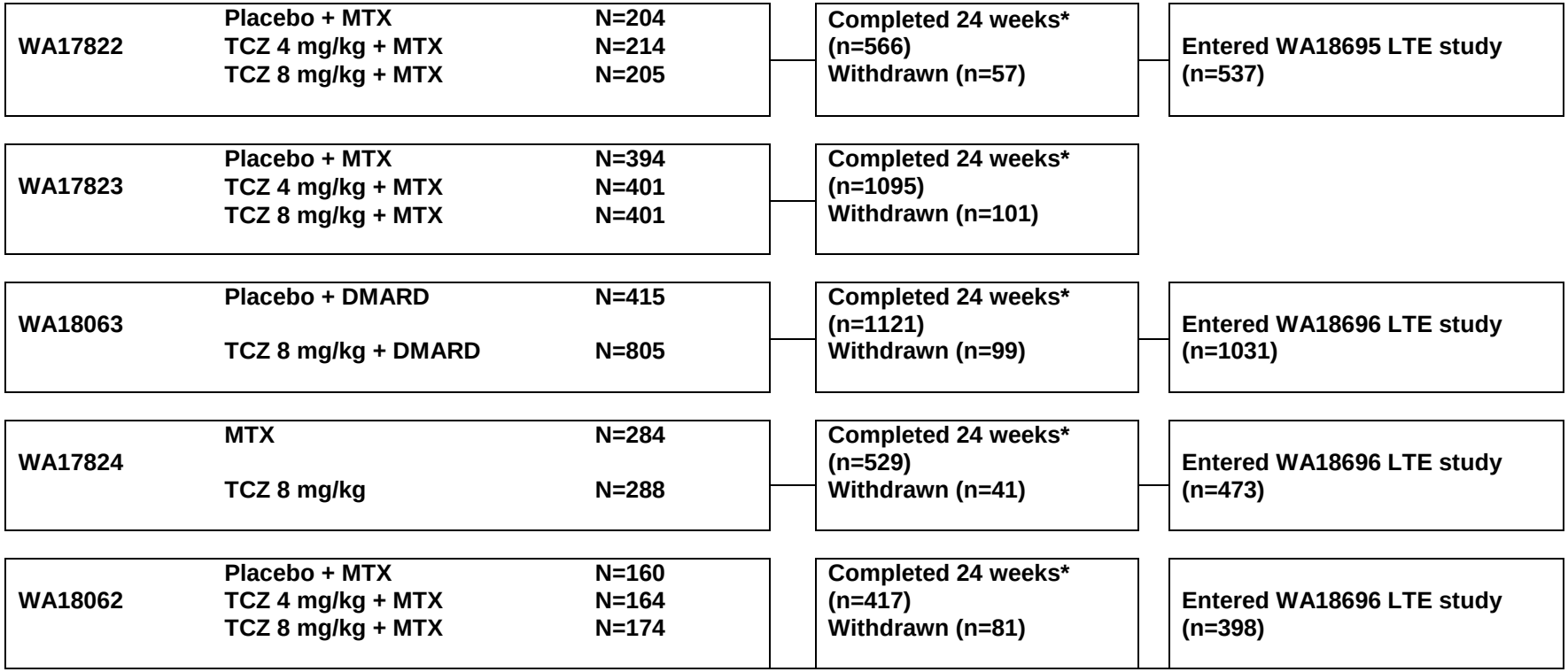
- **Study WA18696** is an open-label extension study to assess the long term safety of TCZ 8 mg/kg as monotherapy or in combination with background DMARD therapy in patients completing treatment in WA17824, WA18062, WA18063 and WA18663.

An overview of the number of patients providing efficacy data and the number of patients entering the long-term extension studies from the pivotal Phase III studies is provided in the figure below.

Chugai Pharmaceutical Co Ltd. has completed a development program for TCZ for the treatment of Castleman's disease, adult RA, systemic juvenile idiopathic arthritis and polyarticular juvenile idiopathic arthritis in Japan.

Figure 6: Overview of the Pivotal Phase III Studies (All Randomized Patients)

Note: Study WA17823 is ongoing. Information on study WA17824 does not include the placebo/TCZ sub-study patients
* Completed 24 weeks of initial or escape therapy



6.2.2 Inclusion and exclusion criteria

State the inclusion and exclusion criteria that were used to identify the studies detailed in the list of relevant RCTs. If additional inclusion criteria were applied to select studies that have been included in the systematic review, these need to be listed separately.

All studies forming part of the development program for TCZ by either Roche or Chugai have been considered. Five studies directly related to the decision problem have been chosen.

For the systematic review, the following Inclusion and Exclusion Criteria were applied:

Inclusion criteria

Published papers or abstracts which evaluated the following were included:

- Tocilizumab (or atlizumab prior to 2005) was the major focus of the paper.
- Rheumatoid arthritis was a major focus of the paper.
- Patient population consisted of patients who had responded inadequately or who were intolerant to one or more DMARDs or TNF antagonists, to be consistent with the EU licence for tocilizumab, including dose
- Controlled clinical studies
- Documents relating to humans

Exclusion criteria

Published papers or abstracts which evaluated the following were excluded:

- Any papers providing a review, update or commentary on data published elsewhere were excluded
- Any papers which only mentioned tocilizumab within a discussion of treatments for rheumatoid arthritis were excluded
- Papers covering the use of tocilizumab in Castleman's disease, juvenile idiopathic arthritis, other autoimmune diseases or other off-licence indications were excluded
- Clinical studies conducted in Japanese patients were not included, as data generated in this patient population was not considered sufficiently relevant to European patients.
- Animal studies or *in vitro* research
- Case reports

6.2.3 List of relevant RCTs

72 citations were identified as potentially relevant to the decision problem. The table below lists all of them and applies the inclusion/exclusion criteria listed in 6.2.2

Table 4: List of publications and abstracts

PUBLICATIONS/ABSTRACTS MEETING INCLUSION CRITERIA		
	Citation	**Reason for Inclusion**
1	GENOVESE MC, MCKAY JD, NASONOV EL ET AL. INTERLEUKIN−6 RECEPTOR INHIBITION WITH TOCILIZUMAB REDUCES DISEASE ACTIVITY IN RHEUMATOID ARTHRITIS WITH INADEQUATE RESPONSE TO DISEASE− MODIFYING ANTIRHEUMATIC DRUGS: THE TOCILIZUMAB IN COMBINATION WITH TRADITIONAL DISEASE−MODIFYING ANTIRHEUMATIC DRUG THERAPY STUDY. ARTHRITIS RHEUM 2008; 58(10): 2968−2980	Full publication of one of the pivotal phase III randomized controlled clinical studies (TOWARD)
2	EMERY P, KEYSTONE E, TONY HP ET AL. IL−6 RECEPTOR INHIBITION WITH TOCILIZUMAB IMPROVES TREATMENT OUTCOMES IN PATIENTS WITH RHEUMATOID ARTHRITIS REFRACTORY TO ANTI−TUMOUR NECROSIS FACTOR BIOLOGICALS: RESULTS FROM A 24−WEEK MULTICENTRE RANDOMISED PLACEBO−CONTROLLED TRIAL. ANN RHEUM DIS 2008; 67(11): 1516−1523	Full publication of one of the pivotal phase III randomized controlled clinical studies (RADIATE)
3	SMOLEN JS, BEAULIEU A, RUBBERT−ROTH A ET AL. EFFECT OF INTERLEUKIN−6 RECEPTOR INHIBITION WITH TOCILIZUMAB IN PATIENTS WITH RHEUMATOID ARTHRITIS (OPTION STUDY): A DOUBLE−BLIND, PLACEBO−CONTROLLED, RANDOMISED TRIAL. LANCET 2008; 371(9617): 987−997	Full publication of one of the pivotal phase III randomized controlled clinical studies (OPTION)
4	JONES G, GU JR, LOWENSTEIN M ET AL. TOCILIZUMAB MONOTHERAPY IS SUPERIOR TO METHOTREXATE MONOTHERAPY IN REDUCING DISEASE ACTIVITY IN PATIENTS WITH RHEUMATOID ARTHRITIS: THE AMBITION STUDY ANN RHEUM DIS 2008;67(SUPPL II):89, ABS OP-0131	First presentation of results from one of the pivotal phase III randomized controlled clinical studies (AMBITION)
5	KREMER JM, FLEISCHMANN RM, HALLAND AM ET AL. TOCILIZUMAB INHIBITS STRUCTURAL JOINT DAMAGE IN RHEUMATOID ARTHRITIS PATIENTS WITH AN INADEQUATE RESPONSE TO METHOTREXATE: THE LITHE STUDY. ARTHRITIS RHEUM 2008; 58 (SUPPL 9) ABS L14	First presentation of results from one of the pivotal phase III randomized controlled clinical studies (LITHE)
PUBLICATIONS NOT MEETING INCLUSION CRITERIA		
	CITATION	**Reason for exclusion**
6	RHEUMATOID ARTHRITIS: TOCILIZUMAB IS MORE EFFECTIVE AS METHOTREXATE. ARZNEIMITTELTHERAPIE 2008; 26(11): 433−434	Not RCT
7	SCHLEGEL A. ANTI−INTERLEUKIN−6 ANTIBODIES: TOCILIZUMAB IN RHEUMATOID ARTHRITIS AND IN JUVENILE	Review

	IDIOPATHIC ARTHRITIS. MED MONATSSCHR PHARM 2008; 31(9): 360−361	
8	MELTON L AND COOMBS A. ACTEMRA POISED TO LAUNCH IL−6 INHIBITORS. NAT BIOTECHNOL 2008; 26(9): 957−959	News article
9	BRUHN C. A NEW BIOLOGIC AGENT FOR THE TREATMENT OF RHEUMATOID ARTHRITIS IN ADULTS AND CHILDREN BEFORE THE APPROVAL. DTSCH−APOTH−ZTG 2008; 148(23): 42−45	Review
10	SCHLESSELMAN LS AND HUSSEY AP. TOCILIZUMAB: A HUMANIZED ANTI−IL−6 RECEPTOR MONOCLONAL ANTIBODY FOR THE TREATMENT OF RHEUMATOID ARTHRITIS. FORMULARY 2008; 43(8): 272−279	Review
11	DOGGRELL SA. IS TOCILIZUMAB AN OPTION FOR THE TREATMENT OF ARTHRITIS? EXPERT−OPIN−PHARMACOTHER 2008; 9(11): 2009−2013	Review
12	DEJACO C AND DUFTNER C. EFFECT OF INTERLEUKIN−6 RECEPTOR INHIBITION WITH TOCILIZUMAB IN PATIENTS WITH RHEUMATOID ARTHRITIS (OPTION STUDY): A DOUBLE−BLIND, PLACEBO−CONTROLLED, RANDOMISED TRIAL. J−MINERALSTOFFWECHSEL 2008; 15(2): 101−102	Repeat data
13	LIPSKY PE. INTERLEUKIN−6 AND RHEUMATIC DISEASES. ARTHRITIS RES THER 2006; 8(SUPPL. 2): S4	Not RCT
14	IKING KC. TOCILIZUMAB IS EFFECTIVE IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS. DTSCH MED WOCHENSCHR 2008; 133(18): 938	News article
15	MIMA T AND NISHIMOTO N. TOCILIZUMAB FOR THE TREATMENT OF RHEUMATOID ARTHRITIS. EXPERT REV CLIN IMMUNOL 2008; 4(2): 165−172	Review
16	IKING KC. TOCILIZUMAB INHIBITS RADIOLOGICAL PROGRESSION IN RHEUMATOID ARTHRITIS. AKTUEL−RHEUMATOL 2008; 33(1): 6−9	Review
17	JUNGMAYR P. RHEUMATOID ARTHRITIS: IL−6 INHIBITION WITH TOCILIZUMAB INTERRUPTS THE INFLAMMATION. DTSCH−APOTH−ZTG 2007; 147(32): 41−42	Letter
18	NISHIMOTO N, HASHIMOTO J, MIYASAKA N ET AL. STUDY OF ACTIVE CONTROLLED MONOTHERAPY USED FOR RHEUMATOID ARTHRITIS, AN IL−6 INHIBITOR (SAMURAI): EVIDENCE OF CLINICAL AND RADIOGRAPHIC BENEFIT FROM AN X RAY READER−BLINDED RANDOMISED CONTROLLED TRIAL OF TOCILIZUMAB. ANN RHEUM DIS 2007; 66(9): 1162−1167	RCT but in patients not relevant to UK population (Japanese)
19	BALINT GP AND BALINT PV. TOCILIZUMAB: A NEW FORM OF BIOLOGICAL THERAPY FOR RHEUMATOID ARTHRITIS. FUTURE RHEUMATOL 2007; 2(4): 361−371	Review

20	OGAWA J, HARIGAI M, AKASHI T ET AL. EXACERBATION OF CHRONIC ACTIVE EPSTEIN−BARR VIRUS INFECTION IN A PATIENT WITH RHEUMATOID ARTHRITIS RECEIVING HUMANISED ANTI− INTERLEUKIN−6 RECEPTOR MONOCLONAL ANTIBODY. ANN RHEUM DIS 2006; 65(12): 1667−1669	Case Report
21	MAINI RN, TAYLOR PC, SZECHINSKI J ET AL. DOUBLE−BLIND RANDOMIZED CONTROLLED CLINICAL TRIAL OF THE INTERLEUKIN−6 RECEPTOR ANTAGONIST, TOCILIZUMAB, IN EUROPEAN PATIENTS WITH RHEUMATOID ARTHRITIS WHO HAD AN INCOMPLETE RESPONSE TO METHOTREXATE. ARTHRITIS RHEUM 2006; 54(9): 2817−2829	RCT but phase II dose-ranging study
22	TOCILIZUMAB MORE EFFECTIVE THAN CONVENTIONAL DMARDS IN RA. PHARM J 2005; 275(7379): 716	News article
23	NISHIMOTO N, TERÃO K, MIMA T ET AL. MECHANISMS AND PATHOLOGIC SIGNIFICANCES IN INCREASE IN SERUM INTERLEUKIN−6 (IL−6) AND SOLUBLE IL−6 RECEPTOR AFTER ADMINISTRATION OF AN ANTI−IL−6 RECEPTOR ANTIBODY, TOCILIZUMAB, IN PATIENTS WITH RHEUMATOID ARTHRITIS AND CASTLEMAN DISEASE. BLOOD 2008 (EPUB: 10 SEP 2008); 112(10): 3959−3964	Pharmacokinetic outcomes, and off-licence use included (Castleman's Disease)
24	HEINZL S. TOCILIZUMAB IN RHEUMATOID ARTHRITIS: INTERLEUKIN 6 AS NEW TARGET. MED MONATSSCHR PHARM 2008; 31(12): 450−453	Review
25	ARINGER M AND SMOLEN JS. TARGETED THERAPIES − MANY WAYS TO (THE PEACE OF) ROME. IMMUNOL ENDOCR METAB AGENTS MED CHEM 2008; 8(3): 200−206	Review
26	NAGASHIMA T AND MINOTA S. LONG−TERM TOCILIZUMAB THERAPY IN A PATIENT WITH RHEUMATOID ARTHRITIS AND CHRONIC HEPATITIS B. RHEUMATOLOGY 2008; 47(12): 1838−1840	Case report
27	CHOY E. RADIATE: MORE TREATMENT OPTIONS FOR PATIENTS WITH AN INADEQUATE RESPONSE TO TUMOR NECROSIS FACTOR ANTAGONISTS. NAT CLIN PRACT RHEUMATOL 2008 (EPUB: 23 DEC 2008);ISSN: 1745−8390.	Review
28	NISHIMOTO N. (IN PROCESS CITATION). JAPANESE JOURNAL OF CLINICAL IMMUNOLOGY 2008; 31(5): 399−404	Review
29	PLUSHNER SL. TOCILIZUMAB: AN INTERLEUKIN−6 RECEPTOR INHIBITOR FOR THE TREATMENT OF RHEUMATOID ARTHRITIS. ANN PHARMACOTHER 2008 (EPUB: 28 OCT 2008); 42(11): 1660−1668	Review
30	BINGHAM CO 3RD. EMERGING THERAPEUTICS FOR RHEUMATOID ARTHRITIS.	Review

	BULL NYU HOSP JT DIS 2008; 66(3): 210−215	
31	JOHNSON J AND WANG MY. INTERLUKIN−6 RECEPTOR INHIBITOR TOCILIZUMAB: A NEW TREATMENT OPTION IN RHEUMATOID ARTHRITIS? NEUROSURGERY 2008; 63(2): N8	News article
ABSTRACTS NOT MEETING INCLUSION CRITERIA		
	CITATION	Reason for exclusion
32	SMOLEN J, BEAULIEU A, RUBBERT-ROTH A ET AL. TOCILIZUMAB, A NOVEL MONOCLONAL ANTIBODY TARGETING IL-6 SIGNALLING, SIGNIFICANTLY REDUCES DISEASE ACTIVITY IN PATIENTS WITH RHEUMATOID ARTHRITIS ANN RHEUM DIS 2007;66(SUPPL II):87, ABS OP0117	Repeat data
33	SEBBA AI, CALVO A, LI X ET AL. , TOCILIZUMAB MONOTHERAPY IMPROVES QUALITY OF LIFE COMPARED WITH METHOTREXATE MONOTHERAPY IN PATIENTS WITH RHEUMATOID ARTHRITIS: THE AMBITION STUDY. ANN RHEUM DIS 2008;67(SUPPL II):342, ABS FRI0174	Repeat data
34	ALTEN R, RAMOS REMUS C, ROVENSKY J ET AL. TOCILIZUMAB, A NOVEL MONOCLONAL ANTIBODY TARGETING IL-6 SIGNALLING, SIGNIFICANTLY IMPROVES QUALITY OF LIFE IN PATIENTS WITH RHEUMATOID ARTHRITIS. ANN RHEUM DIS 2007;66(SUPPL II):428, ABS SAT0001	Repeat data
35	BEAULIEU AD, MCKAY JD, PAVELKA K ET AL. TREATMENT WITH THE HUMANIZED ANTI-INTERLEUKIN-6 RECEPTOR ANTIBODY TOCILIZUMAB RESULTS IN RAPID IMPROVEMENTS IN THE SIGNS AND SYMPTOMS OF RHEUMATOID ARTHRITIS: RESULTS FROM A POOLED ANALYSIS OF CLINICAL TRIAL DATA FROM OPTION AND TOWARD. ANN RHEUM DIS 2008;67(SUPPL II):195, ABS THU0184	Repeat data
36	COSSON V, FREY N, GRANGE S ET AL. POPULATION PK/PD ANALYSIS OF THE RELATIONSHIP BETWEEN TOCILIZUMAB EXPOSURE AND NEUTROPHIL COUNT IN PATIENTS WITH RHEUMATOID ARTHRITIS. ANN RHEUM DIS 2008;67(SUPPL II):192, ABS THU0175	Repeat data
37	LEVI M, FREY N, GRANGE S ET AL. REDUCTION IN INFLAMMATORY BIOMARKERS WITH INCREASING EXPOSURE TO THE IL-6 INHIBITOR, TOCILIZUMAB, IN PATIENTS WITH RHEUMATOID ARTHRITIS: GRAPHICAL ANALYSIS OF POOLED DATA. ANN RHEUM DIS 2008;67(SUPPL II):192, ABS THU0177	Repeat data
38	SMOLEN J, MYSLER EF, RUBBERT-ROTH A ET AL. TOCILIZUMAB RAPIDLY AND SIGNIFICANTLY REDUCES DAS28 IN PATIENTS WITH RHEUMATOID ARTHRITIS INADEQUATELY RESPONDING TO DMARDS: POOLED ANALYSIS. ANN RHEUM DIS 2008;67(SUPPL II):341, ABS FRI0172	Repeat data

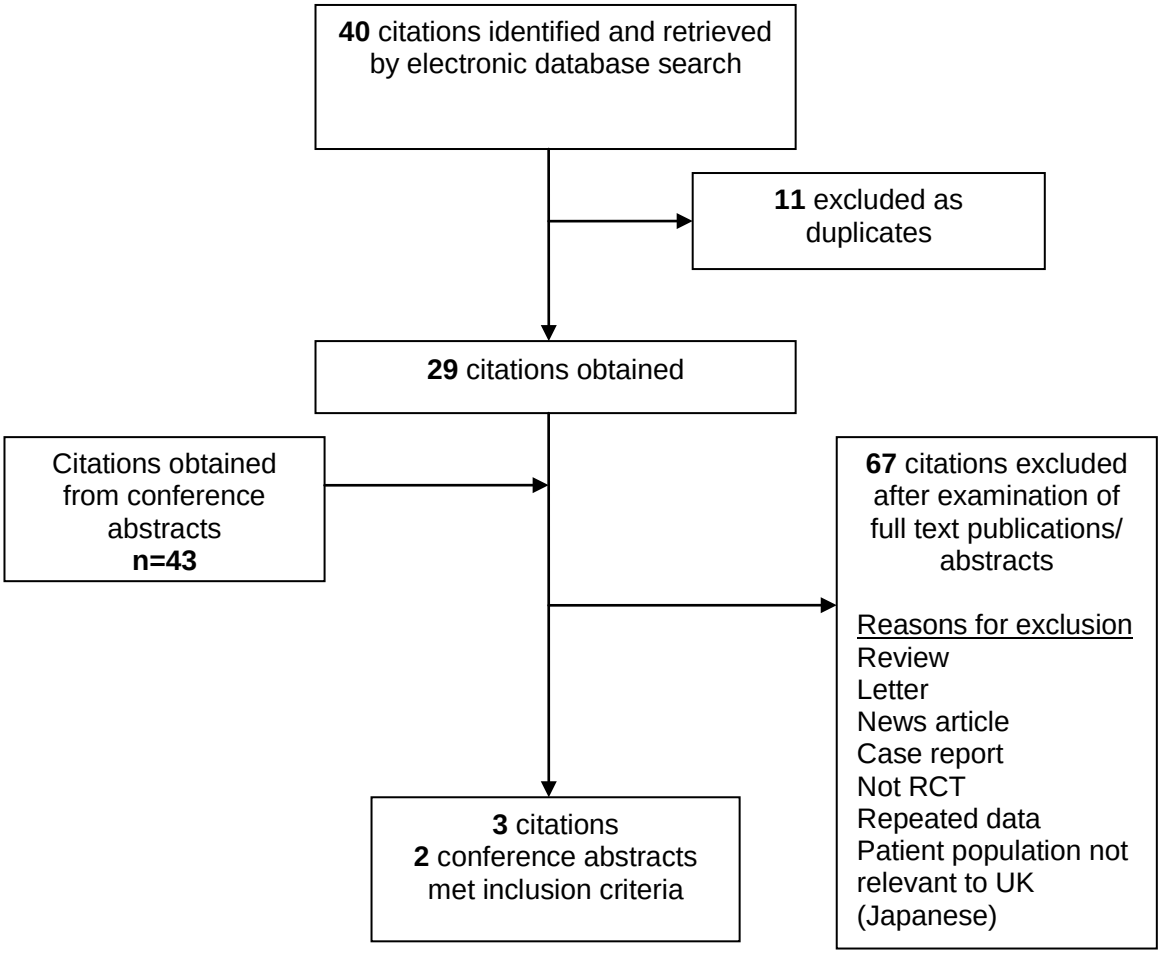
39	EMERY P, KEYSTONE E, TONY H ET AL. TOCILIZUMAB (TCZ) SIGNIFICANTLY IMPROVES DISEASE OUTCOMES IN PATIENTS WITH RHEUMATOID ARTHRITIS WHOSE ANTI-TNF THERAPY FAILED: THE RADIATE STUDY TOCILIZUMAB (TCZ) SIGNIFICANTLY IMPROVES DISEASE OUTCOMES IN PATIENTS WITH RHEUMATOID ARTHRITIS WHOSE ANTI-TNF THERAPY FAILED: THE RADIATE STUDY. ANN RHEUM DIS 2008;67(SUPPL II):127	Repeat data
40	GENOVESE MC, BEAULIEU AD, RAMOS-REMUS C ET AL. EFFICACY OF TOCILIZUMAB IN COMBINATION WITH DMARDS IS SUPERIOR TO DMARDS ALONE IN MODERATE-TO-SEVERE RHEUMATOID ARTHRITIS BASED ON ACR CRITERIA: A POOLED ANALYSIS OF CLINICAL TRIAL DATA FROM OPTION AND TOWARD. ANN RHEUM DIS 2008;67(SUPPL II):195, ABS THU0185	Repeat data
41	LEVI M, FREY N, GRANGE S ET AL. EFFECT OF TOCILIZUMAB EXPOSURE ON IL-6 AND IL-6 RECEPTOR LEVELS IN PATIENTS WITH RHEUMATOID ARTHRITIS: GRAPHICAL ANALYSIS OF POOLED DATA FROM FOUR PHASE 3 CLINICAL TRIALS**.** ANN RHEUM DIS 2008;67(SUPPL II):192, ABS THU0176	Repeat data
42	SMOLEN J, MARTIN-MOLA E, RUBBERT-ROTH A ET AL. EFFICACY AND SAFETY OF TOCILIZUMAB IN RHEUMATOID ARTHRITIS IN PATIENTS ABOVE AND BELOW 65 YEARS OF AGE WITH AN INADEQUATE RESPONSE TO DMARDS. ANN RHEUM DIS 2008;67(SUPPL II):338, ABS FRI0164	Repeat data
43	GENOVESE MC, RUBBERT-ROTH A, NASONOV E ET AL. THE EFFICACY AND SAFETY OF TOCILIZUMAB IN THE TREATMENT OF EARLY AND ESTABLISHED RHEUMATOID ARTHRITIS. ANN RHEUM DIS 2008;67(SUPPL II):125, ABS OP0245	Repeat data
44	SMOLEN JS, CHESTER WASKO M, RAMOS REMUS CR ET AL. TOCILIZUMAB IMPROVES HEMOGLOBIN LEVELS AND FACIT-FATIGUE SCORES IN PATIENTS WITH RHEUMATOID ARTHRITIS. ANN RHEUM DIS 2008;67(SUPPL II):189, ABS THU0168	Repeat data
45	LEVI M, FREY N, GRANGE S ET AL. EXPOSURE TO TOCILIZUMAB, AN INHIBITOR OF IL-6, IS ASSOCIATED WITH REDUCTIONS IN DISEASE ACTIVITY SCORE IN PATIENTS WITH RHEUMATOID ARTHRITIS: A POPULATION PK/PD ANALYSIS. ANN RHEUM DIS 2008;67(SUPPL II):191, ABS THU0174	Repeat data
46	RAMOS REMUS CR, NASONOV E, ROVENSKY J ET AL. TOCILIZUMAB IMPROVES QUALITY OF LIFE OUTCOMES IN RHEUMATOID ARTHRITIS PATIENTS REGARDLESS OF AGE IN PATIENTS WITH AN INADEQUATE RESPONSE TO DMARDS. ANN RHEUM DIS 2008;67(SUPPL II):610, ABS AB0381	No data presented

47	KREMER J, POPE J, DIKRANIAN A ET AL. IMPROVEMENTS IN HEALTH RELATED QUALITY OF LIFE MEASURES WITH TOCILIZUMAB (TCZ) TREATMENT IN PATIENTS WITH RHEUMATOID ARTHRITIS DESPITE PRIOR ANTI-TNF THERAPY: THE RADIATE STUDY. ANN RHEUM DIS 2008;67(SUPPL II):609, ABS AB0366	No data presented
48	PAVELKA K, GOMEZ-REINO JJ, FAIRFAX MJ ET AL. RAPID IMPROVEMENT IN HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH RHEUMATOID ARTHRITIS WITH AN INADEQUATE RESPONSE TO A RANGE OF DMARDS WITH TOCILIZUMAB TREATMENT**.** ANN RHEUM DIS 2008;67(SUPPL II):611, ABS AB0393	No data presented
49	GARNERO P, MAREAU E, THOMPSON E ET AL. THE ANTI-IL6 RECEPTOR INHIBITOR TOCILIZUMAB (TCZ) COMBINED WITH METHOTREXATE (MTX) HAS BENEFICIAL EFFECTS ON BONE AND CARTILAGE METABOLISM IN PATIENTS WITH RHEUMATOID ARTHRITIS (RA): RESULTS OF A PHASE III 24 WEEK RANDOMIZED PLACEBO CONTROLLED STUDY. ANN RHEUM DIS 2008;67(SUPPL II):193, ABS THU0178	Repeat data
50	SMOLEN J, PAVELKA K, ROVENSKY J ET AL. TOCILIZUMAB RAPIDLY IMPROVES QUALITY OF LIFE IN PATIENTS WITH RHEUMATOID ARTHRITIS INADEQUATELY RESPONDING TO DMARDS: POOLED ANALYSIS. ANN RHEUM DIS 2008;67(SUPPL II):608, ABS AB0353	No data presented
51	SMOLEN JS, VAN VOLLENHOVEN R, RUBBERT-ROTH A ET AL. ANALYSIS OF BASELINE DATA AND NEUTROPHIL COUNTS IN PATIENTS WITH SERIOUS INFECTIONS FROM TWO TOCILIZUMAB CLINICAL TRIALS. ANN RHEUM DIS 2008;67(SUPPL II):190, ABS THU0169	Repeat data
52	BEAULIEU A, COMBE B, RUBBERT-ROTH A ET AL. LIVER TRANSAMINASES AND TOTAL BILIRUBIN LEVELS DURING TOCILIZUMAB TREATMENT IN PATIENTS WHO FAILED PRIOR DMARD TREATMENT. ANN RHEUM DIS 2008;67(SUPPL II):341, ABS FRI0173	Repeat data
53	SMOLEN J, BONFIGLIOLI R, BEAULIEU A ET AL. SAFETY OF TOCILIZUMAB IN PATIENTS WITH RA WITH INADEQUATE RESPONSE TO DMARDS. ANN RHEUM DIS 2008;67(SUPPL II):338, ABS FRI0163	Repeat data
54	SMOLEN J, ROVENSKY J, RAMOS-REMUS C ET AL. TARGETING THE IL-6 RECEPTOR WITH THE MONOCLONAL ANTIBODY TOCILIZUMAB SIGNIFICANTLY IMPROVES QUALITY OF LIFE IN PATIENTS WITH RHEUMATOID ARTHRITIS. ACR 2007 ABS 292	Repeat data
55	FREY N, GRANGE S, WOODWORTH T ET AL.	Repeat data

	RELATIONSHIP BETWEEN SERUM CONCENTRATIONS OF THE INTERLEUKIN-6 RECEPTOR INHIBITOR TOCILIZUMAB AND C-REACTIVE PROTEIN REDUCTION IN RA PATIENTS: 6 MONTHS' DATA FROM A PHASE 3 STUDY. ACR 2007 ABS 259	
56	GOMEZ-REINO JJ, FAIRFAX MJ, PAVELKA K ET AL. TARGETED INHIBITION OF IL-6 SIGNALLING WITHTOCILIZUMAB IMPROVES QUALITY OF LIFE AND FUNCTION IN PATIENTS WITH RHEUMATOID ARTHRITIS WITH INADEQUATE RESPONSE TO A RANGE OF DMARDS. ACR 2007 ABS L6	Repeat data
57	GENOVESE M, MCKAY J, NASONOV E ET AL. IL-6 RECEPTOR INHIBITION WITH TOCILIZUMAB REDUCES DISEASE ACTIVITY IN PATIENTS WITH RHEUMATOID ARTHRITIS WITH INADEQUATE RESPONSE TO A RANGE OF DMARDS: THE TOWARD STUDY. ACR 2007 ABS L15	Repeat data
58	BEAULIEU AD, RUBBERT-ROTH A, WOODWORTH T ET AL. TARGETED INHIBITION OF THE IL-6 RECEPTOR WITH TOCILIZUMAB EFFECTIVELY REDUCES DISEASE ACTIVITY IN PATIENTS WITH RHEUMATOID ARTHRITIS. ACR 2007 ABS 2089	Repeat data
59	SMOLEN JS, BEAULIEU AD, DIKRANIAN A ET AL. SAFETY OF TOCILIZUMAB IN PATIENTS WITH RHEUMATOID ARTHRITIS: POOLED ANALYSIS OF FIVE PHASE 3 CLINICAL TRIALS. ACR 2008 ABS 1669	Repeat data
60	SMOLEN JS, CHURCHILL M, RIZZO W ET AL. TOCILIZUMAB TREATMENT RESULTS IN RAPID IMPROVEMENTS IN THE SIGNS AND SYMPTOMS OF MODERATE-TO-SEVERE RHEUMATOID ARTHRITIS IN FOUR PATIENT POPULATIONS WITH DIFFERENT PRIOR THERAPY EXPOSURE. ACR 2008 ABS 989	Repeat data
61	GENOVESE MC, SMOLEN JS, EMERY P ET AL. CONCOMITANT USE OF STATINS IN TOCILIZUMAB-TREATED PATIENTS WITH RHEUMATOID ARTHRITIS WITH ELEVATED LOW DENSITY LIPOPROTEIN CHOLESTEROL: ANALYSIS OF FIVE PHASE 3 CLINICAL TRIALS. ACR 2008 ABS 1672	Repeat data
62	EMERY P, KEYSTONE E, TONY HP ET AL. TOCILUZUMAB (TCZ) RAPIDLY AND SIGNIFICANTLY IMPROVES OUTCOMES IN PATIENTS WITH RHEUMATOID ARTHRITIS (RA) WHO HAVE INADEQUATE RESPONSE (IR) TO TNF ANTAGONISTS. ACR 2008 ABS 1209	Repeat data
63	JONES G, GU JR, LOWENSTEIN M ET AL. THE AMBITION STUDY: SUPERIORITY OF TOCILUZUMAB (TCZ) VS METHOTREXATE (MTX) MONOTHERAPY IN PATIENTS WITH RHEUMATOID ARTHRITIS (RA). ACR 2008 ABS 1210	Repeat data
64	KREMER JM, JOHN AK, MALAMET R ET AL. HEPATIC AMINOTRANSFERASES AND BILIRUBIN	Repeat data

	LEVELS DURING TOCILIZUMAB TREATMENT OF PATIENTS WITH RHEUMATOID ARTHRITIS: POOLED ANALYSIS OF FIVE PHASE 3 CLINICAL TRIALS. ACR 2008 ABS 1667	
65	GENOVESE M, SIRI D, TOMSIC M ET AL. TOCILUZUMAB (TCZ) MONOTHERAPY IMPROVES RHEUMATOID ARTHRITIS (RA) OUTCOMES REGARDLESS OF DISEASE DURATION. ACR 2008 ABS 988	Repeat data
66	EMERY P, KEYSTONE E, TONY HP ET AL. PATIENTS ACHIEVE SIGNIFICANT IMPROVEMENT IN RHEUMATOID ARTHRITIS (RA) OUTCOMES WITH TOCILUZUMAB (TCZ) REGARDLESS OF PRIOR INADEQUATE RESPONSE (IR) TO TNF ANTAGONISTS. ACR 2008 ABS 990	Repeat data
67	KREMER J, POPE J, TONY HP ET AL. TOCILUZUMAB (TCZ) IMPROVES QUALITY OF LIFE (QOL) IN PATIENTS WITH RHEUMATOID ARTHRITIS (RA) WHO HAD INADEQUATE RESPONSE (IR) TO TNF ANTAGONISTS. ACR 2008 ABS 991	Repeat data
68	GENOVESE MC, SMOLEN JS, EMERY P ET AL. LIPID AND INFLAMMATORY BIOMARKER PROFILES IN PATIENTS RECEIVING TOCILIZUMAB FOR RHEUMATOID ARTHRITIS: ANALYSIS OF FIVE PHASE 3 CLINICAL TRIALS. ACR 2008 ABS 987	Repeat data
69	GARNERO P, MAREAU E, THOMPSON L ET AL. THE ANTI-IL6 RECEPTOR INHIBITOR TOCILIZUMAB (TCZ) COMBINED WITH METHOTREXATE (MTX) INDUCES A RAPID AND SUSTAINED DECREASE OF BONE AND CARTILAGE DEGRADATION IN PATIENTS WITH RHEUMATOID ARTHRITIS (RA). ACR 2008 ABS 992	Repeat data
70	RAMOS-REMUS C, GENOVESE MC, HARRELL RA ET AL. LOW IMMUNOGENIC POTENTIAL OF TOCILIZUMAB IN PATIENTS WITH RHEUMATOID ARTHRITIS: ANALYSIS OF FOUR PHASE 3 CLINICAL TRIALS. ACR 2008 ABS 993	Repeat data
71	VAN VOLLENHOVEN RF, SMOLEN J, TONY HP ET AL. SAFETY OF TOCILIZUMAB IN PATIENTS WITH RHEUMATOID ARTHRITIS: AN INTERIM ANALYSIS OF LONG-TERM EXTENSION TRIALS WITH A MEAN TREATMENT DURATION OF 1.5 YEARS. ACR 2008 ABS 1670	Repeat data
72	KREMER JM, VAN VOLLENHOVEN RF, RIDLEY DJ ET AL. RELATIONSHIP BETWEEN PATIENT CHARACTERISTICS AND THE DEVELOPMENT OF SERIOUS INFECTIONS IN PATIENTS RECEIVING TOCILIZUMAB: RESULTS FROM LONG-TERM EXTENSION STUDIES WITH A FOLLOW-UP DURATION OF 1.5 YEARS. ACR 2008 ABS 1668	Repeat data

QUORUM flow of relevant RCTs



6.2.4 List of relevant non-randomised controlled trials

There are no non randomised controlled trials to be considered in this submission

6.2.5 Ongoing studies

Data from the long term extension studies described in section 6.2.1 will be cut during the next 12 months.

WA17823 will report 104 week radiographic endpoints in mid to late 2009

A study investigating changes in atherogenic indices over time following treatment with TCZ 8mg/kg in patients who have previously had an inadequate response to MTX will also report during the next 12 months. This study is a multinational study with US, Canadian and UK involvement. The UK has once centre participating.

6.3 Summary of methodology of relevant RCTs

The five pivotal phase III studies are randomised controlled trials using the licensed dose of tocilizumab

The total number of patients included is 3778

The three DMARD IR studies are comparable in baseline characteristics and were designed to allow the pooling of results presented in section 6.5

All outcomes specified in the trial protocols will be presented, however special attention will be paid to ACR, DAS and HAQ-DI in relation to the decision problem

6.3.1 Methods

An overview of the key design features of the five pivotal Phase III studies is provided in the table below. All five Phase III studies were multi-center, randomized, double-blind, controlled trials. All five studies included an escape arm.

The objectives of the studies were similar. The primary efficacy objective of studies WA17822, WA17823 and WA18062 was to assess the efficacy of TCZ vs. placebo in patients with moderate to severe active RA with regard to reduction in signs and symptoms over 6 months of treatment **in combination with background MTX therapy**. Studies WA17822 and WA17823 were conducted in patients with an inadequate clinical

response to MTX and study WA18062 was conducted in patients who had had inadequate response to one or more anti-TNF therapies.

The primary objective of study WA18063 was to assess the efficacy of TCZ vs. placebo in patients with moderate to severe active RA, with regard to reduction in signs and symptoms over 6 months of treatment **in combination with background DMARD therapy**. This study was conducted in patients with an inadequate clinical response to current DMARD therapy.

The primary objective of study WA17824 was to assess the efficacy of TCZ monotherapy vs. MTX in patients who had not been treated with MTX within 6 months prior to randomization and who had not discontinued previous MTX treatment as a result of clinically important toxic effects or lack of response (as determined by the investigator). Secondary and additional study objectives are presented for all Phase III pivotal studies below in table 5.

With the exception of WA17823, all studies had a 24-week treatment period and the primary endpoint was the proportion of ACR20 responders at week 24.

Study WA17823 is an ongoing study with two planned interim analyses; primary endpoints are evaluated at 6, 12 and 24 months. The 6-month primary endpoint was the proportion of ACR20 responders at week 24. The 12 and 24 month primary endpoints are the change from baseline in modified Sharp total radiographic score and change in physical function as measured by the area under the curve for the change from baseline in the Health Assessment Questionnaire-Disability Index (HAQ-DI). After year 2, patients can enter an optional open-label extended treatment period of up to 3 years.

Study WA17824 was designed to demonstrate non-inferiority against MTX and included a 3-arm randomized, double-blind, double-dummy, parallel-group substudy with a placebo arm (8 weeks of placebo treatment followed by 16 weeks of TCZ 8 mg/kg) as an internal control for efficacy. The substudy was conducted only at sites in the USA, Canada and Israel (countries which allowed this short duration of placebo treatment). On completion of 24 weeks of treatment, all patients had the option to enter an open-label extension (WA18696) or, if responding well to their double-blind treatment (defined as achieving a $\geq$ 50% improvement in swollen joint count [SJC] and tender joint count [TJC] at week 24 for two consecutive visits, ie, weeks 20 and 24), they had the option to remain on blinded treatment after week 24 until the study was un-blinded. This was termed the 'transition phase'. Study treatment remained blinded until the last patient completed his/her last visit in the double-blind treatment portion of the study and the study database was locked, after which patients had the option to enter WA18696.

Table 5: Key Design Features of the Pivotal Phase III Studies

	WA17822	WA17823	WA17824	WA18062	WA18063	WA18695	WA18696
Design and Duration	DB, R, PC: 24-week	DB, R, PC; year 1 DB, year 2 OL	DB, DD, R, PC: 24-week	DB, R, PC: 24-week	DB, R, PC: 24-week	OL extension study; approximately 5 years*	OL extension study; approximately 5 years*
Patient Population	Moderate to severe active RA in MTX inadequate responders	Moderate to severe active RA in MTX inadequate responders	Active RA; MTX naïve or MTX discontinued but not due to lack of efficacy or toxic effect	Moderate to severe active RA in patients with inadequate response to anti-TNF agent(s)	Moderate to severe active RA in patients with inadequate response to DMARDs	Patients completing treatment in WA17822	Patients completing treatment in WA17824, WA18062, WA18063, WP18663
Treatment	**3 arm study**: Tocilizumab: 4 or 8 mg/kg or placebo iv every 4 weeks + MTX 10-25 mg/week	**3 arm study**: Tocilizumab: 4 or 8 mg/kg or placebo iv every 4 weeks + MTX 10-25 mg/week	**2 arm study**: Tocilizumab: 8 mg/kg iv every 4 weeks **or** MTX 7.5-20 mg/week (po) **Substudy includes 3rd arm:** Placebo (8 weeks placebo then 16 weeks TCZ 8 mg/kg)	**3 arms**: Tocilizumab: 4 or 8 mg/kg or placebo iv every 4 weeks plus MTX 10-25 mg/week	**2 arms**: Tocilizumab: 8 mg/kg or placebo iv every 4 weeks plus standard DMARD(s)	**1 arm**: Tocilizumab: 8 mg/kg iv every 4 weeks plus MTX	**1 arm**: Tocilizumab: 8 mg/kg iv every 4 weeks alone or plus MTX / other DMARD(s)
Escape therapy	Week 16: TCZ 8 mg/kg	Week 16 onwards: TCZ 4 or 8 mg/kg	Substudy only, up to Week 8: TCZ 8 mg/kg	Week 16: TCZ 8 mg/kg	Week 16: adjustment of background DMARD	-	-
Total Randomized Patients	623	1196	673	499	1220	537**	1902**
Primary Endpoint at Week 24	ACR20 response rate	ACR20 response rate	ACR20 response rate	ACR20 response rate	ACR20 response rate	Long term safety/efficacy	Long term safety/efficacy

DB = double blind, R = randomized, PC = placebo controlled, DD = double dummy, OL = open label
* Or when tocilizumab becomes commercially available in the participating country, or when the sponsor decides to discontinue the study.
** Patients were not randomized into WA18695 and WA18696, but enrolled from studies WA17822, WA18063, WA18062 and WA17824

Table 6: Objectives for All Pivotal Phase III Studies (WA17822, WA17823, WA18063, WA17824 and WA18062)

WA17822	WA17823	WA18063	WA17824	WA18062
To assess the efficacy of tocilizumab vs placebo, both in combination with MTX, with regard to reduction inthe signs and symptoms over 6 months of treatment, in patients with moderate to severe active RA who have previously had an inadequate clinical response to MTX.	Primary: to assess the efficacy of treatment with tocilizumab versus placebo, in combination with MTX, with regard to the following three primary endpoints in patients with moderate to severe, active RA who have had an inadequate response to MTX: – Reduction in signs and symptoms over 6 months – Prevention of structural joint damage over 12 months (confirmation at 24 months) – Improvement in physical function over 12 months (confirmation at 24 months).	Primary: to assess the efficacy of treatment with tocilizumab vs placebo, both in combination with stable, ongoing therapy, with regard to reduction in signs and symptoms in patients with moderate to severe active RA and inadequate response to current DMARD treatment.	Primary: to assess the efficacy of tocilizumab alone vs. MTX alone with regard to reduction in signs and symptoms in patients with active RA who had not been treated with MTX within 6 months prior to randomization, and who had not discontinued previous MTX treatment as a result of clinically important toxic effects or lack of response as determined by the investigator.	Primary: to assess the efficacy of treatment with tocilizumab vs placebo, both in combination with MTX, with regard to reduction in signs and symptoms over 6 months of treatment, in patients with moderate to severe active RA who have had an inadequate clinical response to one or more anti-TNF therapies.
To assess the safety of tocilizumab vs placebo, both in combination with MTX, with regard to adverse events and laboratory assessments.	To assess the safety of tocilizumab versus placebo, in combination with MTX, with regard to AEs and laboratory assessments.	To assess the safety of tocilizumab vs placebo, both in combination with stable, ongoing therapy, with regard to adverse events and Laboratory assessments in patients with moderate to severe active RA and inadequate response to current DMARD treatment	To assess the safety of tocilizumab alone vs. MTX alone with regard to adverse events and laboratory assessments in patients with active RA.	To assess the safety of tocilizumab vs placebo, both in combination with MTX, with regard to adverse events and laboratory assessments.

In all studies PK and PD plus immunology were also examined

6.3.2 **Participants**

Comparison of Key Selection Criteria for Pivotal Phase III Trials

	WA17822	WA17823	WA18063	WA17824	WA18062
Inclusion Criteria					
RA duration (ACR criteria) ≥ 6 months ≥ 3 months	X	X	X	 X	X
Joint counts SJC ≥ 6 (of 66) and TJC ≥ 8 (of 68)	X	X	X	X	X
Acute Phase Reactants CRP ≥ 1 mg/dL (10 mg/L) or ESR ≥ 28 mm/h	X	X	X	X	X
MTX Taking MTX for at least 12 weeks immediately prior to baseline, of which the last 8 weeks must have been at a stable dose of between 10 and 25 mg/week (po or parenteral).	X	X			X
MTX naïve or not treated with MTX within 6 months prior to randomization; did not discontinue MTX as a result of clinically important toxic effects or lack of response				X	
Other DMARDs • DMARDs including biologics other than MTX withdrawn prior to baseline	X	X			X
• All previous DMARDs withdrawn				X	
• Stable dose of permitted DMARDs (traditional, no biologics) for at least 8 weeks prior to baseline			X		

SJC = Swollen Joint Count, TJC = Tender Joint Count, CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; ACR = American College of Rheumatology

Comparison of Key Selection Criteria for Pivotal Phase III Trials (Cont.)

	WA17822	WA17823	WA18063	WA17824	WA18062
Inclusion Criteria continued					
Previous anti-TNF agents • See under Excluded Previous and Concomitant Medications below	X	X	X	X	
• Within one year prior to randomization, experienced an inadequate response to previous or current treatment with etanercept, infliximab or adalimumab because of toxicity or inadequate efficacy*.					X
Previous NSAIDs /oral corticosteroids Oral corticosteroids (≤ 10 mg/day prednisone or equivalent) and NSAIDs (up to the maximum recommended dose) were permitted if the dose had been stable for at least 6 weeks prior to baseline	X	X	X	X	X
Exclusion Criteria					
Functional class IV as defined by the ACR Classification of Functional Status in RA.	X	X	X	X	X
Excluded Previous or Concomitant Therapy • Unsuccessful treatment with an anti-TNF agent (ie, significant safety issues or lack of efficacy)	X	X	X	X	
• Intra-articular or parenteral corticosteroids within four weeks prior to screening.	X	X	X	X	X

Note: In addition, for study WA17823, patients had to have radiographic evidence of at least one joint with definite erosion attributable to RA, as determined by a central reading site.
* Etanercept ≥ 3 months at 25 mg twice a week (or 50 mg weekly), or at least 4 infusions of infliximab at ≥ 3 mg/kg or adalimumab at a minimum of 40 mg every other week for ≥ 3 months

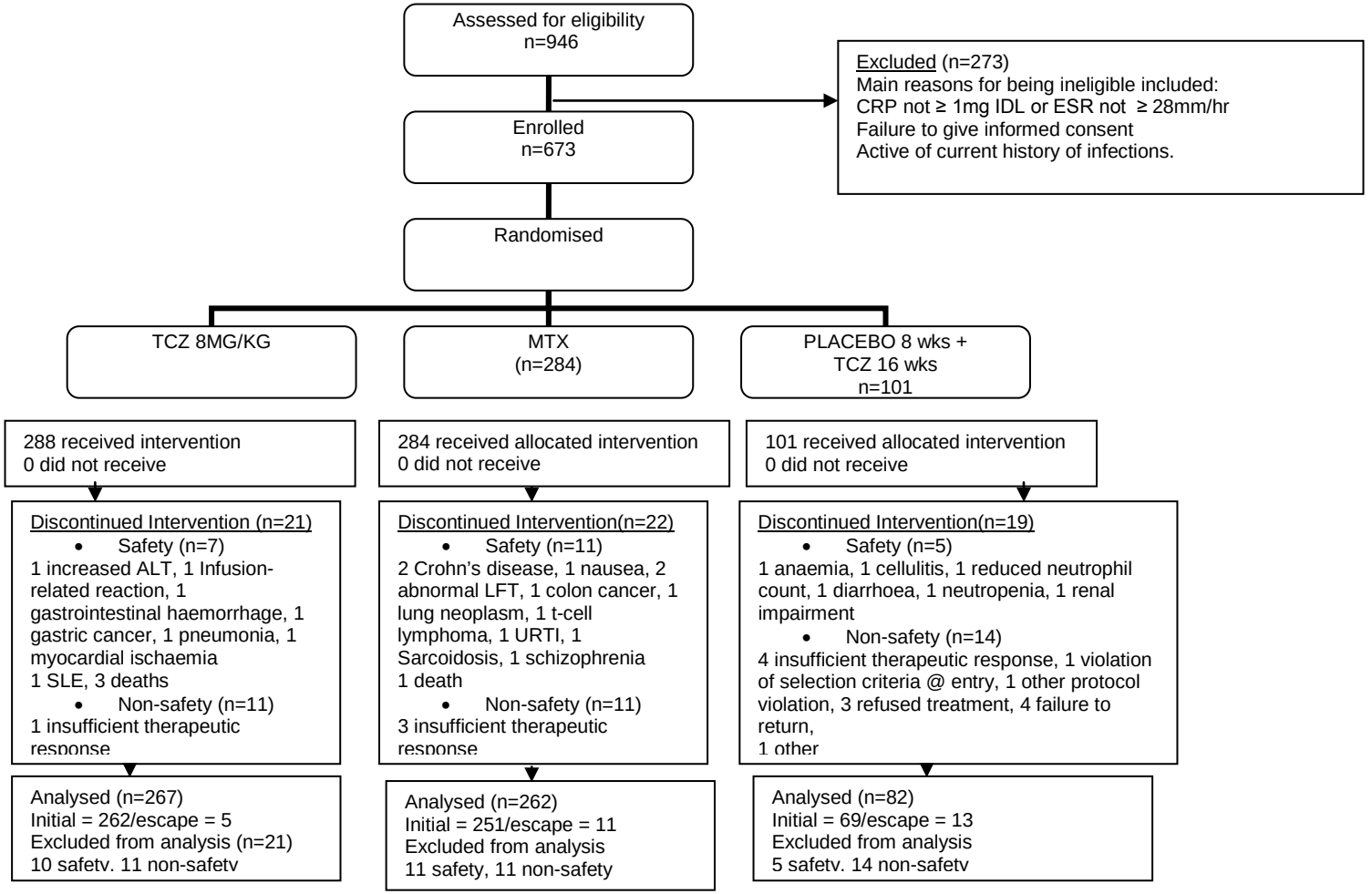
Table 7: Baseline characteristics of TCZ and placebo groups (8mg/kg dose, ITT population)

	WA17822		WA17823		WA18063		Pooled DMARD IR		WA17824		WA18062	
	TCZ 8mg + MTX	PLO + MTX	TCZ 8mg + MTX	PLO + MTX	TCZ 8mg + MTX	PLO + MTX	TCZ 8mg + MTX	PLO + MTX	TCZ 8mg + MTX	PLO + MTX	TCZ 8mg + MTX	PLO + MTX
Female (%)	85	78	82	83	81	68	82	82	83	81	84	79
Age, Mean, Yrs	51	51	53	51	53	54	53	52	51	50	54	53
Duration RA, Mean, Yrs	7.5	7.8	9.3	9.0	9.8	9.8	9.3	9.1	6.4	6.3	12.6	11.4
RF Positive (%)	83	71	83	82	78	75	80	77	74	75	79	75
DAS28, Mean	6.8	6.8	6.6	6.5	6.7	6.6	6.7	6.6	6.8	6.8	6.8	6.8
SJC/TJC, Mean	20/32	20/32	17/29	17/28	20/30	18/29	19/30	18/29	19/32	23/35	19/32	19/30
CRP, Mean, mg/dL	2.6	2.4	2.3	2.24	2.6	2.6	2.5	2.4	3.0	2.9	2.8	3.7
HAQ, Mean	1.6	1.7	1.5	1.5	1.5	1.5	1.5	1.5	1.6	1.5	1.7	1.7
No. Prior DMARDs, Mean	1.5	1.7	1.6	1.6	1.6	1.6	1.6	1.6	1.2	1.1	1.9	2.1
MTX Dose, Mean, mg/Wk	14.5	14.9	15.4	15.0	14.7	15	15.0	15.1	-	-	15.7	16.5
Weight (kg)			74	72	74	73	73	73	72	73	74	75

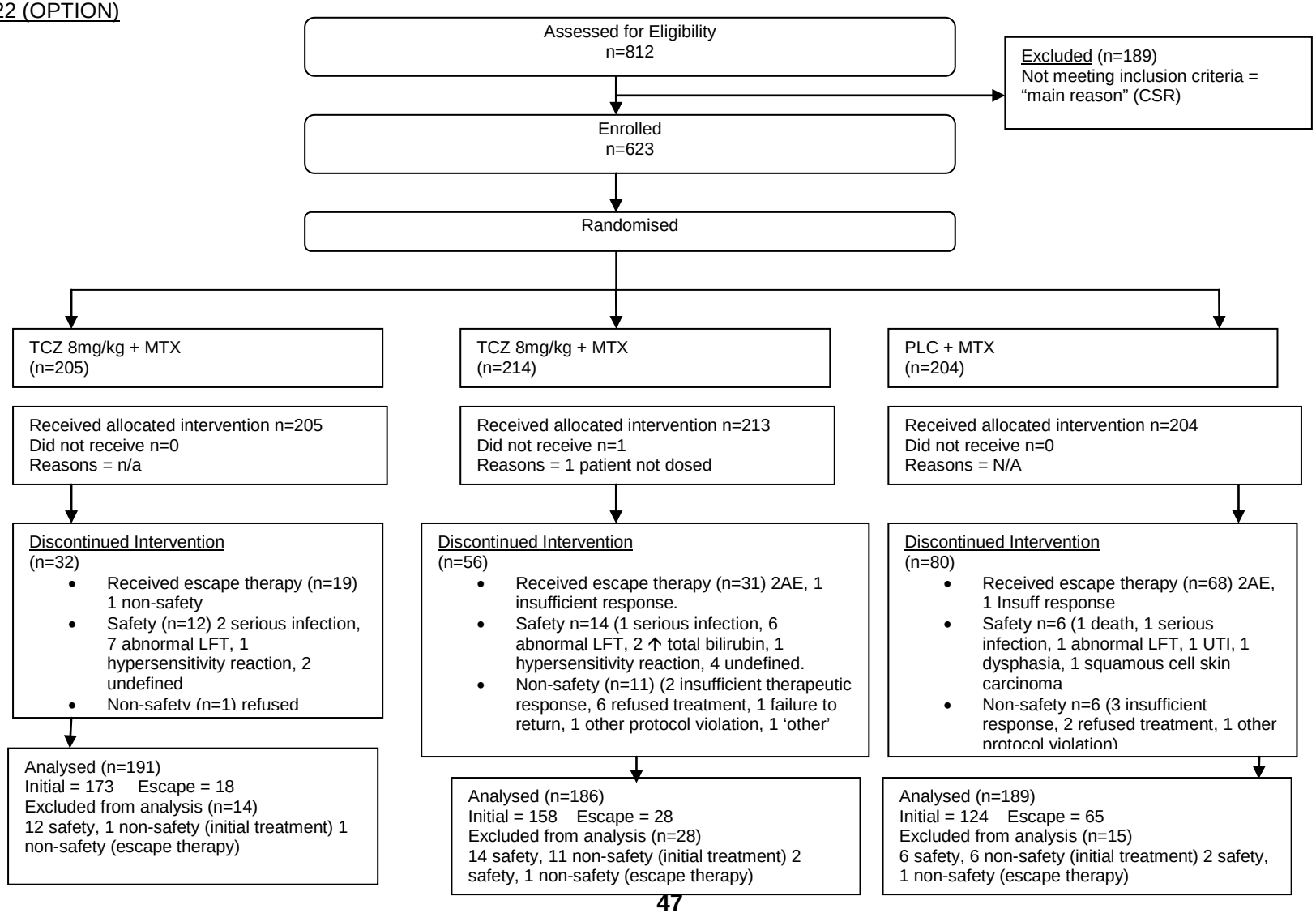
6.3.3 **Patient numbers**

The following 5 diagrams are the CONSORT flows for the 5 RCTs related to the decision problem

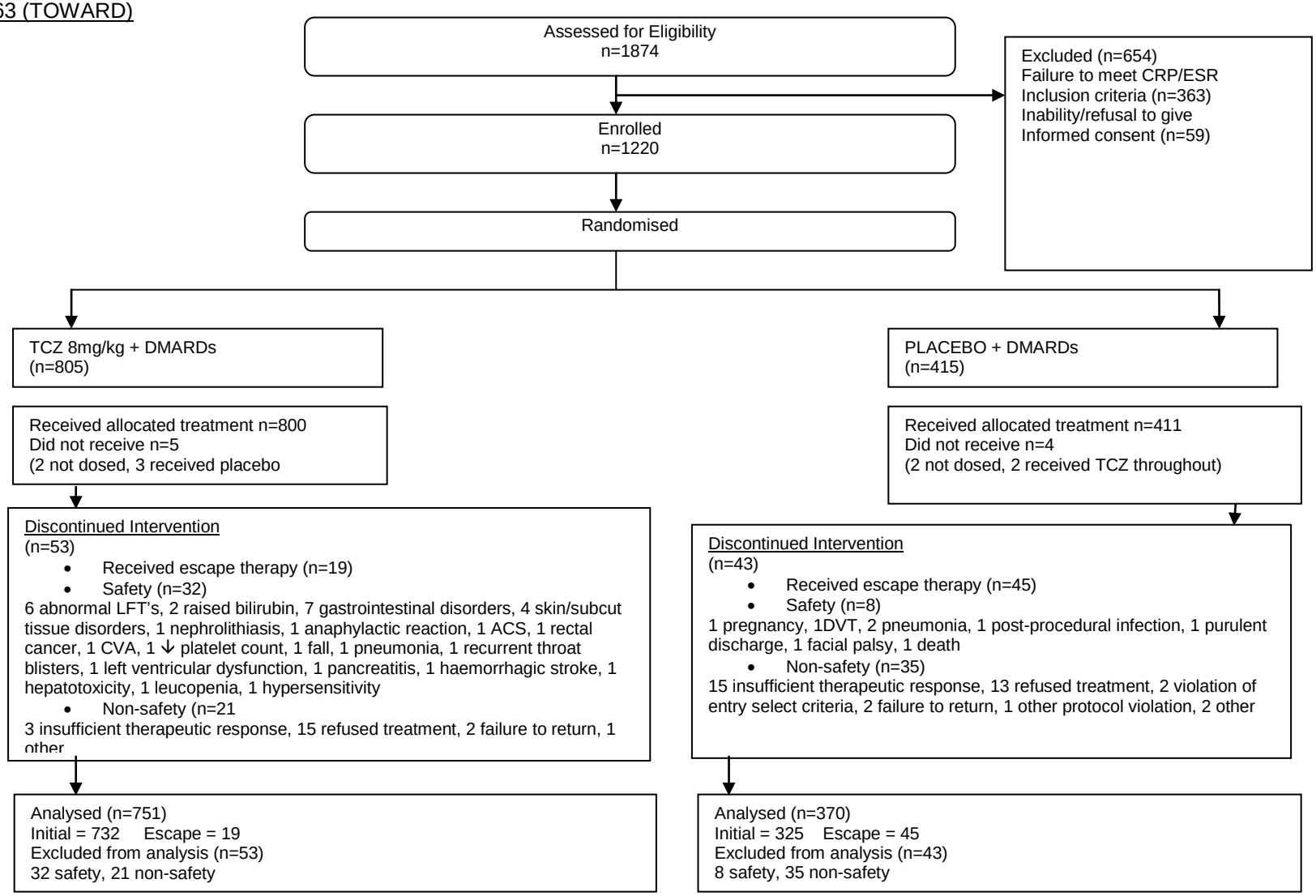
WA17824 (AMBITION)



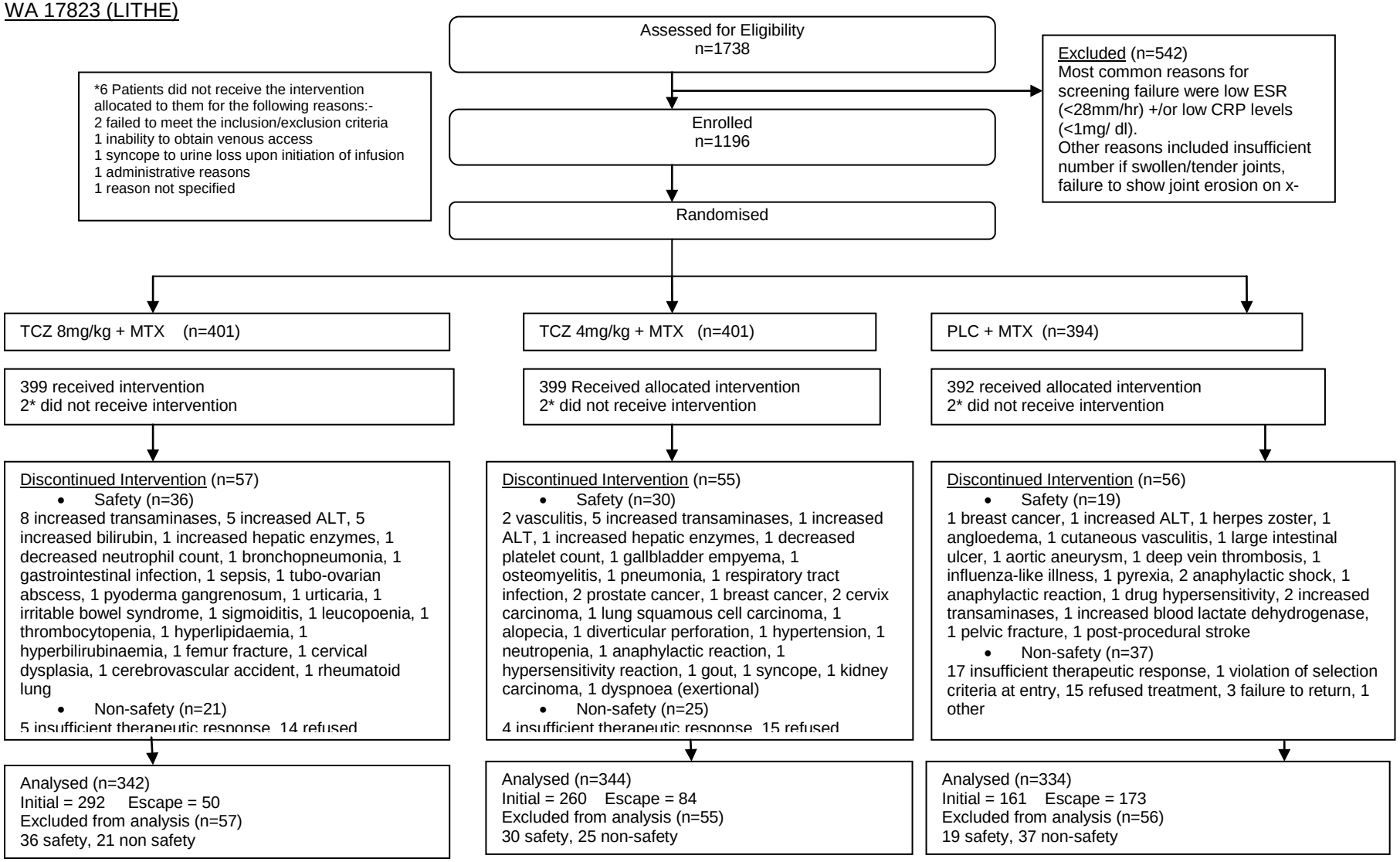
WA 17822 (OPTION)



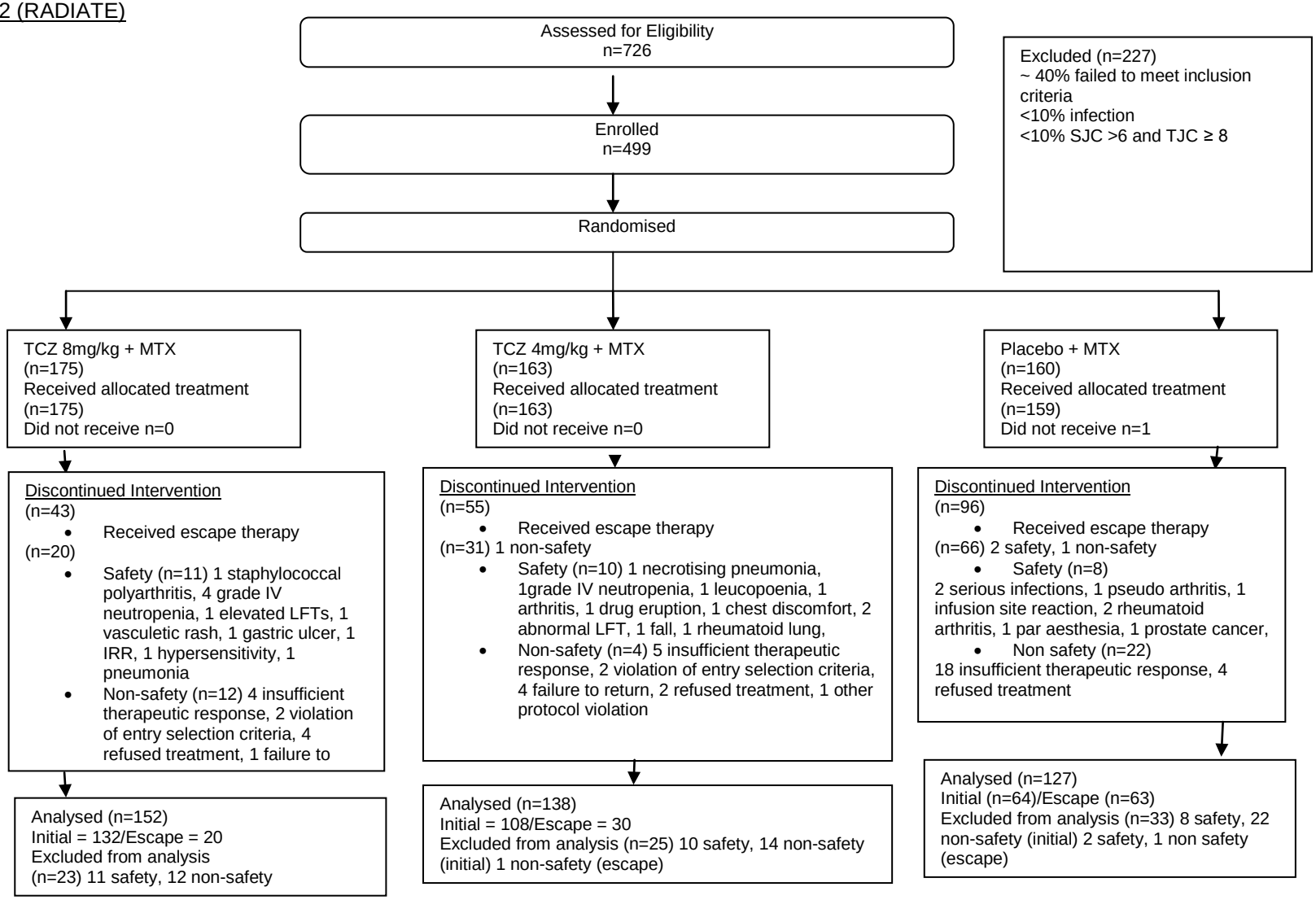
WA 18063 (TOWARD)



WA 17823 (LITHE)



WA 18062 (RADIATE)



6.3.4 **Outcomes**

Provide details of the outcomes investigated and the measures used to investigate those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the specification of the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of quality of life and social outcomes, and any arrangements to measure concordance. Data provided should be from prespecified outcomes rather than post-hoc analyses. Where appropriate, also provide details of the principal outcome measure(s), including details of length of follow-up, timing of assessments, scoring methods, evidence of reliability/validity, and current status of the measure (such as approval by professional bodies or licensing authority).

The following primary, secondary and exploratory endpoints are all pre-specified outcomes.

WA18063, 17823, 17822, 17824 and WA18062

Primary:

- Proportion of patients with an ACR20 response at week 24

Secondary:

- Proportion of patients with ACR50 and ACR70 responses at 24 weeks;
- Longitudinal generalized estimating equations (GEE) analysis of ACR20, ACR50 and ACR70 responses;
- Time to onset of ACR20, ACR50 and ACR70 response;
- Changes from baseline in the individual ACR core set parameters at 24 weeks;
- Area under the curve (AUC) of the ACRn;
- Change from baseline in the Disease Activity Score (DAS) 28 at 24 weeks;
- AUC of the mean DAS28
- Proportion of patients with DAS28 < 2.6 at 24 weeks;
- Categorical DAS28 responders (EULAR response) at week 24;
- Change from baseline in hemoglobin at 24 weeks;
- Change in rheumatoid factor (RF) (IU/mL) at 24 weeks in those patients who were RF positive (+);
- Proportion of patients who withdrew due to lack of sufficient therapeutic response;
- Proportion of patients in each treatment group who received escape therapy; and
- Health Assessment Questionnaire disability index (HAQ-DI), SF36, and Functional Assessment of Chronic Illness Therapy (FACIT)-fatigue scale scores at 24 weeks.

Exploratory:

- Logistic regression analysis of ACR20, ACR50 and ACR70 responses at week 24 by baseline characteristics;
- ACR90;
- Categorical changes from baseline in HAQ-DI; and
- Proportion of patients with swollen joint counts (SJC) and tender joint counts (TJC) of zero

In a**ddition** WA17823 looked at ACR remission at 24 weeks as a secondary end point

In **addition** WA17824 pre specified the following secondary end points
– Proportion of patients with an ACR20 response at Week 8.
– Median time to improvement in daily pain VAS (25% decline in pain VAS from baseline).
– Time to onset of ACR20, 50 and 70 by treatment group

In considering the decision problem the following outcomes will be presented and discussed, all outcomes stated above will also be tabulated:

- *Proportion of patients with an ACR20 response at week 24*
- *Proportion of patients with ACR50 and ACR70 responses at 24 weeks;*
- *Time to onset of ACR20, ACR50 and ACR70 response;*
- *Change from baseline in the Disease Activity Score (DAS) 28 at 24 weeks;*
- *Proportion of patients with DAS28 < 2.6 at 24 weeks;*
- *Health Assessment Questionnaire disability index (HAQ-DI).*

As previously stated the 5 studies used in approaching the decision problem formed the basis of the regulatory submission to different regulatory agencies worldwide. The assessments/outcomes considered in addressing the decision problem formed the core components in demonstrating efficacy to these agencies. The reliability and validity of these outcomes in demonstrating efficacy of any given therapeutic in the RA population has been reported widely.[38,39,40,41]

The schedule of assessments during the first 24 weeks was similar across all 5 studies. These are shown in the table below. Additional X rays were required during the WA17823. Additional PK/PD samples were also taken in different studies.

The decision problem.

Table 8: Schedule of Assessments for the 5 studies being considered in approaching

	-3*	0*	2	4	6	8	12	14	16	20	24
	SC	BL									
Informed consent	x										
Demographics	x										
Medical history	x	x									
Inclusion/exclusion	x	x									
Pregnancy test (urine)	x	x		x		x	x		x	x	x
Physical examination	x										x
Vital signs, weight	x	x		x		x	x		x	x	x
Study drug infusion		x		x		x	x		x	x	
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x
ECG	x										x
Chest radiograph	x										
Efficacy											
Joint counts	x	x	x	x		x	x		x	x	x
PT/INV global		x	x	x		x	x		x	x	x
Pain VAS		x	x	x		x	x		x	x	x
HAQ-DI		x	x	x		x	x		x	x	x
FACIT-Fatigue		x		x		x	x		x	x	x
SF-36		x				x			x		x
MRU		x		x		x	x		x	x	x
High sensitivity CRP	x	x	x	x	x	x	x	x	x	x	x
ESR	x	x	x	x	x	x	x	x	x	x	x
SAA		x	x	x	x	x	x	x	x	x	x
Serum ferritin		x	x	x	x	x	x	x	x	x	x
Haemoglobin		x	x	x	x	x	x	x	x	x	x
Safety											
Adverse events		x	x	x	x	x	x	x	x	x	x
Haematology (CBC)	x	x	x	x	x	x	x	x	x	x	x
Blood chemistry (including LFTs)	x	x	x	x	x	x	x	x	x	x	x
Lipid panel	x	x			x			x			x
Urinalysis	x	x		x		x			x		x
Hemolysis profile		x									x
General immunology											
RF	x	x									x

As described in section 6.2.4 all patients who completed the 24 week period of the primary studies were continued to be followed up in the ongoing long term extension studies. Those patients who did not complete the 24 week primary study period were followed up and assessed at weeks 4, 8 and 12 after the last infusion.

6.3.5 Statistical analysis and definition of study groups

State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were preplanned or post-hoc.

WA17822, WA17823 and WA18063

The primary analysis was performed on the intent-to-treat (ITT) population and compared the proportion of patients with an ACR20 response at week 24 in each tocilizumab arm with the placebo arm using a Cochran-Mantel-Haenszel (CMH) chi-squared test with adjustment for the stratification factor applied at randomization ('site'). The longitudinal probability of an ACR20 response was also compared between the treatment groups using a model based on GEE. As supportive analyses, ACR20 response rates were summarized descriptively. Time to first ACR20 response was summarized by treatment group as cumulative incidences over time using Kaplan-Meier estimates. ACR20 response rates were analyzed using logistic regression, including 'site' in the model.

Secondary endpoints of ACR50 and ACR70 responses were analyzed using the same statistical methodology as described for the primary endpoint. Secondary endpoints of AUC of ACRn, changes from baseline in the individual ACR core set parameters, AUC and change from baseline in DAS28, and changes from baseline in the SF-36 and FACIT-fatigue questionnaire scores, hemoglobin values and RF titers were summarized descriptively and compared between the treatment groups using an analysis of variance (ANOVA) model with 'site' included in the model. A comparison between treatment groups of the proportion of patients who achieve remission according to the DAS28 criterion at week 24 (ie, DAS28 < 2.6) was performed using a CMH chi-squared test adjusting for 'site'. Additionally, the proportions of patients who withdrew from the study due to a lack of therapeutic response and the proportions of patients who received escape therapy were compared between treatment groups using logistic regression, including 'site' in the model.

In order to control the rate of false positive conclusions, a fixed sequence approach was applied, which enabled the null hypothesis of each secondary endpoint to be tested at the same significance level of α (5%) without any adjustment, as the null hypotheses were hierarchically ordered and were tested in a pre-defined sequential order. There was no break in the hierarchically ordered testing of the secondary endpoints, therefore, all p-values reported can be considered to be statistically valid. For efficacy and quality of life parameters, the primary analysis population was the intent-to-treat (ITT) population. Assessments were also performed on the per protocol (PP) population, these PP analyses have not been presented here.

Safety data were listed and summarized by treatment group for the safety population using descriptive statistics.

WA18062

The primary analysis was performed on the intent-to-treat (ITT) population and compared the proportion of patients with an ACR20 response at Week 24 in each tocilizumab arm with the placebo arm using a Cochran-Mantel-Haenszel (CMH) chi-squared test with adjustment for the stratification factor applied at randomization ('site'). The longitudinal probability of an ACR20 response was also compared between treatment groups using a model based on GEE. As supportive analyses, ACR20 response rates were summarized descriptively. Time to first ACR20 response was summarized by treatment group as cumulative incidences over time using Kaplan-Meier estimates. ACR20 response rates were analyzed using logistic regression, including 'region' in the model. Secondary endpoints of ACR50 and ACR70 responses were analyzed using the same statistical methodology as described for the primary endpoint. Secondary endpoints of AUC of ACRn, changes from baseline in the individual ACR core set parameters, AUC and change from baseline in DAS28, and changes from baseline in the SF-36 and FACIT-fatigue questionnaire scores, hemoglobin values and RF titers were summarized descriptively and compared between the treatment groups using an analysis of variance (ANOVA) model with 'site' included in the model. A comparison between treatment groups of the proportion of patients who achieved remission according to the DAS28 criterion at Week 24 (ie, DAS28 < 2.6) was performed using a CMH chi-squared test adjusting for 'site'. Additionally, the proportions of patients who withdrew from the study due to lack of therapeutic response and the proportions of patients who received escape therapy were compared between treatment groups using logistic regression, including 'region' in the model. In order to control the rate of false positive conclusions, a fixed sequence approach was applied, which enabled the null hypothesis of each secondary endpoint to be tested at the same significance level of α without any adjustment, as the null hypotheses were hierarchically ordered and were tested in a pre-defined sequential order. There was a break in the hierarchically ordered testing of the secondary endpoints. There was no plan to analyze efficacy according to individual anti-TNF therapies.

For efficacy and quality of life parameters, the primary analysis population was the ITT population. Assessments were also performed on the per protocol (PP) population. PP analyses are not presented in this submission

Safety data were listed and summarized by treatment group for the safety population using descriptive statistics.

WA17824

The primary efficacy analysis was a non-inferiority comparison of tocilizumab with MTX. The null hypothesis tested was that the proportion of patients with an ACR20 response at Week 24 in the tocilizumab treatment arm was more than 12 percentage points lower than the proportion of patients with an ACR20 response at Week 24 in the MTX arm. Representing the proportion of patients with an ACR20 response at Week 24 for MTX by p1, and by p2 for the tocilizumab treatment arm: the null hypothesis, H0, is p2< p1.

The null hypothesis was to be rejected if the lower limit of the two-sided 95% confidence interval for the difference in proportions of ACR20 responders on tocilizumab minus MTX was not less than -0.12. If tocilizumab was shown to be non-inferior to MTX in ACR20 response at Week 24, testing was also to be conducted for superiority. The analysis was based upon all patients receiving either MTX or tocilizumab and excluded patients who were initially randomized to placebo. Patients who began escape therapy (applied only to patients in the substudy up to Week 8) or withdrew from the study prior to the Week 24 ACR assessment, and all patients in whom the ACR20 response could not be determined due to missing data, were considered non-responders in the primary analyses.

To support the conclusions from the primary analysis a comparison (based upon the ITT population) was made at Week 8, between the tocilizumab treatment group and the placebo group, using the extended Mantel-Haenszel statistic.

Time to first ACR20 response was summarized by treatment group as cumulative incidences over time using Kaplan-Meier estimates. ACR20 response rates were analyzed using logistic regression, including 'site' and 'disease duration' in the model.

Secondary endpoints of ACR50 and ACR70 responses were analyzed. Secondary endpoints of AUC of ACRn, changes from baseline in the individual ACR core set parameters, AUC and change from baseline in DAS28, and changes from baseline in the SF-36 and FACIT-fatigue questionnaire scores and hemoglobin values were summarized descriptively and compared between the treatment groups using an analysis of variance (ANOVA) model. A comparison between treatment groups of the proportion of patients who achieved remission according to the DAS28 criterion at Week 24 (ie, DAS28 < 2.6) was performed. Additionally, the proportions of patients who withdrew from the study due to lack of therapeutic response and the proportions of patients who received escape therapy were compared between treatment groups using logistic regression. No non inferiority limits were pre-defined for secondary endpoints however, if the lower limit of 95% CI for treatment difference between tocilizumab and MTX was > 0, superiority had been achieved. In order to control the rate of false positive conclusions, a fixed sequence approach was applied, which allows for the superiority null hypothesis of each secondary endpoint to be tested at the same significance level of α without any adjustment, as long as the null hypotheses to be tested are hierarchically ordered and are tested in a pre defined sequential order.

For efficacy and quality of life parameters, the primary analysis population was the per protocol population (PP) population. Assessments were also performed on the intent-to treat population (ITT) population.

Safety data were listed and summarized by treatment group for the safety population using descriptive statistics.

Power calculations

WA17822

In the LRO301 Phase II dose-finding study, ACR20 response rates of 60%-70% were seen in the 4mg/kg + MTX and 8mg/kg + MTX treatment arms, and a response rate

of 40% was seen in the MTX/placebo arm. Assuming an TCZ/MTX ACR20 response of 60% and placebo/MTX comparator ACR20 response of 40%, and allowing for 15% of patients in each treatment arm being classified as non-responders because of missing data or early withdrawal, the selected sample size of 210 patients per arm (630 patients in total) is expected to give 90% power. Due to multiple active treatment arms an alpha of 0.03 was used in the sample sizing

WA17823

The calculation of sample size in this study was based on numbers of patients needed to show prevention of joint destruction at 12 months. Keystone *et. al.*[42] report differences between MTX control and active treatment arms of 1.9 – 2.6 units (Sharp score change from baseline to 12 months), with standard deviations ranging from 4.8 – 6.8. Klareskog *et. al*[43]*.* report differences between MTX control and active treatment arms ranging from 2.3 – 3.3 units in Sharp score change from baseline to 12 months, but do not report information on standard deviations. Lipsky *et. al.*[44] report differences (Sharp score change from baseline to 12 months) between MTX control and active treatment arms ranging from 5.4 – 7.7 units, with standard deviations ranging from 3.6 – 10.8.

Based on this information, the assumption was made that the difference between 12 month mean Sharp score changes on the MTX control arms and the TCZ arms in this study would be approximately 30% of the standard deviation (e.g. a mean difference of 3 units with a standard deviation of 11 units; although any similar ratio of mean difference to standard deviation gives the same sample size estimate).

Based on these assumptions, a sample size of 390 patients per treatment arm was expected to give 90% power. Due to multiple active treatment arms and time points an alpha of 0.0125 was used in the sample sizing.

These conservative sample size assumptions provided some protection against diminished treatment effects arising from patient withdrawal and data imputation. Assuming an TCZ/MTX ACR20 response of 50% and placebo/MTX comparator ACR20 response of 30%, and allowing for 15% of patients in each treatment arm being classified as non-responders because of missing data or early withdrawal, a sample size of 390 patients per treatment group gave >90% power to detect a difference between the TCZ/MTX combination group and the MTX group (two-sided test, corrected for multiple comparison of active arms with control).

Data on change from baseline in HAQ Disability Index score are less readily available, but a difference between active and control arms of 0.3 with a standard deviation of 0.5 were assumed to be plausible outcomes. Given these assumptions, the planned sample size of 390 patients per treatment arm gave >90% power to detect a difference between the TCZ/MTX combination group and the MTX group.

WA18063

A total of 1200 patients were allocated in a 2:1 ratio to the two treatment groups, TCZ 8 mg/kg (800) or placebo (400) i.v. every 4 week. This sample size was chosen in order to provide the required numbers of patients exposed to TCZ for the purposes of compilation of a safety database. For the ACR20 response, this sample size

(800:400) gave greater than 90% power to detect a difference between the TCZ and the placebo arms at week 24

WA17824

A review of the literature on clinical trials in MTX naïve patients suggested that the ACR20 response at 24 weeks in patients treated with MTX would be in the range 60% -70%.[45,46] Data from Phase II studies of 8 mg/kg TCZ given as mono-therapy suggested that the likely 24 week ACR20 response on this dose will be approximately 70%.

Sample size and power calculations assuming a MTX rate of 65% and TCZ rate of between 66% and 70% showed that a study recruiting 275 patients per arm would have 90% or greater power to demonstrate TCZ non-inferior to MTX using a 12 percentage point non-inferiority margin. Due to multiple active treatment arms an alpha of 0.025 was used in this sample sizing.

Data from Phase II studies suggested that the likely 8 week ACR20 response on 8mg/kg TCZ given as mono-therapy would be approximately 50%, and the likely 8 week ACR20 response on placebo would be approximately 30%. Sample size and power calculations based on these assumptions showed that a comparison of 100 placebo patients with the 275 TCZ patients would have greater than 90% power to demonstrate TCZ superior to placebo. The requirement for both the primary analysis of TCZ versus MTX in ACR20 at Week 24 and the supporting comparison of TCZ versus placebo in ACR20 at Week 8 to be statistically significant for a positive conclusion would result in an overall power of the study of between 80% and 90%.

WA18062

In the LRO301 Phase II study, ACR20 response rates of 60%-70% were seen in the 4mg/kg+MTX and 8mg/kg+MTX treatment arms, and a response rate of 40% was seen in the MTX/placebo arm. The response rates in WA18062 were expected, on clinical grounds to be lower than these rates, in view of the patient population being studied.

It was assumed that a TCZ/MTX ACR20 response of 50% and placebo/MTX comparator ACR20 response of 30%, also allowing for 15% of patients in each treatment arm being classified as non-responders because of missing data or early withdrawal, a sample size of 150 enrolled patients per treatment group (total of 450 patients) giving 80% power to detect a difference between the TCZ/MTX combination groups and the MTX group (two-sided test, corrected for multiple comparison). Due to multiple active treatment arms an alpha of 0.03 was used in this sample sizing.

6.3.6 **Critical appraisal of relevant RCTs**

The five studies reviewed can be considered reflective of UK clinical practice

One area where the UK population varies from that examined in the studies is the mean number of prior DMARDs before going onto biologic therapy, this is thought to reflect the difference between the EU/US and UK in terms of guidelines prior to biologic use and the earlier availability of biologic therapy in clinical trials versus real clinical practice

Differences within subgroups were small in all core studies and no confounding factors were identified.

How was allocation concealed?	For all 5 core trails allocation was concealed via the use of a randomised, double blind, double dummy, placebo controlled, parallel group design
What randomisation technique was used?	Patients were randomly assigned to treatment groups and centrally randomised using an interactive voice response system. Patients were stratified by site and disease duration
Was a justification of the sample size provided?	Yes. The calculation of the sample size for each of the core studies can be found in section 6.3.5. These rationales were derived from the clinical study reports for each of the studies discussed.
Was follow-up adequate?	Yes. RA is a chronic disease. All patients completing the primary 24 week end point (or 104 week for WA17823) were eligible for entry into the long term follow up of 264 weeks (5 years) .
Were the individuals undertaking the outcomes assessment aware of allocation?	No. To prevent potential blind breaks due to observed efficacy or laboratory changes, a dual assessor approach was used to evaluate safety and efficacy in the 5 core studies. The joint assessor performed swollen and tender joint counts and had no access to any other patient data. Neither assessors were given any prior indication of the allocation however given the profound effect of TCZ on CRP and its potential to cause a change in lipid profile in nearly 25% of patients, irrespective of any other variables (e.g. disease duration) the use of a dual assessor approach was a significant 'safety net' in ensuring bias was kept to the absolute minimum possible and within regulatory expectations.
Was the design parallel-group or crossover?	Parallel group design in all 5 core studies

Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?	All 5 core studies were multinational. The UK contributed to ONLY WA18062 (anti TNF inadequate responders) with 13 centers and 33 patients in total. **WA17822**- *73 centers in 17 countries worldwide: Argentina (3 centers), Australia (3 centers), Austria (4 centers), Brazil (2 centers), Bulgaria (3 centers), Canada (11 centers), France (7 centers), Germany (8 centers), Hong Kong (3 centers), Hungary (3 centers), Israel (6 centers), Italy (5 centers), Mexico (6 centers), Singapore (2 centers), Slovakia (1 center), Switzerland (2 centers), Thailand (4 centers).* **WA17823** -*137 centers in 15 countries: Australia (4), Brazil (5), China (5), Denmark (2), Finland (2), France (12), Greece (3), Italy (16), Mexico (7), The Netherlands (1), Poland (11), Switzerland (1), South Africa (4), Spain (6) and the USA (58)* **WA18063** - *130 centers in 18 countries worldwide: Argentina (3 centers), Australia (1 center), Brazil (3 centers), Canada (5 centers), China (6 centers), Costa Rica (1 center), Czech Republic (3 centers), Finland (2 centers), France (9 centers), Germany (6 centers), Mexico (4 centers), Panama (1 center), Russia (8 centers), Spain (5 centers), Sweden (2 centers), Thailand (3 centers), USA (65 centers) and South Africa (3 centers).* **WA17824** - *120 centers in 18 countries worldwide: Argentina (4 centers), Australia (4 centers), China (3 enters), Denmark (1 centers), France (5 centers), Italy (5 centers), Lithuania (5 centers), Mexico (5 centers), Norway (2 centers), Peru (3 centers), Portugal (1 center), Serbia/Montenegro (2 centers), Slovenia (2 centers), South Africa (6 centers) and Spain (5 centers).* *Patients who were enrolled into the placebo controlled sub-study came from centers in Canada (9 centers), Israel (4 centers), and the USA (54 centers), only.* **WA18062** - *128 centers in 13 countries (Australia, Belgium, Canada, France, Germany, **United Kingdom**, Iceland, Italy, Mexico, The Netherlands, Sweden, Switzerland, and the United States)* Patients were recruited worldwide: **1438 (34%) from Europe, 1493 (35%) from North America (1302 [31%] from the USA)**, 833 (20%) from South America and 447 (11%) from rest of world. There is variation in the management of RA from one region to the next although the guidelines for the management of RA are broadly similar especially when you compare the EU and US from which the majority of the patients in these studies were drawn.[47,48] There is some notable variation in terms of use of certain treatments at different stages of the disease. When comparing the UK to other Western countries it would appear that perhaps the UK isn't as aggressive in using biologic therapies. This is both in terms of depth of prescribing of biologics in the RA population as well as the fact that the UK guidelines only permit the use of biologics in severe RA patients[49] whereas in the US for example moderate disease can be managed by biologics if the patients disease exhibits certain aggressive characteristics. When we look at the large EU countries, all of which participated in the 5 core trials there is a difference in the proportion of RA patients who are receiving any given therapy however the sequence of therapy and the therapies used are the same irrespective of which country the patient is in .

	Therefore it is reasonable to highlight that clinical practice in the counties that took part in these studies, especially the US and EU doesn't vary that significantly from the UK, and as such the efficacy outcomes seen in these studies can be reasonably expected to be translated into clinical effectiveness seen in the UK RA population. Similarly the safety profile in the trials would be similar in the UK patient population as the treatment environment and prior immuno-suppression with either DMARDs or anti TNFs would be similar. Subpopulations variations within the core studies are discussed in depth in appendix 4.
How do the included in the RCT participants compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting.	When considering the baseline characteristics of the DMARD IR and TNF IR studies the mean disease duration and DAS score in the pooled DMARD IR population is 9.3 years with a DAS 28 of 6.7, and the TNF IR population a disease duration of 12.6 years with a baseline DAS28 of 6.8. The UK baseline characteristics can be seen in the table below. The trail population is broadly similar to the patient population in which the drug is licensed in the UK. Where there is a notable difference is in the number of prior DMARDs prior to the commencement of biologic therapies which is twice as great as the mean in the trials. This difference maybe due to a variation in the use of combination DMARDs in the UK, the fact that biologic drug was made available earlier through the clinical trials than perhaps would be allowed under national guidelines and also the fact biologic therapies is limited to severe disease with a requirement to have failed a minimum of 2 DMARDs with trials of at least 6 months on each.

	DMARD IR					Anti TNF IR	
-	WA17822	WA17823	WA18063	Pooled DMARD IR	BSRBR characteristics (n=7818) *recently commenced TNF**	WA18062	BSRBR characteristics (n=6739) *IR to TNF***
Female (%)	85	82	81	**82**	**77**	**84**	**77**
Age, Mean, Yrs	51	53	53	**53**	**56**	**54**	**55**
Duration RA, Mean, Yrs	7.5	9.3	9.8	***9.3***	***14***	***12.6***	***14***

	RF Positive (%) 83 / 83 / 78 / **80** / Not available / **79** / Not available DAS28, Mean 6.8 / 6.6 / 6.7 / ***6.7*** / ***6.6*** / ***6.8*** / ***6.6*** SJC/TJC, Mean 20/32 / 17/29 / 20/30 / **19/30** / Not available / **19/32** / Not available CRP, Mean, mg/dL 2.6 / 2.3 / 2.6 / **2.5** / Not available / **2.8** / Not available HAQ, Mean 1.6 / 1.5 / 1.5 / **1.5** / **2.1** / **1.7** / **2.1** No. Prior DMARDs, Mean 1.5 / 1.6 / 1.6 / **1.6** / **4** / **1.9** / **4** Oral CS/NSAIDs (%) 55/65 / 61/71 / 51/72 / **55/70** / **49/XX** / **52/62** / **49/XX** MTX Dose, Mean, mg/Wk 14.5 / 15.4 / 14.7 / **15.0** / Not available / **15.7** / Not available *Hyrich et al, Ann Rheum Diseases 2006; 65: 895-898 **Hyrich et al, Arthritis Rheum 2007; 56: 13-20
For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?	In three of the 5 core trials (WA17822, 17823 and WA180620 two doses were studied 4mg/kg and 8mg/kg. In the other two WA18063 and WA17824 only the 8mg/kg was used. The pooled DMARD IR analysis only considered the licensed dose of 8mg/kg. The 8mg/kg is the dose referenced within our SmPC however section 5.1 of the SmPC outlines the results from both doses and the safety analysis also includes all patients.
Were the study groups comparable?	The study groups were comparable for the monotherapy, DMARD IR and TNF IR populations.
Were the statistical analyses used appropriate?	Yes. The statistical analysis chosen were appropriate to test the pre-specified null hypotheses for each of the trials used in assessing the decision problem. The particulars of these analyses are described in depth in section 6.3.5. They are consistent with the analysis expected by the regulatory authorities. In all cases the statistical models for the analysis of both primary and secondary endpoints assumed that the proportion of responders in each of the treatment groups, or the mean or median level of response in each of the treatment groups were related only to the treatment received, after adjustment for any imbalance in the stratification applied at randomisation.
Was an intention-to-treat analysis undertaken?	Yes. Studies WA17822, 17823, 18063 and WA18062: For efficacy and quality of life parameters, the primary analysis population was the ITT population. This was done using the CMH chi squared test Study WA17824: This was a non inferiority study. For efficacy and quality of life parameters, the primary analysis population was the per protocol population (PP) population. Assessments were also

	performed on the intent-to treat population (ITT) population.
Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?	Differences within subgroups were small in all core studies. Lower ACR20 response rates were observed in a small subgroup of patients aged > 75 years, in black patients, patients > 100 kg, RF-negative patients and in North American patients in the pooled DMARD IR population. No obvious reason was identified to explain these small differences; however, it is likely that a number of confounding factors exist, e.g. North American and black patients were shown to be heavier. A discussive analysis looking at subpopulations in both DMARD IR and TNF IR can be found in appendix 4

6.4 Results of the relevant comparative RCTs

Data from the DMARD IR, TNF IR and monotherapy trials is presented

DMARD IR outcomes are presented in more depth as part of section 6.5 *Meta-analysis*

All outcomes specified in the trial protocols are presented however special attention is paid to ACR, DAS and HAQ-DI in relation to the decision problem

TCZ has a significant effect on both signs and symptoms, patient reported outcomes and radiographic progression in the DMARD IR population, as well as significantly improving signs and symptoms and patient reported outcomes over 24 weeks in both the monotherapy and TNF inadequate responder population

Tocilizumab in combination with MTX can provide a rapid onset of treatment effect, and a durable remission (DAS28<2.6) in patients with an inadequate response to either DMARDs or anti TNFs

Tocilizumab monotherapy can provide superior remission (DAS28) and ACR20, 50 and 70 scores compared to MTX alone

Long term outcomes data demonstrates the ongoing efficacy of TCZ beyond 24 weeks

Long term HAQ-DI shows continued improvement over 132 weeks

Introduction

Considering the 3 tocilizumab studies available in the DMARD IR population, the following section should be considered in conjunction with section 6.5 *Meta-analysis* which presents a pooled analysis within the DMARD IR setting.

This section will firstly present the clinical outcomes for the DMARD IR population and secondly the TNF IR population. To help manage the volume of potential data reported considering the 2 indications and multiple phase III studies the endpoints/ clinical outcomes are restricted to those considered of most relevance to the appraisal considering previous NICE RA technology appraisals. For the DMARD IR population the following structure will be followed:

- ACR response at 24 weeks
- interim radiographic data from WA17823
- detailed tabulated breakdown of primary and secondary outcomes.

When the 3 DMARD IR trials were designed (WA17822, WA17823 and WA18063) the intention was always to perform a pre specified meta-analysis which is presented in section 6.5. In that section a detailed discussion of the outcomes relevant to the decision problem will be made:

- ACR changes at 24 weeks and response over time
- DAS change and proportions of patients achieving low disease or DAS remission
- HAQ-DI changes

When considering the TNF IR population one study was performed therefore the following outcomes will be presented:

- ACR changes at 24 weeks and response over time
- DAS change and proportions of patients achieving low disease or DAS remission
- HAQ-DI changes
- detailed tabulated breakdown of primary and secondary outcomes.

The following outcomes generated from the mono-therapy study WA17824 will also be presented for both the per protocol and ITT populations:

- ACR changes at 24 weeks and response over time
- DAS change and proportions of patients achieving low disease or DAS remission
- HAQ-DI changes
- detailed tabulated breakdown of primary and secondary outcomes.

For all three populations, where long term data is available from individual trials, it will be presented. For the DMARD IR population the long term outcomes are presented as a pooled analysis within section 6.5 *Meta-analysis*

Estimates of comparative efficacy relative to other existing treatment options are presented in the mixed treatment comparison in section 6.6 below.

DMARD Inadequate Responder Population

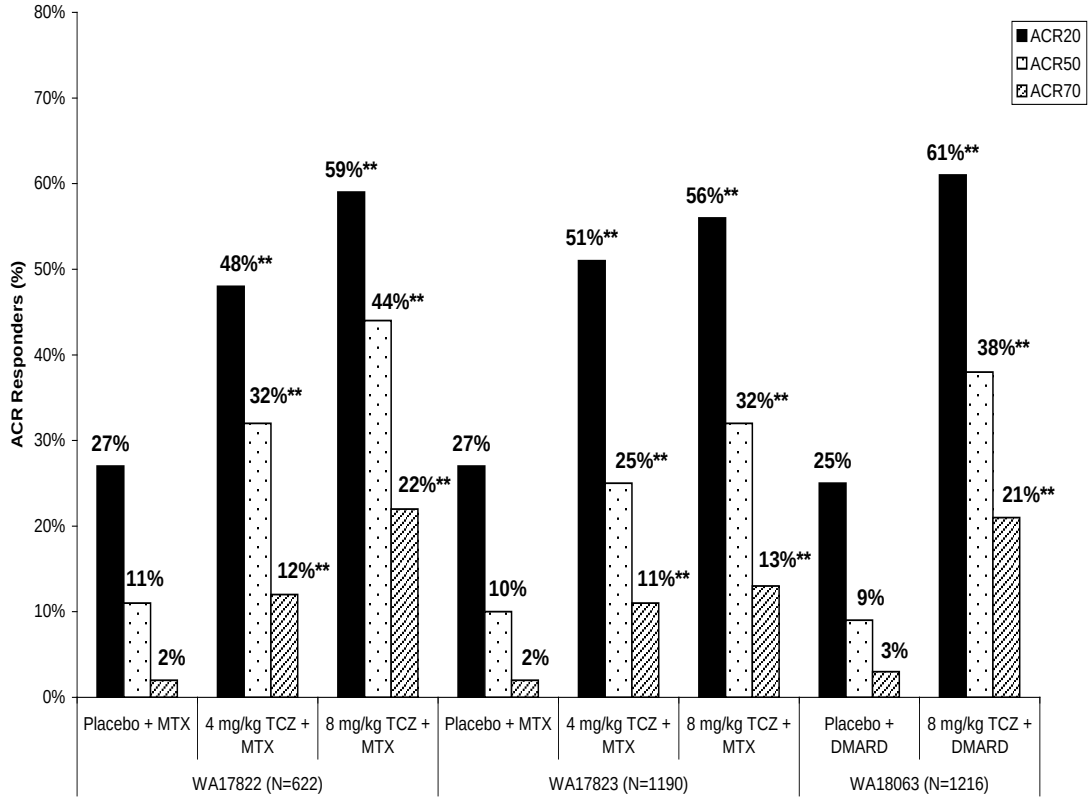
WA17822, WA17823 and WA18063 were randomized, double-blind, placebo-controlled, parallel group studies in adult patients with moderate to severe active RA who had previously experienced an inadequate clinical response to treatment with MTX and/or other traditional DMARDs[50,51,52]

a) ACR response rates

All three studies met the primary endpoint (ACR20 response at week 24). More importantly, statistically significant improvements compared with placebo + DMARD were achieved in the higher clinical disease hurdles of ACR50, ACR70 (figure 7 below) and DAS28 remission rates (< 2.6) in patients who received TCZ 8 mg/kg + DMARD (see section c summary table on page 70).

Across all three studies, consistent results were observed for the primary and secondary endpoints. The 95% confidence intervals of the ACR20 scores across the three studies can be seen in figure 8 below indicating a clear consistency of response across the studies. The greatest response was observed in the TCZ 8 mg/kg + DMARD group, particularly with respect to the higher clinical disease hurdles, with marked improvements over placebo + DMARD in ACR50 and ACR70 response and disease activity indices such as EULAR good response and DAS28 remission rates. The onset of response was rapid in the TCZ + DMARD groups, with differences between the TCZ + DMARD and placebo + DMARD groups becoming apparent as early as week 2 (ie, the first scheduled assessment). Furthermore, in study WA18063, ACR and DAS28 responses were consistent regardless of background DMARDs.

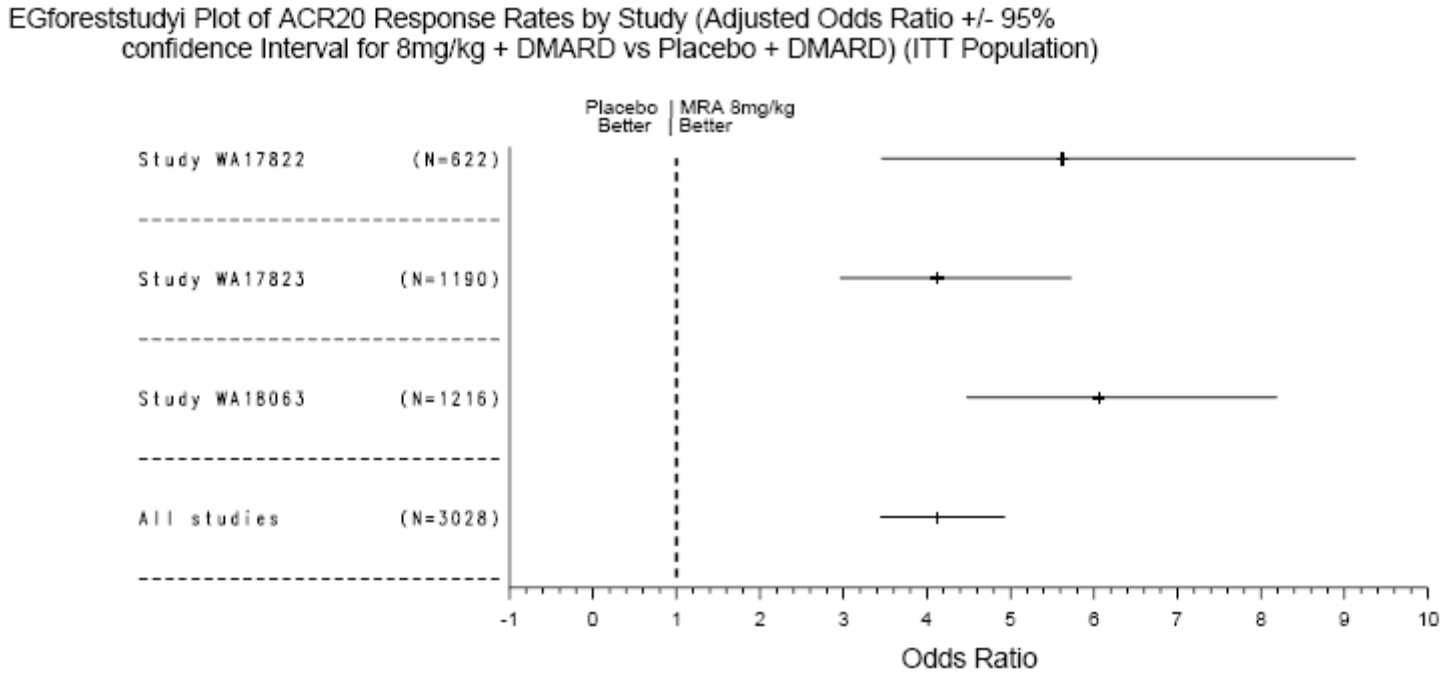
Figure 7: Proportion of ACR20, ACR50 and ACR70 Responders at Week 24 for Studies WA17822, WA17823 and WA18063 (DMARD Inadequate Responders, ITT Population)



* p < 0.01, TCZ vs. placebo + MTX/DMARD
** p < 0.0001, TCZ vs. placebo + MTX/DMARD

As highlighted in the introductory text the following outcomes will be discussed in section 6.5 *Meta-analysis*, mean ACR changes at 24 weeks and response over time, DAS change and proportions of patients achieving low disease or DAS remission along with HAQ-DI changes.

Figure 8: Plot of ACR20 Response Rates by Study (Adjusted Odds Ratios +/- 95% confidence Interval for 8mg/kg + DMARD vs Placebo + DMARD) (ITT Population)



b) Interim 52 week radiographic data: WA17823 only

WA17823 is a two year signs and symptoms, joint damage and physical function study in combination with methotrexate which had a pre-specified 12 month analysis of radiographic progression. The analysis population (ITT) included 1190 randomized patients (TCZ 8 mg/kg n=398, TCZ 4 mg/kg n=399, control n=393). Mean joint erosion, joint space narrowing, and total Genant-modified Sharp scores showed significant inhibition of radiographic progression from baseline in both tocilizumab groups compared with placebo. The results from the licensed 8mg/kg dose can be seen below (see Table 9). Tocilizumab 8 mg/kg showed substantial (74%) inhibition of radiographic progression at one year which correlates with the clinically significant ACR and DAS responses seen, as well as patient-reported outcomes with tocilizumab that are significantly superior to the placebo control group. These data give a clear indication that tocilizumab has a significant potential in inhibiting disease progression as well as managing the signs and symptoms of the disease. The 104 week analysis is expected in mid 2009 and will be submitted for inclusion in the Summary of Product Characteristics thereafter.

Table 9: Radiographic changes at 52 weeks (and other efficacy measures) in DMARD IR patients from WA17823 (Interim results ITT population)

WA17823	TCZ 8 mg/kg +MTX (n=398)	Placebo + MTX (n=393)
Disposition, % (n)		
Completed 52 weeks	86 (342)	85 (334)
Remaining on randomized treatment	73 (292)	41 (161)
Received rescue therapy	15 (59)	50 (195)
Total Genant-modified Sharp score, mean (SD)		
Baseline score	29.1 (28.5)	28.8 (32.4)
Change from baseline	0.3 (1.3)*	1.1 (3.0)
Annualized progression rate	0.2 (1.1)	0.8 (1.9)
Joint erosion score change from baseline, mean (SD)	0.2 (0.9)*	0.7 (1.9)
Joint space narrowing score change from baseline, mean (SD)	0.1 (0.6)**	0.4 (1.7)
No progression in joint erosion, % (n)	87 (302)	70 (203)
No progression in joint space narrowing, % (n)	91 (315)	85 (245)
No progression in total Genant-modified Sharp score, % (n)	85 (294)	67 (195)
HAQ-DI		
Baseline score, mean (SD)	1.5 (0.6)	1.5 (0.6)
AUC change from baseline, adjusted mean	-144.1	-58.1
Treatment difference vs control (95% CI)	-86.0 (-112.7, -59.2)*	-
ACR20, % (n)	56 (222)*	25 (97)
ACR50, % (n)	36 (145)*	10 (39)
ACR70, % (n)	20 (80)*	4 (15)
DAS28 clinical remission (<2.6), % (n)	47 (127)*	8 (12)
Low disease activity (≤3.2), % (n)	64 (171)*	19 (28)

*p≤0.0001; **p<0.01 versus control

c) Summary Table of Primary and Secondary end points including ACR core set

The table below includes all the primary and secondary endpoints for the licensed 8mg/kg dose

	WA17822			WA17823			WA18063		
Secondary end point	Placebo +MTX (n=204)	TCZ 8mg/kg+MTX (n=213)	p-value	Placebo +MTX (n=393)	TCZ 8mg/kg+MTX (n=399)	p-value	Placebo +MTX (n=413)	TCZ 8mg/kg+MTX (n=803)	p-value
ACRn (adjusted mean)	13.55 (5.34)	39.94 (4.429)	<.0001	10.55 (3.82)	31.96 (3.16)	<0.0001	-3.35 (4.18)	29.59 (3.23)	<0.0001
DAS28 remission (<2.6)	0.8%	27.5%	<.0001	3.8%	33.3%	<0.0001	3.4%	30.2%	<0.0001
Change in DAS (adjusted mean (SE)	-1.55 (0.150)	-3.43 (0.124)	<.0001	-1.45 (0.11)	-3.11 (0.09)	<0.0001	-1.16 (0.09)	-3.17 (0.07)	<0.0001
EULAR response									
None	65.2%	20.5%	<.0001	64.5%	25.6%	<0.0001	62.5%	20.3%	<0.0001
Moderate	31.9%	41.5%		28.8%	33.7%		33.2%	39.7%	
Good	2.9%	38.0%		5.9%	40.7%		4.4%	40.0%	
Change in ACR core set (Adjusted mean (SE))									
SJC	-4.3 (0.82)	-10.5 (0.80)	<.0001	-2.5 (0.56)	-8.5 (0.55)	<0.0001	-4.9 (0.57)	10.3 (0.47)	<0.0001
TJC	-7.4 (1.25)	-17.1 (1.23)	<.0001	-4.9 (0.86)	-14.0 (0.85)	<0.0001	-8.5 (0.81)	15.7 (0.67)	<0.0001
Patient Global Assessment	-17.8 (2.72)	-32.5 (2.25)	<.0001	-18.4 (2.14)	-25.7 (1.76)	0.0036	-16.3 (1.75)	33.2 (1.36)	<0.0001
Physician Global Assessment	-32.7 (2.15)	-41.6 (1.78)	0.0002	-28.2 (1.70)	-38.3 (1.4)	<0.0001	-21.6 (1.42)	-35.9 (1.10)	<0.0001
HAQ	-0.34 (0.068)	-0.55 (0.057)	0.0082	-0.30 (0.04)	-0.50 (0.04)	0.0002	0.20 (0.03)	-0.47 (0.03)	<0.0001
Pain assessment	-14.0 (2.67)	-29.8 (2.21)	0.0004	-13.1 (2.07)	-22.2 (1.71)	0.0002	-12.8 (1.76)	-29.9 (1.36)	<0.0001
CRP (mg/dl)	-0.35 (0.31)	-2.51 (0.26)	0.0004	-0.14 (0.19)	-1.89 (0.16)	<0.0001	-0.27 (0.19)	2.19 (0.15)	<0.0001
ESR (mm/h)	-7.1 (2.65)	-39.5 (2.17)	<.0001	-7.1 (1.93)	-34.6 (1.58)	<0.0001	-4.7 (1.59)	-35.6	<0.0001
Change in SF36 domains [Adjusted mean (SE)]									
Mental	2.7 (1.26)	7.3 (1.05)	0.0012	2.8 (0.93)	4.2 (0.79)	0.2220	2.3 (0.73)	5.3 (0.56)	0.0001
Physical	5.0 (0.98)	9.5 (0.82)	<.0001	5.6 (0.68)	8.1 (0.57)	0.0013	4.1 (0.55)	8.9 (0.42)	<0.0001
Change in FACIT F [Adjusted mean (SE)]	4.01 (1.03	8.60 (0.855)	<.0001	5.36 (0.795)	6.40 (0.664)	0.2630	3.60 (0.65)	7.97 (0.50)	<0.0001
Change in Haemoglobin [Adjusted mean(SE)]	-0.286 (1.43)	12.44 (1.163)	<.0001	0.44 (1.05)	10.45 (0.88)	<0.0001	-1.28 (0.83)	9.75 (0.64)	<0.0001

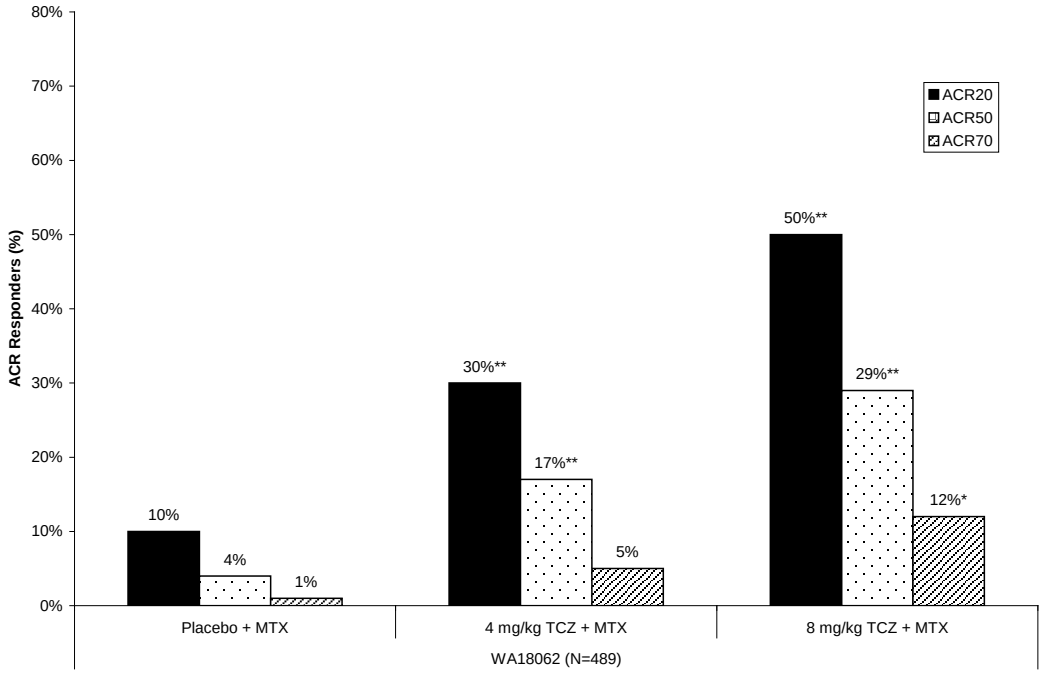
Anti-TNF Inadequate Responders

Study WA18062 was a randomized, double-blind, placebo-controlled, parallel group study in adult patients with moderate to severe RA who had previously experienced an inadequate clinical response to previous anti-TNF therapy[53]. Over half of the patients had failed at least two anti-TNF treatments (51% TCZ 8 mg/kg + MTX, 54% TCZ 4 mg/kg + MTX, and 58% placebo + MTX) prior to entering this study. Few patients (< 5% in each group) failed a previous anti-TNF treatment due to toxicity alone.

ACR20, 50 and 70 response rates at 24 weeks and over time

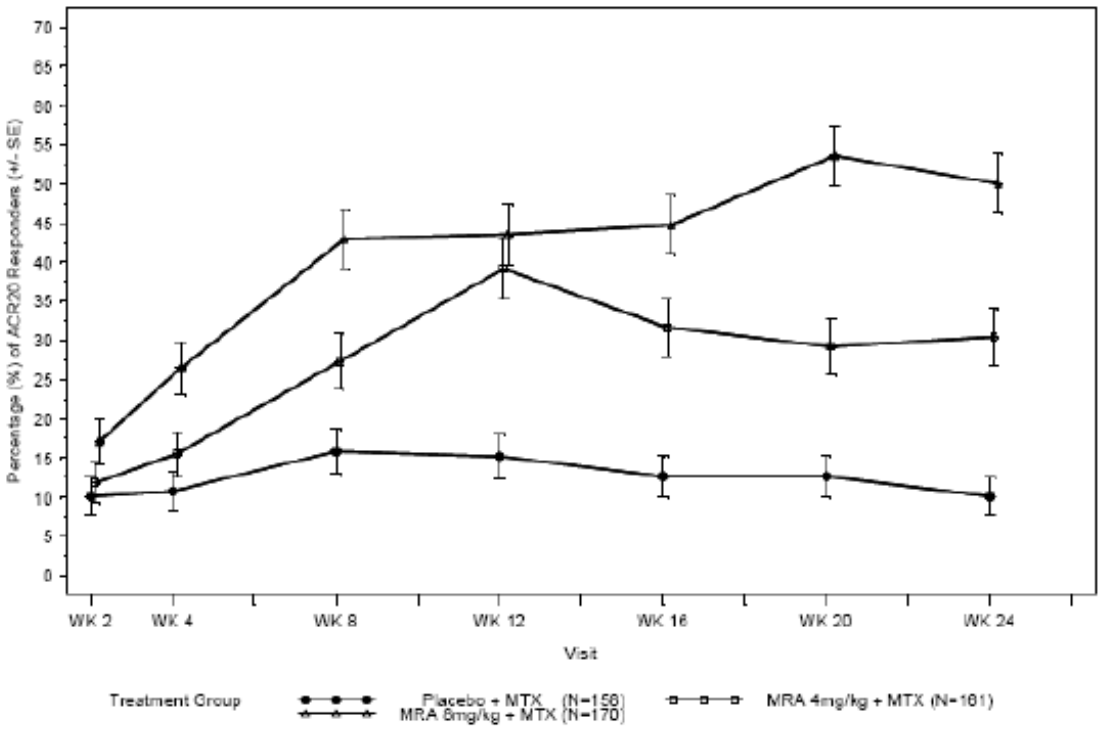
The study met the primary endpoint (ACR20 response at week 24). The greatest response was observed in the TCZ 8 mg/kg + MTX group, particularly with respect to the higher clinical disease hurdles, with marked improvements over placebo + MTX in ACR50 and ACR70 response (figure 9 below). Onset of response was rapid in the TCZ 8 mg/kg + MTX group, with differences between the TCZ 8 mg/kg + MTX and placebo + MTX groups becoming apparent as early as week 2 (ie, the first scheduled assessment) as seen in figures 10,11 and 12 below.

Figure 9: Proportion of ACR20, ACR50 and ACR70 Responders at Week 24 in Study WA18062 – (Anti-TNF Inadequate Responders, ITT Population)



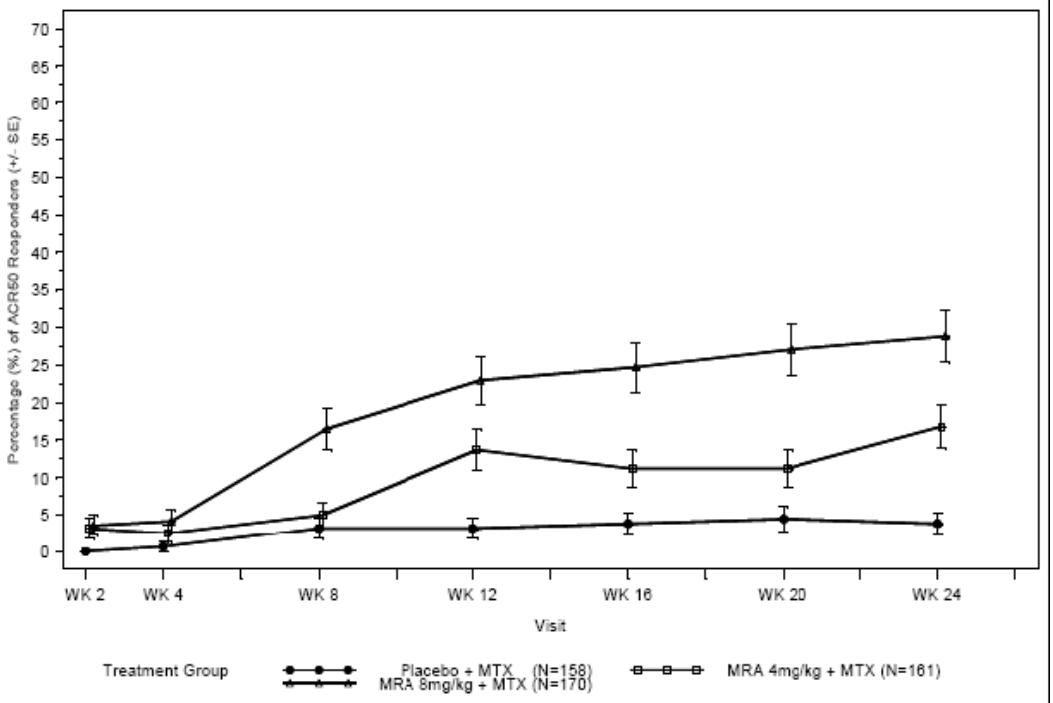
* p < 0.01, TCZ vs. placebo + MTX
** p < 0.0001, TCZ vs. placebo + MTX

Figure 10: ACR20 Response Rates Over Time (ITT Population)



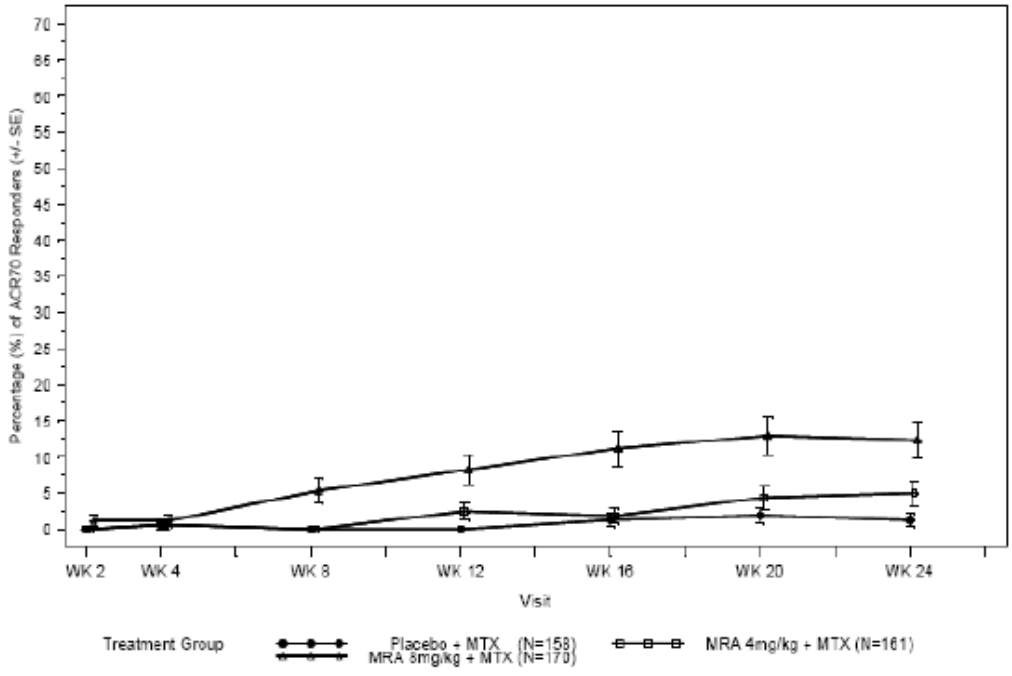
LOCF used for tender and swollen joint counts. No imputation used for missing HAQ score, CRP, ESR and VAS assessments. CRP is used primarily for the calculation of the ACR response, if missing, ESR will be substituted. Patients who receive escape therapy, withdraw prematurely or where an ACR can not be calculated, will be set to 'Non Responder'.

Figure 11: ACR50 Response Rates Over Time (ITT Population)



LOCF used for tender and swollen joint counts. No imputation used for missing HAQ score, CRP, ESR and VAS assessments. CRP is used primarily for the calculation of the ACR response, if missing, ESR will be substituted. Patients who receive escape therapy, withdraw prematurely or where an ACR can not be calculated, will be set to 'Non Responder'.

Figure 12: ACR70 Response Rates Over Time (ITT Population)



LOCF used for tender and swollen joint counts. No imputation used for missing HAQ score, CRP, ESR and VAS assessments. CRP is used primarily for the calculation of the ACR response, if missing, ESR will be substituted. Patients who receive escape therapy, withdraw prematurely or where an ACR can not be calculated, will be set to 'Non Responder'.

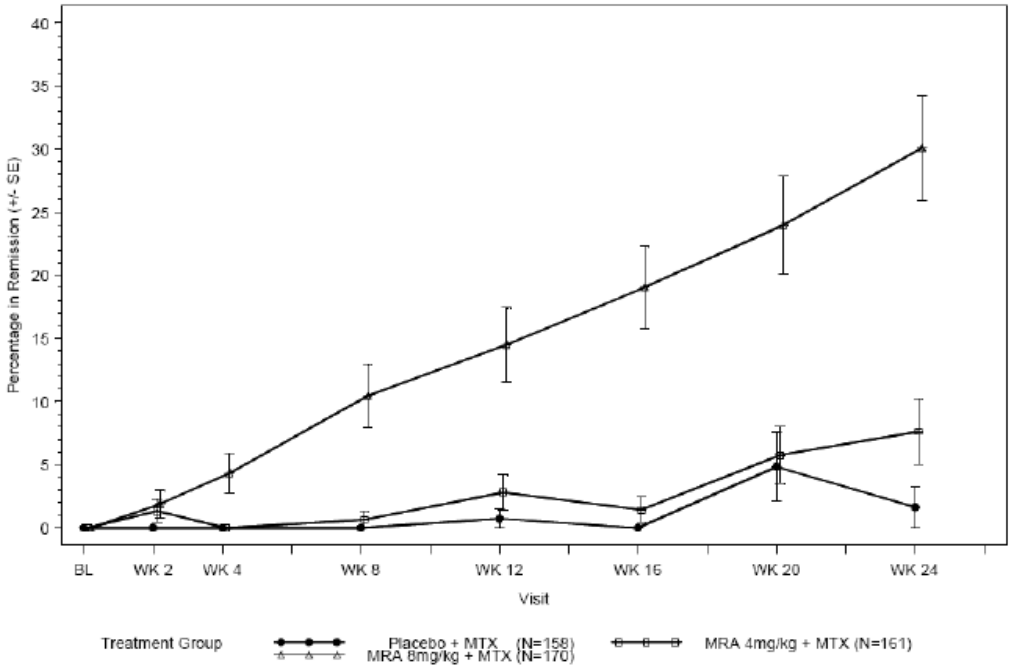
Change in DAS28 and proportion of patients achieving low disease activity or DAS28 Remission

At Week 24, the adjusted mean change from baseline in DAS28 was -3.16, and -0.95 in the tocilizumab 8 mg/kg + MTX, and placebo + MTX groups, respectively. This represented a substantial improvement in the tocilizumab 8 mg/kg + MTX (mean DAS28 scores of 3.6), with the mean score in the 8 mg/kg + MTX group approaching the threshold for low disease activity, while the mean score in the placebo + MTX group (DAS28 5.6) remained above the threshold for severe disease. The change from baseline in adjusted mean DAS28 at Week 24 was highly statistically significantly greater in each tocilizumab + MTX group than in the placebo + MTX group ($p < 0.0001$), as shown by the results obtained from the ANOVA model. This significant difference is repeated when looking at the proportion of patients achieving low disease activity (DAS28<3.2) or DAS28 remission at 24 weeks. (see Table 10 below). The proportion of patients achieving DAS remission by visit is graphically represented in figure 13 below. It can be concluded that tocilizumab has a significant and profound effect on disease activity in this patient's population with remission rates similar to that seen in the DMARD IR population at 24 weeks.

Table 10: Change from Baseline in DAS (28 Joint Count) and DAS Low Disease Activity and Remission at Week 24 –ANOVA Results (ITT Population)

WA18062	Placebo+MTX N=158	TCZ 8mg/kg+MTX N=170
n	60	123
Adjusted Mean	-0.95	-3.16
Difference		-2.21
95% CI for difference		(-2.73, -1.69)
p-value		<.0001
DAS Low disease activity (<3.2) %	4.9	51.2 P=0.0001
DAS remission (<2.6) %	**1.6**	**30.1** **P=0.0001**

Figure 13: Percentage of Patients in Clinical Remission as defined by DAS28 <2.6 by Visit (ITT Population)



LOCF used for tender and swollen joint counts, no imputation used for ESR and Patient's Global Assessment of Disease Activity VAS.
All assessments are set to missing from the time a patient receives escape therapy.

HAQ-DI Outcomes

The mean change in HAQ-DI from baseline at 24 weeks for the tocilizumab group was 0.39 compared to the 0.05 for the placebo group. This was statistically significant (P<.0001). HAQ-DI results have also been summarised by category improved, unchanged, and worsened) according to three different thresholds of improved (defined as a decrease from baseline of ≤ -0.25, ≤ -0.30, or ≤ -0.50) and three different thresholds of worsened (defined as an increase from baseline ≥ of 0.25, ≥ 0.30, or ≥ 0.50) (see Table below). Consistently, a greater number of patients achieved improvements in HAQ-DI (decrease from baseline of ≤ -0.25, ≤ -0.30, or ≤ -0.50) in the tocilizumab + MTX groups than in the placebo + MTX group, conversely, the proportion of patients classed as worsened (increase from baseline ≥ of 0.25, ≥0.30, or ≥ 0.50) was consistently greatest in the placebo + MTX group.

Table 11: Number and Percentage of Patients with Clinically Relevant Improvements in HAQ-DI at Week 24 –Anti-TNF Inadequate Responders (ITT Population)

WA18062	Anti-TNF Inadequate Responders	
	Placebo + MTX	TCZ 8 mg/kg + MTX
	N=158	N=170
≥ 0.25 Improvement		
N	62	130
% Patients	20 (32.3%)	86 (66.2%)
≥ 0.3 Improvement		
N	62	130
% Patients	15 (24.2%)	72 (55.4%)
≥ 0.5 Improvement		
N	62	130
% Patients	5 (8.1%)	58 (44.6%)

Summary Table of Primary and Secondary end points including ACR core set

The table below includes all the primary and secondary endpoints for the licensed 8mg/kg dose

WA18062	Placebo +MTX (n=158)	TCZ 8mg/g = MTX (n=170)	P value
ACR20	10.1%	50.0%	<.0001
Secondary Endpoint			
ACR50	3.8%	28.8%	<.0001
ACR70	1.3%	12.4%	0.0002
ACRn [Adjusted Mean(SE)]	-19.51 (7.990)	25.75 (5.303)	<.0001
DAS28 Remission (<2.6)	1.6%	30.1%	0.0001
Change in DAS28 [Adjusted Mean(SE)]	-0.95 (0.215)	-3.16 (0.144)	<.0001
EULAR Response (%)			
None	83.5%	32.4%	<.0001
Moderate	14.6%	30.6%	
Good	1.9%	37.1%	
Change in ACR Core Set [Adjusted Mean(SE)]			
SJC	-0.5 (1.07)	-7.8 (1.01)	<.0001
TJC	0.3 (1.45)	-14.8 (1.37)	<.0001
Patient's Global Assessment	-15.4 (4.38)	-32.8 (2.89)	0.0011
Physician's Global Assessment	-20.0 (3.42)	-38.2 (2.28)	<.0001
HAQ	-0.05 (0.070)	-0.39 (0.046)	<.0001
Pain Assessment	-8.6 (4.13)	32.5 (2.72)	<.0001
CRP (mg/dL)	-0.0600 (0.50687)	-2.5807 (0.33724)	<.0001
ESR (mm/h)	-3.0 (3.67)	-37.2 (2.43)	<.0001
Change in SF-36 Domains [Adjusted Mean(SE)]			
Mental Component Score	4.1 (1.87)	4.1 (1.25)	0.9966
Physical Component Score	2.2 (1.30)	8.0 (0.87)	0.0003
Change in FACIT-F [Adjusted Mean(SE)]	4.22 (1.568)	8.83 (1.018)	0.0150
Change in Hemoglobin [Adjusted Mean(SE)]	-2.888 (1.8281)	11.904 (1.2705)	<.0001

Tocilizumab monotherapy

Efficacy Results

The primary analysis group used for efficacy includes all patients who were receiving either MTX or tocilizumab. As this was a non-inferiority comparison between treatments, the per protocol (PP) population was the population used in the primary efficacy analysis.

Primary Efficacy Parameter - ACR20 Response at Week 24

The primary endpoint was the proportion of patients with an ACR20 response at Week 24. The proportion of ACR20 responders at Week 24 was 52.1% in the MTX group and 70.6% in the tocilizumab group (see Table 12 below). The weighted difference in ACR20 response at 24 weeks was 0.21 (95% CI 0.13 to 0.29). The lower limit of the CI was 0.13 which is well above the –0.12 non inferiority level. Thus, treatment with tocilizumab was considered non inferior to treatment with MTX.

Table 12: Proportion of Patients with an ACR20 Response at Week 24 – Primary Analysis Group (PP Population)

ACR20	MTX	TCZ 8mg/kg
n	259	265
Responders	135 (52.1%)	187 (70.6%)
Weighted difference vs. MTX 95% C.I. of weighted difference		0.21 (0.13, 0.29)*

* Non-Inferiority demonstrated if lower limit of 95% CI TCZ minus MTX >= -0.12

As tocilizumab was shown to be at least non inferior to MTX in the primary analysis, further testing for superiority to MTX was conducted. For the purposes of this assessment the intent to treat (ITT) population was used. The weighted difference in ACR20 response at 24 weeks was 0.19 (95% CI 0.11 to 0.27). Since the lower limit of the 95% CI of the treatment difference was greater than 0, treatment with tocilizumab 8 mg/kg was superior to treatment with MTX (see Table 13 below). This result was highly statistically significant ($p < 0.0001$).

Table 13: Proportion of Patients with an ACR20 Response at Week 24 – Primary Analysis Group (ITT Population)

ACR20	MTX	TCZ 8mg/kg
n	284	286
Responders	149 (52.5%)	200 (69.9%)
Weighted difference vs. MTX 95%C.I. of weighted difference		0.19 (0.11, 0.27)
p-value		<.0001

Consistent with the ACR20 results, the proportion of ACR50 and ACR70 responders at Week 24 was also higher in the tocilizumab treatment group compared with the MTX group (ACR50: 43.4% vs. 32.8% in the MTX group; ACR70: 27.5% vs. 15.1%, respectively) (Table 14 below). Treatment with tocilizumab did not appear to be inferior to treatment with MTX for ACR50 or ACR70 based on the PP population. The weighted difference between tocilizumab and MTX was 0.13 (95% CI 0.04 to 0.21) for ACR50 response and 0.14 (95% CI 0.06 to 0.22) for ACR70 response.

Consistent results were obtained for the PP sensitivity analysis (using the LOCF method for imputation of data), which also demonstrated no evidence of inferiority of treatment with tocilizumab to treatment with MTX (ACR50 weighted difference = 0.12 [95% CI 0.03 to 0.20]; ACR70 weighted difference = 0.13 [95% CI 0.05 to 0.21]).

Results from the ITT population demonstrate with statistical significance that treatment with tocilizumab is superior to treatment with MTX, for both ACR50 and ACR70 response (ACR50 - p = 0.0023; ACR70 - p =0.0002) [see Table 15]. ACR20, 50 and 70 are presented in Figure 14 below.

Table 14: ACR50 and ACR70 Responses at Week 24 – Primary Analysis Group (PP Population)

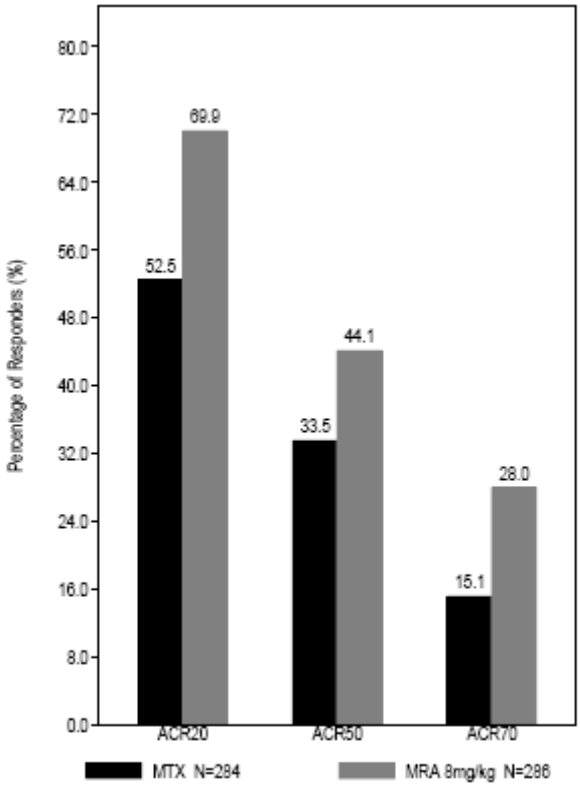
ACR50 8mg/kg	MTX	TCZ
n	259	265
Responders Weighted difference vs. MTX 95% C.I. of weighted difference	85 (32.8%)	115 (43.4%) 0.13 (0.04, 0.21)
ACR70		
n	259	265
Responders Weighted difference vs. MTX 95% C.I. of weighted difference	39 (15.1%)	73 (27.5%) 0.14 (0.06, 0.22)

Table 15: ACR50 and ACR70 Responses at Week 24 – Primary Analysis Group (ITT Population)

ACR50	MTX	TCZ 8mg/kg
n	284	286
Responders Weighted difference vs. MTX 95% C.I. of weighted difference p-value	95 (33.5%)	126 (44.1%) 0.12 (0.04, 0.20) 0.0023
ACR70		
n	284	286
Responders Weighted difference vs. MTX 95% C.I. of weighted difference p-value	43 (15.1%)	80 (28.0%) 0.14 (0.07, 0.22) 0.0002

Figure 14: ACR20, ACR50 and ACR70 Responders at Week 24 – Primary Analysis Group (ITT Population)

efpercrespacr_50itt Plot of the Percentage of ACR20, ACR50 and ACR70 Responders a
Week 24 - All Patients excluding Placebo Patients (ITT Population)

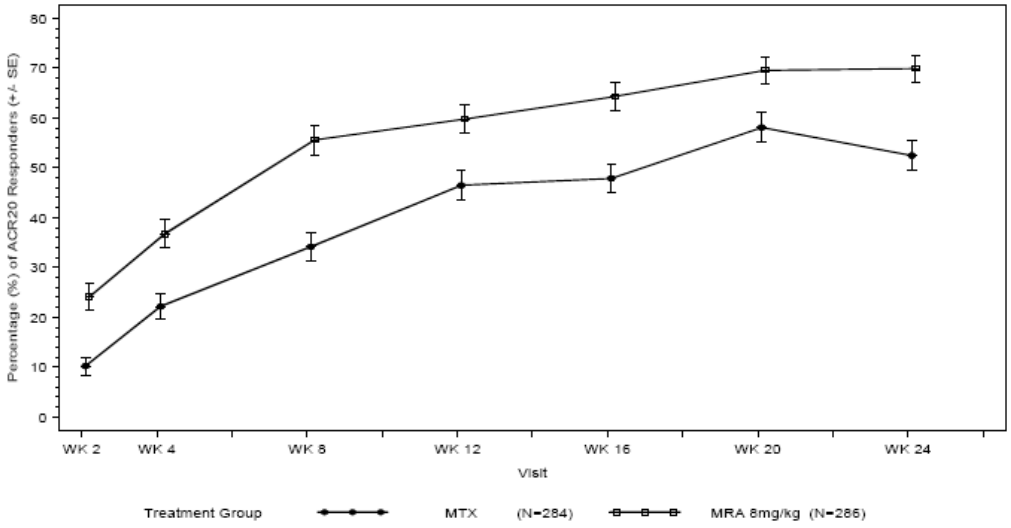


LOCF used for tender and swollen joint counts. No imputation used for missing HAQ score, CRP, ESR and VAS assessments. CRP is used primarily for the calculation of the ACR response, if missing, ESR will be substituted. Patients who receive escape therapy, withdraw prematurely or where an ACR can not be calculated, will be set to 'Non Responder'.

ACR response rates over time

The proportion of patients with an ACR20 response at Weeks 2, 4, 8, 12, 16, 20 and 24 is shown in Figure 15 below for the ITT population. Similar plots of ACR50 and ACR70 responses are presented in Figure 16 below and Figure 17. ACR20 response rates in the tocilizumab group were consistently higher than those in the MTX group over the course of the study. Clear separation between the tocilizumab and MTX groups was observed from as early as Week 2 for ACR20 response, at which point the response rate was 24.1% in the tocilizumab group vs. 10.2% in the MTX group. The ACR20 response rates increased over time in both the tocilizumab and MTX groups before stabilizing at Week 20 to Week 24 and decreasing in the MTX group.

Figure 15: ACR20 Response Rates Over Time – Primary Analysis Group (ITT Population)



In line with ACR20 response, the ACR50 and ACR70 response rates were also consistently higher in the tocilizumab group compared with the MTX group. A clear separation in response rates was observed from as early as Week 4 and Week 8, for ACR50 and ACR70 response, respectively. For both the tocilizumab and MTX groups ACR50 and ACR70 response rates continued to increase over time however, the ACR50 response rate at Week 24 was lower than at Week 20 in the tocilizumab group.

Figure 16: ACR50 Response Rates Over Time – Primary Analysis Group (ITT Population)

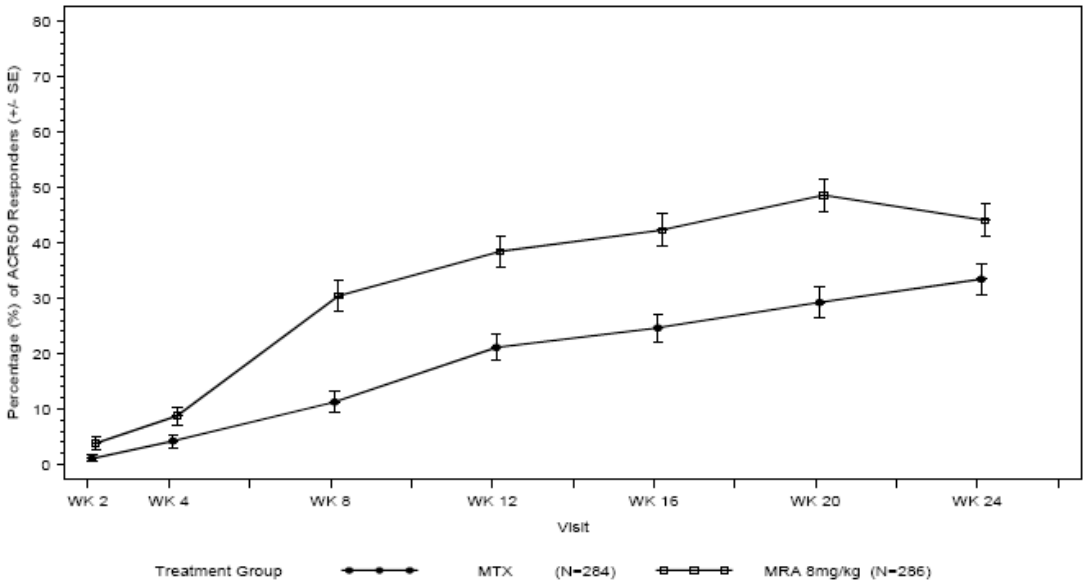
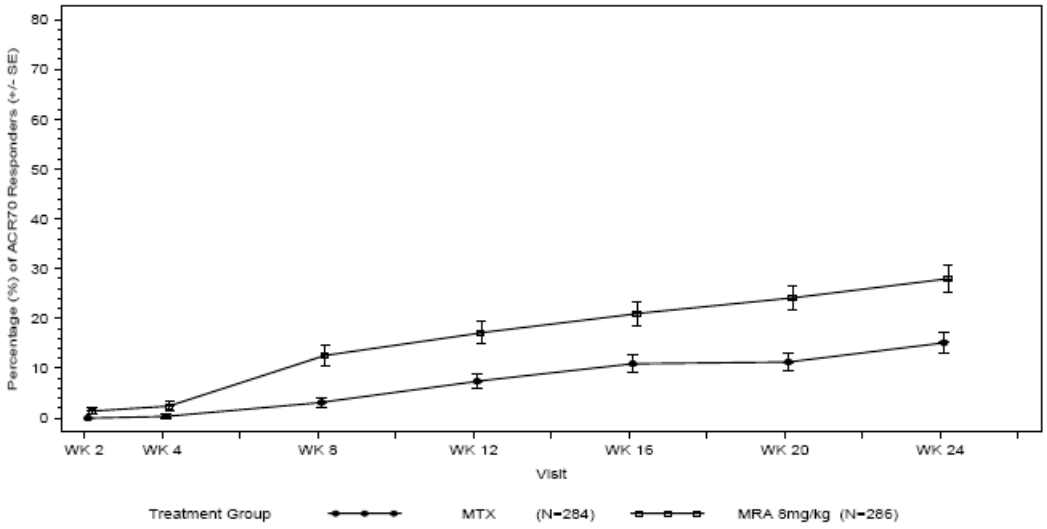


Figure 17: ACR70 Response Rates Over Time – Primary Analysis Group (ITT Population)



Change in DAS28 and proportion of patients achieving low disease activity or DAS28 Remission

Mean DAS28 over time for the MTX and tocilizumab group is shown in Figure 18 below. At baseline, mean DAS28 was 6.78 in each treatment group. By the first scheduled assessment at Week 2 there was a marked decrease (i.e. improvement) from baseline of 0.38 and 1.41 points, in the MTX and tocilizumab groups, respectively. Mean DAS28 continued to decrease over time in both treatment groups; however mean decreases were consistently greater in the tocilizumab group. From as early as Week 2 an apparent separation was observed between the MTX and tocilizumab group, which was maintained through to Week 24. At Week 24, the mean DAS28 score was 3.49 in the tocilizumab group and 4.67 in the MTX group. This represents a substantial improvement in the tocilizumab group, with mean score approaching the threshold for low disease activity.

The adjusted mean change from baseline in DAS28 at Week 24 was –1.99 and -3.29 in the MTX and tocilizumab groups, respectively, with an adjusted mean difference between MTX and tocilizumab groups of -1.30 (95% CI -1.58 to -1.03) (Table 16 below). There was no evidence to suggest tocilizumab was inferior to MTX with respect to DAS28 score.

Figure 18: Mean DAS (28 Joint Count) Over Time – Primary Analysis Group (PP Population)

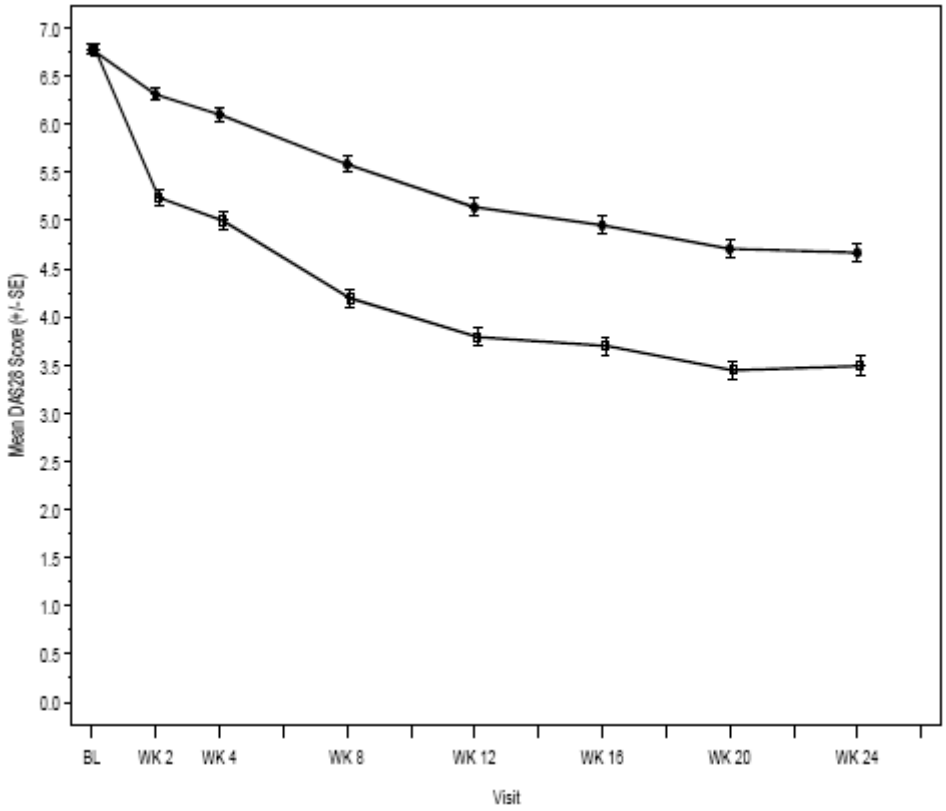
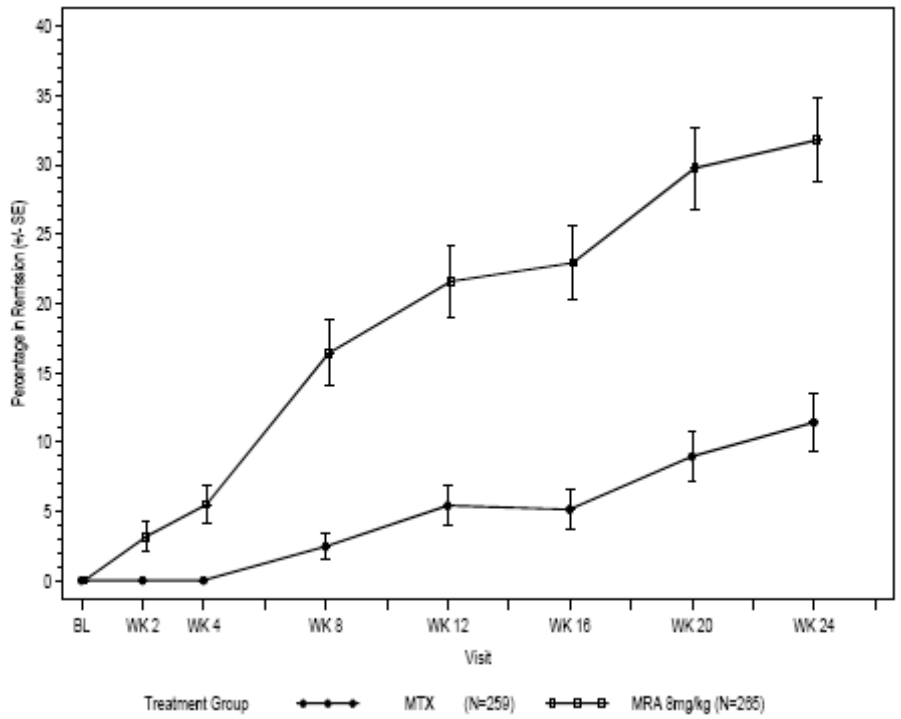


Table 16: Change from Baseline in DAS (28 Joint Count) at Week 24 – ANOVA Results – Primary Analysis Group (PP Population)

	MTX	TCZ 8mg/kg
n	227	235
Adjusted Mean Difference	-1.99	-3.29 -1.30
95% CI for difference		(-1.58, -1.03)

Remission (DAS28 < 2.6) was first achieved for some patients in the tocilizumab group by Week 2 compared with Week 8 in the MTX group. At all time points post-baseline, the tocilizumab group had the highest proportion of patients with low disease activity or remission. By Week 24, the proportion of patients with low disease activity in the tocilizumab was more than double that in the MTX group (44.1% vs. 18.4% in the MTX group) and the proportion of patients in remission was almost three times higher than that in the MTX group (31.8% in the tocilizumab group compared with 11.4% in the MTX group). The proportion of patients in remission (DAS28 < 2.6) over time is presented graphically in Figure 19 below

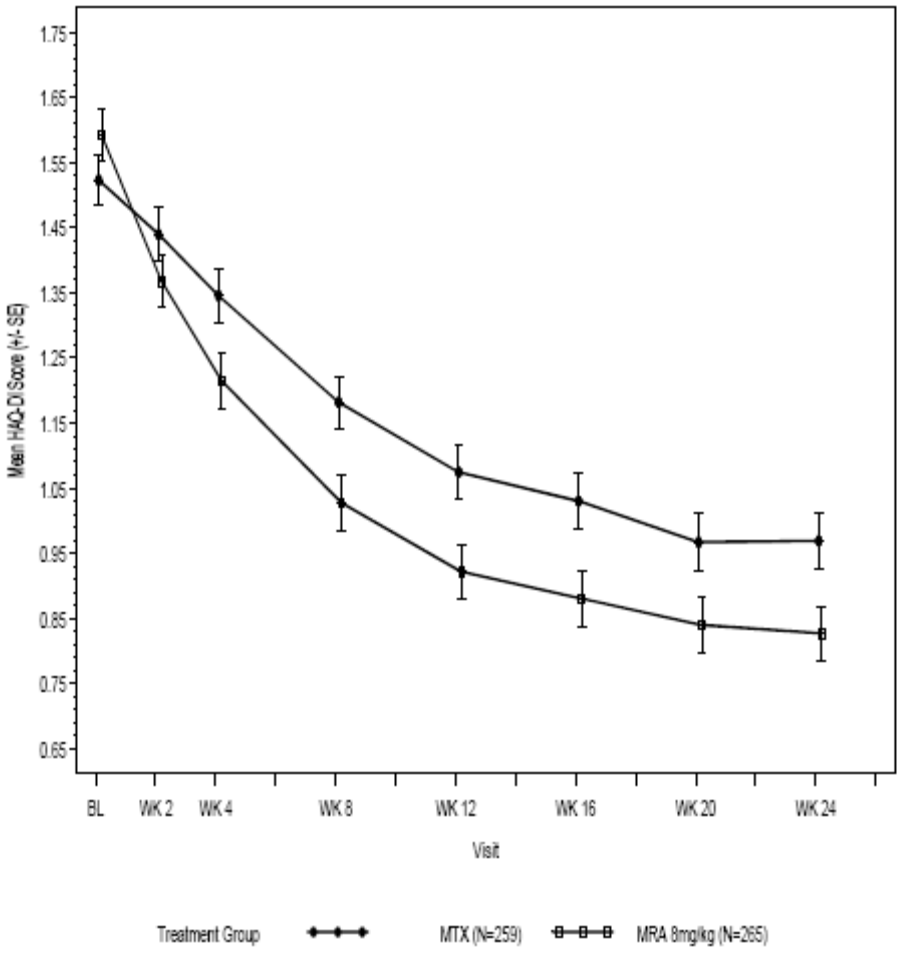
Figure 19: Proportion of Patients in Clinical Remission (DAS28 <2.6) Over Time – Primary Analysis Group (PP Population)



HAQ-DI over 24 weeks

When considering treatment effect on HAQ-DI over the 24 week treatment period mean HAQ-DI scores, which were slightly higher in the tocilizumab group at baseline (1.59 vs 1.52), decreased (i.e., improved) in both the tocilizumab and the MTX group until Week 20, and then began to stabilise.

Figure 20: Mean HAQ-DI Scores by Visit – Primary Analysis Group – (PP Population)



No imputation used for missing HAQ score
All assessments are set to missing from the time a patient receives escape therapy.

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10JUL2007 6:00

n values over time	BL	WK 2	WK 4	WK 8	WK 12	WK 16	WK 20	WK 24
MTX	n=258	n=253	n=254	n=248	n=241	n=236	n=236	n=231
MRA 8 mg/kg	n=265	n=260	n=261	n=247	n=245	n=246	n=246	n=243

As an exploratory analysis, HAQ-DI results were also summarized by category (improved, unchanged and worsened) according to three different thresholds of improved, and three different thresholds of worsened.

Using the important clinical benefit cut-off for improvement (change of ≤ -0.5), the proportion of patients classed as improved was greater in the tocilizumab (62.1%) compared with the MTX group (51.7%) (Table 17 below]. Improvements of≤ -0.25 and ≤ -0.30 were reported more frequently in the tocilizumab group compared with the MTX group (≦ 0.25: 67.8% vs. 77.0%; ≤ 0.30: 59.1% vs. 72.0%, in the MTX and tocilizumab groups, respectively)

Table 17: Categorical Summary of Change from Baseline in HAQ-DI Scores – Primary Analysis Group (PP Population)

	MTX (N=259)	TCZ 8mg/kg (N=265)
Category 1	n 230	243
Improved (<=-0.25) Unchanged (>-0.25 to <0.25) Worsened (>=0.25)	156 (67.8%) 56 (24.3%) 18 (7.8%)	187 (77.0%) 42 (17.3%) 14 (5.8%)
Category 2 n	230	243
Improved (<=-0.3) Unchanged (>-0.3 to <0.3) Worsened (>=0.3)	136 (59.1%) 81 (35.2%) 13 (5.7%)	175 (72.0%) 59 (24.3%) 9 (3.7%)
Category 3 n	230	243
Improved (<=-0.5) Unchanged (>-0.5 to <0.5) Worsened (>=0.5)	119 (51.7%) 103 (44.8%) 8 (3.5%)	151 (62.1%) 85 (35.0%) 7 (2.9%)

Summary of primary and secondary endpoints

Results at Week 24-Primary	MTX	TCZ	Treatment
Analysis Group ***(PP population)***		8 mg/kg	Difference [95% CI]
Primary Endpoint			
ACR20	52.1%	70.6%	0.21 [0.13, 0.29]
Key Secondary Endpoints			
ACR50	32.8%	43.4%	0.13 [0.04, 0.21]
ACR70	15.1%	27.5%	0.14 [0.06, 0.22]
DAS28 Remission [<2.6]	11.4%	31.8%	
Change in DAS28 - adjusted mean	-1.99	-3.29	-1.30 [-1.58, -1.03]
EULAR Response			
Good	16.2%	38.9%	
Moderate	48.6%	43.8%	
No Response	35.1%	17.4%	
Hemoglobin (g/L) adjusted mean (PP population)	0.498	11.707	11.209 [8.529, 13.889]
Results at Week 24-Primary	MTX	TCZ8 mg/kg	Treatment Difference [95% CI]
Analysis Group ***(ITT Population)***			
ACR20	52.5%	69.9%	0.19 [0.11, 0.27] (p< 0.0001)
Key Secondary Endpoints			

ACR50	33.5%	44.1%	0.12[0.04, 0.20] (p=0.0023
ACR70	15.1%	28.0%	0.14 [0.07, 0.22] (p=0.0002)
Change in ACR core set – adjusted mean			
Swollen Joint Count	-8.2	-11.7	-3.5 [-5.2, -1.7]
Tender Joint Count	-13.9	-17.2	-3.3 [-5.9, -0.6]
Patients Global VAS (mm)	-30.7	-34.5	-3.8 [-8.9, 1.3]
Physicians Global VAS (mm)	-31.7	-41.3	-9.6 [-13.5, -5.6]
Pain VAS (mm)	-29.9	-31.9	-2.0 [-6.9, 3.0]
CRP	-1.9	-2.8	-0.9 [-1.5, -0.3]
ESR	-16.1	-37.3	-21.1 [-26.0, -16.2]
HAQ-DI	-0.52	-0.70	-0.18 [-0.3, -]

Long term extension data: Persistence of Efficacy beyond 24 weeks

Key findings:

- Overall response rates to therapy with TCZ 8 mg/kg (with or without concomitant DMARD) were maintained or continued to improve with duration of treatment, with increasing numbers of patients achieving the higher hurdles of efficacy over time.

- Patients who were randomized to placebo or TCZ 4 mg/kg in the core study and at 24 weeks switched to 8 mg/kg open label therapy in the extension studies had an improvement in their disease activity.

Maintenance of the clinical benefit of TCZ beyond 24 weeks has been assessed using data from the extension studies WA18695 and WA18696.[54] In these studies, baseline was defined as the first active dose of TCZ (either in the core study or the extension study).

All patients received TCZ 8 mg/kg on entering the extension studies. Efficacy was assessed every 12 weeks in the long-term extension studies and summarized in three study groups according to the type of patient population treated in the core studies: the pooled group (which consisted of DMARD inadequate responder patients entering from core studies WA17822 and WA18063), the WA17824 group (monotherapy) and the WA18062 group (anti-TNF inadequate responders).

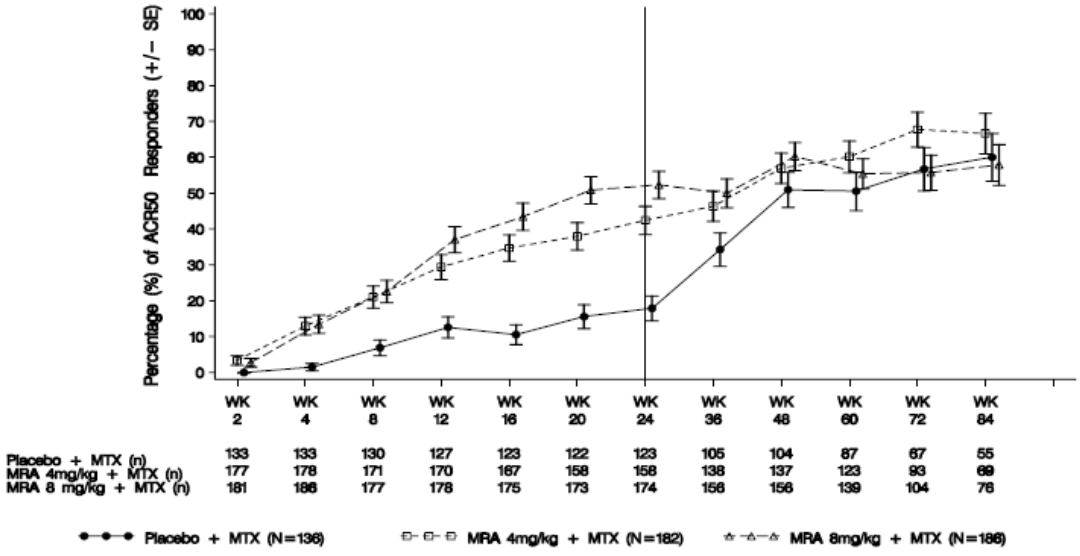
At the data cut-off point (April 20, 2007), a small proportion of patients had discontinued from the study due to insufficient therapeutic response (58/2439 patients: 31 in DMARD inadequate responder group, 4 in monotherapy group and 23 in anti-TNF inadequate responder population).

Efficacy was either maintained or continued to improve in patients who entered the long term extension studies, as demonstrated by continued improvements in ACR responses, DAS28 and EULAR scores, as well as patient-reported outcomes such as

SF-36 and FACIT-Fatigue. Importantly, continued treatment with TCZ 8 mg/kg provided incremental benefit over time, as demonstrated by increasing proportions of patients achieving the higher hurdle endpoints; ACR50 (example from WA17822 see Figure 21 below), ACR70, DAS28 remission for anti TNF and mono-therapy patients (Figure 22 below) and the proportion of patients who achieved clinically relevant improvements in ACR components (patients with zero tender or swollen joints, VAS and HAQ-DI scores of zero, (Table 18 below). These improvements and patterns of improvement were evident in all study populations.

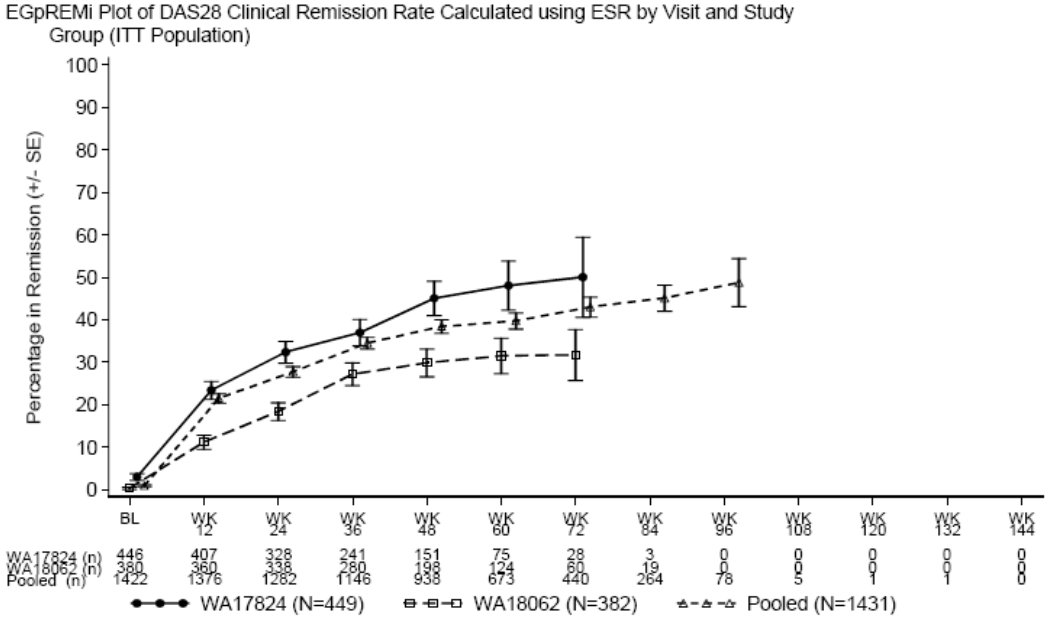
The majority of the patients on TCZ 8 mg/kg in the extension studies were on a background traditional DMARDs, however analyses in a subgroup of 299 patients who remained on TCZ 8 mg/kg monotherapy showed maintenance of ACR20 response rates, and further improvements with duration of treatment in ACR50, ACR70 and DAS28 scores

Figure 21: Plot of ACR50 Response Rates by Visit – WA17822 Study Group (ITT Population)



LOCF used for tender and swollen joint counts, no imputation used for HAQ Score, CRP, ESR and VAS assessments. CRP is used primarily, however if the change in CRP is not calculable, the change in ESR is used if available.
Escape patients are excluded.

Figure 22: Plot of DAS28 (Monotherapy and anti TNF IR) Clinical Remission Rate Calculated using ESR by Visit and Study Group (ITT Population)



Clinical Remission is defined as DAS28 < 2.6
LOCF used for tender and swollen joint counts. No imputation used for ESR and Patient's Global Assessment of Disease Activity VAS.
Lines are only displayed at a timepoint when n is >= 5% of N.

Table 18: Patients with Clinically Significant Improvement of ACR Components at Week 48, Mono-therapy, anti TNF IR and pooled DMARD IR (ITT Population)

	WA17824 (N=499)	WA18062 (N=382)	Pooled (N=1431)
Joint count			
n	213	253	1085
zero TJC (68)	31 (14.6%)	27 (10.7%)	190 (17.5%)
zero SJC (66)	62 (29.1%)	34 (13.4%)	238 (21.9%)
zero TJC and zero SJC	19 (8.9%)	15 (5.9%)	109 (10.0%)
1 TJC (68)	26 (12.2%)	17 (6.7%)	83 (7.6%)
1 SJC (68)	20 (9.4%)	16 (6.3%)	105 (9.7%)
1 TJC and 1 SJC	4 (1.9%)	3 (1.2%)	21 (1.9%)
2 TJC (68)	13 (6.1%)	14 (5.5%)	96 (8.8%)
2 SJC (68)	16 (7.5%)	15 (5.9%)	112 (10.3%)
2 TJC and 2 SJC	0 (>0.1%)	1 (0.4%)	
3 TJC (68)	14 (6.6%)	10 (4.0%)	66 (6.1%)
3 SJC (68)	15 (7.0%)	18 (7.1%)	93 (8.6%)
3 TJC and 3 SJC	2 (0.9%)	2 (0.8%)	12 (1.1%)
4 TJC (68)	10 (4.7%)	11 (4.3%)	77 (7.1%)
4 SJC (68)	12 (5.6%)	20 (7.9%)	86 (7.9%)
4 TJC and 4 SJC	2 (0.9%)	3 (1.2%)	12 (1.1%)
Patient's Global VAS (mm)			
n	166	213	971
Patients Global VAS = 0	13 (7.8%)	4 (1.9%)	39 (4.0%)
Physician's Global VAS (mm)			
n	164	210	965
Physician's Global VAS = 0	7 (4.3%)	5 (2.4%)	41 (4.2%)
Patient's Pain VAS (mm)			
n	166	213	971
Patient's Pain VAS = 0	14 (8.4%)	4 (1.9%)	44 (4.5%)
HAQ-DI			
n	165	212	967
HAQ-DI = 0	33 (20.0%)	11 (5.2%)	147(15.2%)

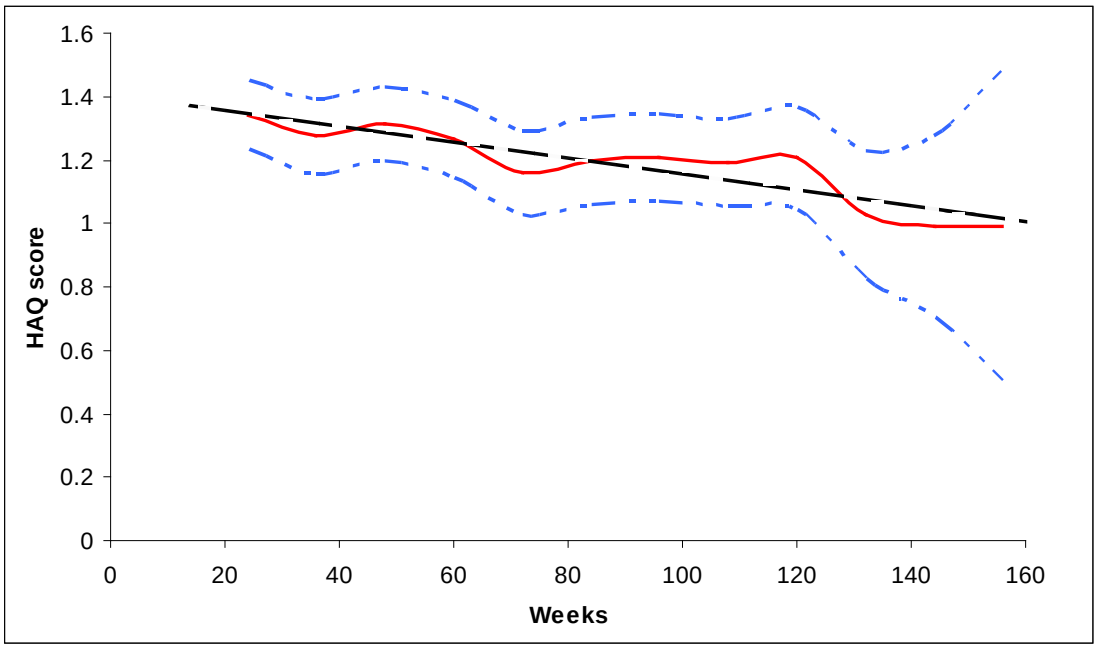
LOCF used for tender and swollen joint counts, no imputation used for missing HAQ score and VAS assessments.

Long term HAQ-DI

Of specific interest to the decision problem is the long term HAQ-DI change in both the DMARD IR and TNF IR populations. The long term HAQ-DI in the DMARD IR population has been pooled from the 3 DMARD IR studies and is presented in section 6.5 *Meta-analysis.* For the anti TNF IR population WA18062 the following

long term pattern can be seen up to 132 weeks in the TCZ 8mg/kg dose in combination with MTX. The trend is clearly for continued HAQ improvement over time whilst on treatment.

Figure 23: **Mean HAQ score over time for patients in the TNF-IR trial**



TNF-IR Jan 2009 follow-up

Week	Patient numbers	Mean HAQ score	95% CI	
24	146	1.343	1.232064	1.45374
36	137	1.2746	1.155628	1.393768
48	132	1.3131	1.198244	1.427956
60	123	1.2663	1.142232	1.390172
72	118	1.16	1.027112	1.292692
84	113	1.1974	1.06216	1.33264
96	106	1.207	1.068232	1.345964
108	106	1.1922	1.053824	1.330772
120	77	1.207	1.044908	1.369092
132	49	1.0281	0.828376	1.227628
144	26	0.9904	0.702476	1.278324
156	13	0.9904	0.501576	1.479224

6.5 Meta-analysis

DMARD IR outcomes are presented as part of a pre-specified pooling protocol of WA17822, WA17823 and WA18063

All outcomes specified in the trial protocols are presented however special attention is paid to ACR, DAS and HAQ-DI in relation to the decision problem

TCZ has a significant effect on both signs and symptoms, patient reported outcomes and radiographic progression in the DMARD IR population

Tocilizumab in combination with MTX can provide a rapid onset of treatment effect, and a durable remission (DAS28<2.6) in patients with an inadequate response to DMARDs

Long term outcomes data demonstrates the ongoing efficacy of TCZ beyond 24 weeks

Long term HAQ-DI shows continued improvement over 156 weeks

The results from the individual studies provide evidence of the efficacy of TCZ in patients with moderate to severe active RA. To provide an estimate of the treatment effect of TCZ in the DMARD inadequate responder patient population and to investigate the effect of TCZ where there are likely to be small differences between the treatment groups, studies WA17822, WA17823 and WA18063 were pooled.[55] These studies have been considered appropriate to pool for the reasons outlined below:

Trial Design

WA17822, WA17823 and WA18063 have a similar study design. They are all double-blind, placebo-controlled studies with a primary endpoint of ACR20 response at week 24. WA17822 and WA17823 were both three-arm studies; TCZ 4 or 8 mg/kg or placebo was administered every 4 weeks while patients remained on a background dose of MTX (between 10-25 mg/week). WA18063 was a two-arm study; TCZ 8 mg/kg or placebo was administered every 4 weeks while patients remained on background traditional DMARDs. In addition, all three studies used the same outcome measures and utilized the same data collection instruments. Moreover, key inclusion and exclusion criteria were identical (with one additional

requirement for patients to have radiographic evidence of at least one joint with an erosion in study WA17823).

Demographic and Baseline Characteristics

WA17822, WA17823 and WA18063 have very similar patient populations, as demonstrated by general demographics (refer to section 6.2.3). In study WA17823, small differences were observed in the baseline disease characteristics; ACR core set parameters were slightly lower in this study. This was reflected in a lower mean DAS28 score at baseline (6.5 vs. 6.8 in studies WA17822 and WA18063). The patient populations in the three studies were comparable with respect to previous DMARD and anti-TNF use; however, baseline oral corticosteroid use was slightly higher in WA17823 compared with WA17822 and WA18063 (61% to 67% vs. 51% to 55%). Importantly, in a subgroup analysis by baseline characteristics, baseline DAS28 or use of corticosteroids did not influence response to TCZ.

Heterogeneity of Treatment Effect

The ACR20 response at week 24 (primary endpoint) was very similar in WA17822, WA17823 and WA18063. The proportions of ACR20 responders from the three studies that comprised the pooled ITT population (WA17822, WA18063 and WA17823) are presented in the table below. In addition, a plot of the odds ratios and confidence intervals of the primary endpoint (ACR20) by study has been produced (see Figure 24 below) and reviewed for heterogeneity of response. At week 24, the proportions of ACR20 responders in the TCZ 8 mg/kg dose group were consistent across the three studies: 59% in WA17822, 61% in WA18063 and 56% in WA17283. Although the odds ratio in WA17823 was lower than the other two studies, all of the studies show both a clinically relevant and statistically significant difference to the placebo group. In a logistic regression analysis that examined the effect of intrinsic/extrinsic factors on ACR20 response, there was no significant interaction found between treatment and study at the 10% level. The results of these analyses can be found in appendix 4

Table 19: Cross-Study Presentation of ACR20 Responses at Week 24 (ITT Population)

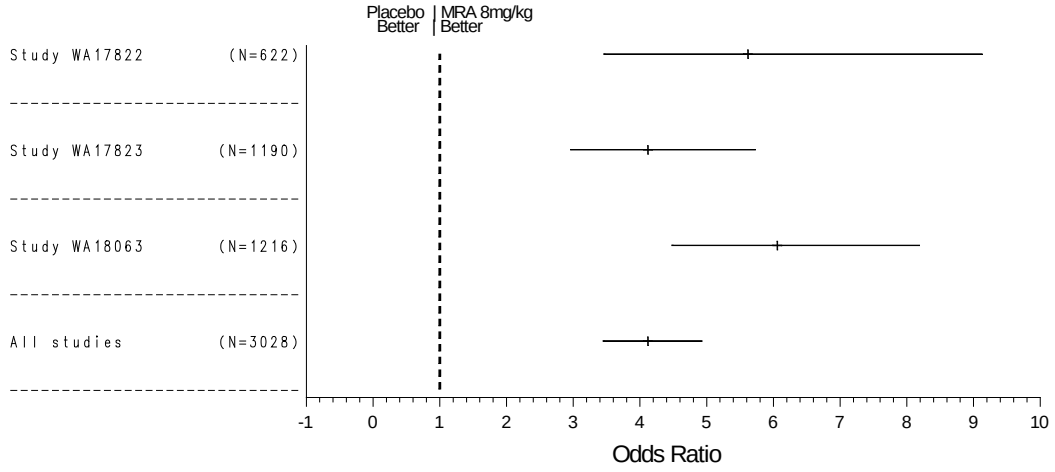
Study	Placebo + DMARD	TCZ 4 mg/kg + MTX	TCZ 8 mg/kg + DMARD
WA17822	N=204	N=213	N=205
	26.5%	47.9%*	58.5%*
WA18063	N=413	-	N=803
	24.5%		60.8%*
WA17823	N=393	N=399	N=398
	27.0%	50.6%*	56.3%*

P-values calculated from Cochran-Mantel-Haenszel analysis

* Comparison with placebo + MTX/DMARD arm within same study (2-sided) $p \leq 0.0001$

Table 20: Plot of ACR20 Response Rates by Study (Adjusted Odds Ratios +/- 95% confidence Interval for 8mg/kg + DMARD vs Placebo + DMARD) (ITT Population)

EGforeststudyi Plot of ACR20 Response Rates by Study (Adjusted Odds Ratio +/- 95% confidence Interval for 8mg/kg + DMARD vs Placebo + DMARD) (ITT Population)



Odds Ratios presented for studies WA17822, WA17823 and WA18063 are adjusted on site
Odds Ratios presented for the pooled studies are adjusted on the study protocol

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In the WA17822 and WA17823 studies, all patients received background MTX therapy, whereas in the WA18063 study, patients could remain on other background DMARDs. The majority of patients (approximately 75%) in study WA18063 were on MTX alone or in combination with other DMARDs at baseline and in an analysis of ACR20, ACR50 and ACR70 at week 24, clinically relevant improvements were evident when TCZ 8 mg/kg was added to any of the background DMARD regimens allowed in this study.

Studies WA18062 and WA17824 are not included in the pooled efficacy analysis as these studies were conducted in different patient populations (the former study conducted in patients refractory to anti-TNF therapy, and the latter study in patients largely naïve to MTX therapy) or who were receiving TCZ monotherapy rather than in combination with background DMARD treatment. No Japanese studies are included in this analysis due to the different patient populations and inclusion and exclusion citeria.

Statistical Methods

Heterogenity across the three studies was examined, as stated previously by logistical regression analysis for a variety of both intrinisic and extrinsic factors on ACR20 between treatment and study groups.

Two analyses were performed using the primary logistic regression model of the ACR20 response on the ITT population based on pooled data from studies WA17822, WA17823 and WA18063.

1. A logistic regression model of the ACR20 response (adjusted on study) for each of the pre-specified intrinsic / extrinsic factors and baseline factors and the treatment by factor interaction.

The intrinsic factors were:	The extrinsic factors were:	The baseline factors were:
Age	Smoking status	CRP
Gender	Number of previous DMARDS	ESR
Race	Oral steroid use	HAQ
Region	Lipid lowering agent use	Swollen joint count
Body weight	Background DMARD	Tender joint count
BMI		
Baseline DAS28		
Duration of RA		
Rheumatoid factor		

2. Analysis of variance models on the change from baseline of the ACR Core set components (adjusted on study) and the interaction between treatment and study.

No significant interactions were found with treatment group at the 10% level indicating that the treatment effect is similar for each category of the factors that were analysed. In addition, no significant interaction between treatment and study (p=0.3950) was found. The results of these analyses can be found in appendix 4

For all the reasons described above the pooling of data from studies WA17822, WA17823 and WA18063 was considered a reasonable and valid approach.

Outcomes

The following table gives the pooled analysis ACR20, 50, 70 and 90 results at 6 months for the ITT population. Comparison to the results of the individual studies and also given below.

Table 21: Analysis of the Percentage of Patients with an ACR20, ACR50, ACR70 AND ACR90 Response at Week 24 – Pooled DMARD Inadequate Responders (ITT Population)

Summary and Analysis of the Percentage of Patients with an ACR20, ACR50, ACR70 and ACR90 Response at Week 24 - 6 Month Pooled Data (ITT Population)

	Placebo + DMARD (N=1010)	TCZ 4mg/kg+MTX (N=612)	TCZ 8mg/kg+DMARD (N=1406)
ACR20			
n	1010	612	1406
Responders	261 (25.8%)	304 (49.7%)	832 (59.2%)
p-value		<.0001	<.0001
ACR50			
n	1010	612	1406
Responders	97 (9.6%)	167 (27.3%)	520 (37.0%)
p-value		<.0001	<.0001
ACR70			
n	1010	612	1406
Responders	24 (2.4%)	70 (11.4%)	260 (18.5%)
p-value		<.0001	<.0001
ACR90			
n	1010	612	1406
Responders	3 (0.3%)	15 (2.5%)	59 (4.2%)
p-value			<.0001

The stratification factor study is included in the model
Cochran-Mantel-Haenszel analysis was used to calculate p-values. All comparisons to placebo + DMARD arm within each study.
LOCF used for tender and swollen joint counts, no imputation used for missing HAQ Score, CRP, ESR and VAS assessments. CRP is used primarily for the calculation of the ACR response, if missing, ESR will be substituted. Patients who receive escape therapy, withdraw prematurely or where an ACR can not be calculated, will be set to 'Non Responder'.
TCZ 4mg/kg + MTX pooled data from WA17822 and WA17823. TCZ 8mg/kg + DMARD pooled data from WA17822, WA17823 and WA18063.

Outcomes of significant interest to the decision problem:

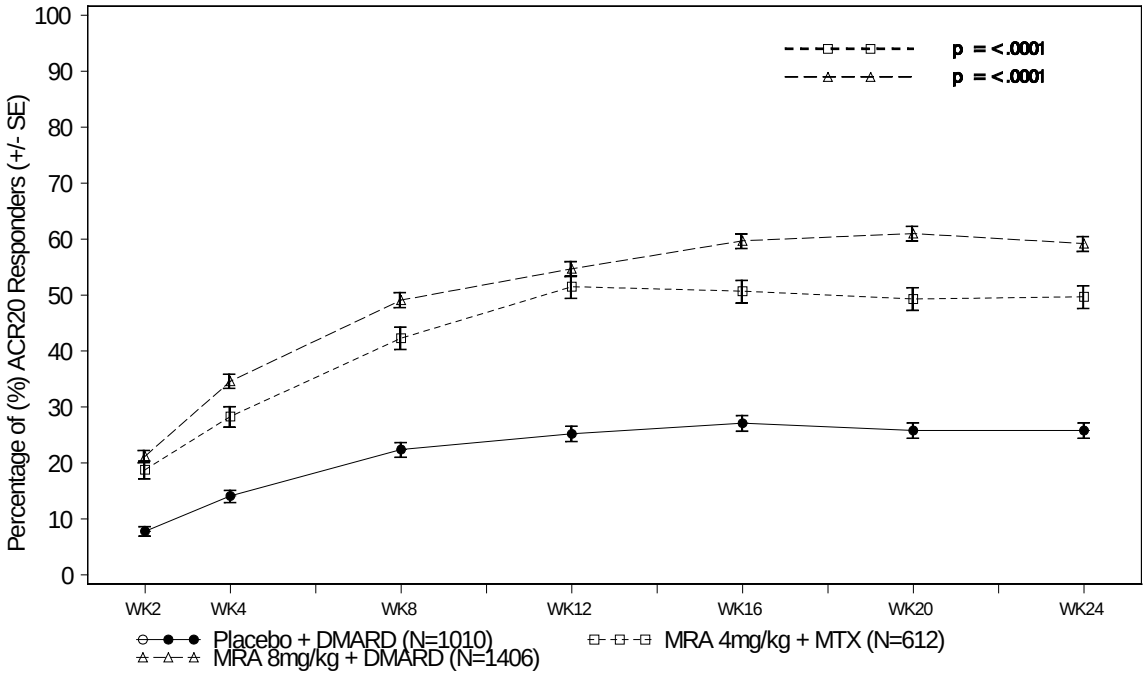
ACR20, ACR50 and ACR70 Response Rates Over Time

Plots of ACR response over time demonstrated a rapid onset of response and a continued improvement in the level of response with time in patients treated with TCZ.

As with the other populations (anti TNF IR, mono-therapy and individual DMARD IR studies) first onset of action of TCZ in the pooled DMARD IR population was seen as early as week 2 (first scheduled assessment), with a clear separation from the control group at all time points (Figure 24 below).

Figure 24: ACR20 Response Rates by Visit – Pooled DMARD Inadequate Responders (ITT Population)

EGacr20pli ACR20 Response Rates by Visit - 6 Month Pooled Data (ITT Population)



Cochran-Mantel-Haenszel analysis was used to calculate p-values. All comparisons to placebo + DMARD. LOCF used for joint counts, no imputation used for missing HAQ Score, CRP, ESR and VAS assessments. CRP is used primarily for the calculation of the ACR response, if missing, ESR will be substituted. Patients who receive escape therapy, withdraw prematurely or where an ACR can not be calculated, will be set to 'Non Responder'.

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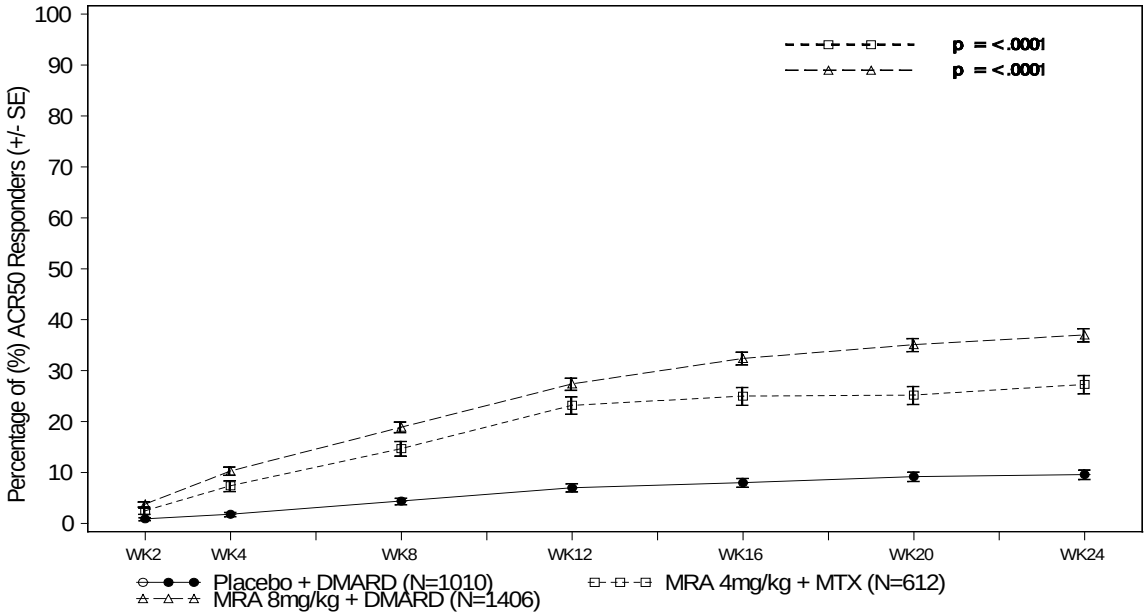
More importantly, the majority of patients in the TCZ groups who achieved an ACR20 response also achieved an ACR50 response In this pooled DMARD inadequate responder population, 520/832 (63%) in the TCZ 8 mg/kg + DMARD who achieved an ACR20 response also achieved an ACR50 response compared with 97/261 (37%) in the placebo + DMARD group. In this population, onset of ACR50 response was evident as early as week 4 (Figure 25 below), with the proportion of patients experiencing this magnitude of benefit increasing over time.

Figure 25: ACR50 Response Rates by Visit - 6 Month Pooled Data (ITT Population)

EGacr50pli ACR50 Response Rates by Visit- 6 Month Pooled Data (ITT Population)



Cochran-Mantel-Haenszel analysis was used to calculate p-values. All comparisons to placebo + DMARD. LOCF used for joint counts, no imputation used for missing HAQ Score, CRP, ESR and VAS assessments. CRP is used primarily for the calculation of the ACR response, if missing, ESR will be substituted. Patients who receive escape therapy, withdraw prematurely or where an ACR can not be calculated, will be set to 'Non Responder'.

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The number of patients who achieved ACR70 and ACR90 responses increased with time. These observations provide initial evidence that, although a 20% improvement is rapidly achieved following treatment initiation, continued treatment provides incremental benefit (ACR50 response and higher) in a substantial subset of patients. This same pattern was seen in the anti TNF IR populations as well.

In a Kaplan Meier analysis of ACR20 response, the median time to response was 57 days in the TCZ 8 mg/kg + DMARD, compared with 141 days for the placebo + DMARD group (Table 22 below).

Table 22: Summary of Time (Days) to First ACR20 Response at Week 24 – Pooled DMARD Inadequate Responders (ITT Population)

etsumtimeacrpoolwk24i Summary of Time (Days) to First ACR20, ACR50 and ACR70 Response at Week 24- 6 Month Pooled Data (ITT Population)

	Placebo + DMARD (N=1010)	TCZ 4mg/kg+MTX (N=612)	TCZ 8mg/kg+DMARD (N=1406)
ACR20			
n	1010	612	1406
Responders	527 (52.2%)	458 (74.8%)	1143 (81.3%)
Censored	483 (47.8%)	154 (25.2%)	263 (18.7%)
Median	**141.0**	57.0	**57.0**
95% CI for Median	(115.0, 141.0)	(57.0, 61.0)	(#, #)
Min-Max	1*-282*	1*-251*	1*-238*
First Quartile	57.0	29.0	28.0
Third Quartile	#	141.0	114.0

Summary statistics are Kaplan Meier estimates.
value not calculable due to insufficient events
* indicates that this is a censored value
LOCF used for tender and swollen joint counts, no imputation used for missing HAQ Score, CRP, ESR and VAS assessments. CRP is used primarily for the calculation of the ACR response, if missing, ESR will be substituted. Patients who receive escape therapy, withdraw prematurely or where an ACR can not be calculated, will be set to 'Non Responder'.
TCZ 4mg/kg + MTX pooled data from WA17822 and WA17823. TCZ 8mg/kg + DMARD pooled data from WA17822, WA17823 and WA18063

Change in DAS 28 and proportion of patients achieving low disease activity or DAS28 remission

TCZ treatment resulted in rapid and continued improvements in DAS28 scores (from week 2 onwards), reflecting the results for ACR response (see Table below)
When considering low disease activity and remission as defined by DAS28<2.6 approximately half of patients treated with licensed TCZ 8 mg/kg dose achieved low disease activity, regardless of the patient population studied and, importantly, approximately one third achieved DAS28 remission. The percentage of TCZ-treated patients achieving DAS28 remission continued to increase during the 24-week study period (see figure 26 below)

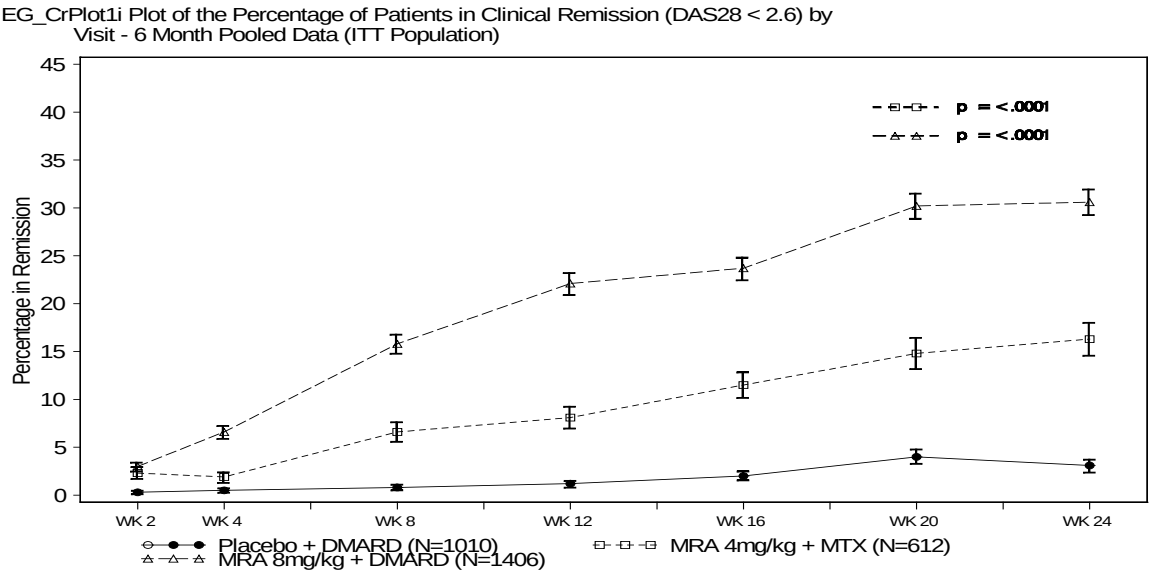
Table 23: Disease Activity Score (28 Joint Count) at Baseline and Week 24 and Change from Baseline at Week 24 – Pooled DMARD Inadequate Responders (ITT Population)

etsumdas28chgpooli Summary of Disease Activity Score (28 joint count) at Baseline and Week 24 and Change from Baseline at Week 24 - 6 Month Pooled Data (ITT Population)

	Placebo + DMARD (N=1010)	TCZ 4mg/kg + MTX (N=612)	TCZ 8mg/kg + DMARD (N=1406)
Baseline			
n	998	606	1395
Mean	6.64	6.60	6.67
SD	0.962	0.938	0.996
Median	6.67	6.64	6.74
Min-Max	3.0-9.0	3.6-9.2	2.1-9.2
Week 24			
n	655	460	1202
Mean	5.27	4.04	3.46
SD	1.417	1.560	1.561
Median	5.26	3.92	3.30
Min-Max	1.0-8.7	0.0-8.1	0.0-8.3
Change from Baseline			
n	649	455	1192
Mean	-1.30	-2.53	-3.22
SD	1.282	1.471	1.499
Median	-1.19	-2.46	-3.21
Min-Max	-5.8-1.8	-7.7-1.3	-7.6-1.5
Difference in treatment effect (95% CI)*		-1.11 (-1.29,-0.92)	-1.94 (-2.08,-1.81)
p-value		<.0001	<.0001

* Difference in adjusted mean change from baseline at Week 24 (with 95%CI) from an analysis of variance comparison to Placebo + DMARD.
The stratification factor study is included in the model
LOCF used for tender and swollen joint counts, no imputation used for ESR and Patient's Global Assessment of Disease Activity VAS.
All assessments are set to missing from the time a patient receives escape therapy and only pre-escape therapy assessments are carried forward.
TCZ 4mg/kg + MTX pooled data from WA17822 and WA17823. TCZ 8mg/kg + DMARD pooled data from WA17822, WA17823 and WA18063

Figure 26: Percentage of Patients in DAS28 Remission (DAS28 < 2.6) by Visit – Pooled DMARD Inadequate Responders (ITT Population)



LOCF used for tender and swollen joint counts, no imputation used for ESR and Patient's Global Assessment of Disease Activity VAS.
All assessments are set to missing from the time a patient receives escape therapy and only pre-escape therapy assessments are carried forward.

Program : $PROD/cd11935h/EG_CrPlot.sas / Output : $PROD/cd11935h/reports/EG_CrPlot1i.cgm
31AUG2007 10:47

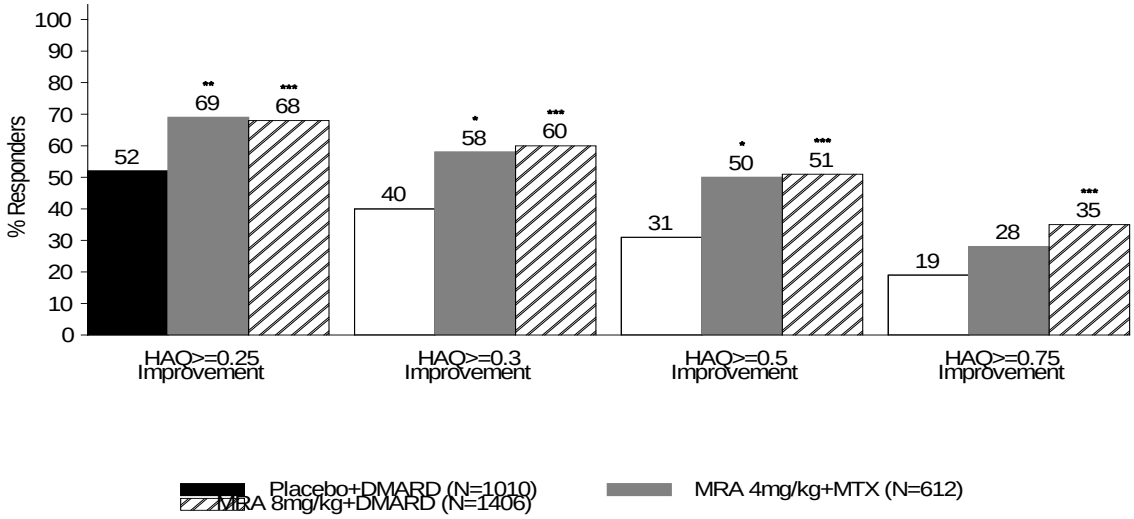
HAQ-DI pooled outcomes

Mean decreases (improvement) from baseline in HAQ-DI score were consistently greater in the TCZ groups compared with the placebo + MTX/DMARD groups in the DMARD inadequate responder population.

In the pooled population at week 24, the proportion of patients achieving a clinically relevant improvement in HAQ-DI (defined as a decrease of ≥ 0.25 in an individual's total score) was higher in the TCZ groups than in the placebo + DMARD group (Figure 27 below). In addition, when summarized according to three higher clinical thresholds of improvement, decrease ≥ 0.30, ≥ 0.50 or ≥ 0.75 from baseline (the latter being two and three times, respectively, the clinically relevant threshold), a significantly higher proportion of patients in the TCZ 8 mg/kg + DMARD group achieved clinically relevant improvements in all categories ($p < 0.0001$). Of the patients in the TCZ 8 mg/kg + DMARD group (68%) who achieved the minimally clinically relevant improvements in HAQ-DI, over half also achieved the more stringent improvement of ≥ 0.75 (35%). Statistically significant improvements in all categories of improvement except ≥ 0.75 were observed in the TCZ 4 mg/kg + MTX group. Consistent with other RA improvement criteria (e.g. ACR and DAS), the time to a clinically relevant improvement in HAQ-DI was rapid in the TCZ groups (Table 24 below).

Figure 27: Number and Percentage of Patients with a HAQ-DI Improvement at Week 24 – Pooled DMARD Inadequate Responders (ITT Population)

EG_HaqBar1i Plot of Number and Percentage of Patients with a HAQ-DI Improvement at Week 24 - 6 Month Pooled Data (ITT Population)



P-values from CMH analysis (stratified by study). All comparisons to placebo + DMARD
* p<=0.05 ** p<=0.01 *** p<=0.0001

Program : $PROD/cd11935h/EG_HaqBar.sas / Output : $PROD/cd11935h/reports/EG_HaqBar1i.cgm
02AUG2007 21:20

Table 24: Time (Days) to First Clinically Relevant Improvement in HAQ-DI by Week 24 – Pooled DMARD Inadequate Responders (ITT [redacted]lation)

etsumtimehaqpoolwk24i Summary of Time (Days) to First Clinical R[redacted]provement in HAQ-DI by Week 24 - 6 Month Pooled Data (ITT Population)

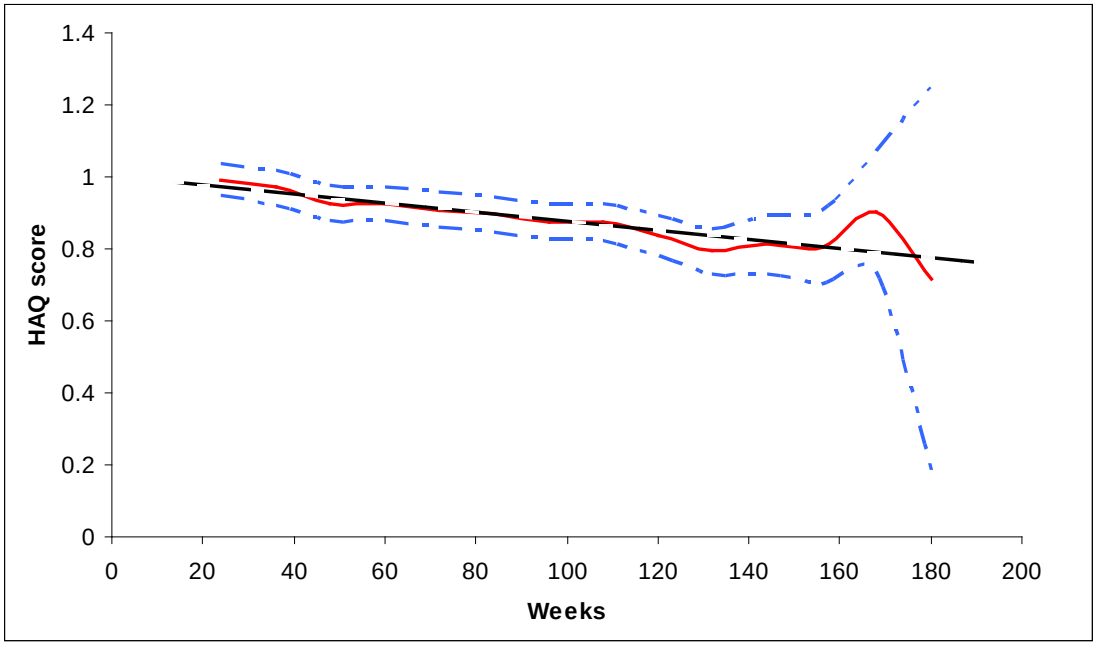
	Placebo + DMAR[redacted] (N=1010)	TCZ 4mg/kg+MTX (N=612)	TCZ 8mg/kg+DMARD (N=1406)
Improvement >= 0.25			
n	1010	612	1406
Responders	639 (63.3%)	455 (74.3%)	1089 (77.5%)
Censored	371 (36.7%)	157 (25.7%)	317 (22.5%)
Median	58.0	29.0	29.0
95% CI for Median	(57.0, 84.0)	(29.0, 32.0)	(#, #)
Min-Max	1*-282*	1*-225*	1*-233*
First Quartile	17.0	15.0	15.0
Third Quartile	#	143.0	116.0
Improvement >= 0.3			
n	1010	612	1406
Responders	521 (51.6%)	383 (62.6%)	985 (70.1%)
Censored	489 (48.4%)	229 (37.4%)	421 (29.9%)
Median	141.0	64.0	57.0
95% CI for Median	(113.0, 169.0)	(57.0, 86.0)	(57.0, 58.0)
Min-Max	1*-282*	1*-226*	1*-253*
First Quartile	29.0	27.0	16.0
Third Quartile	#	#	#

Summary statistics are Kaplan Meier estimates.
No imputation used for missing data.
value not calculable due to insufficient events
* indicates that this is a censored value
TCZ 4mg/kg + MTX pooled data from WA17822 and WA17823. TCZ 8mg/kg + DMARD pooled data from WA17822, WA17823 and WA18063.

Long term HAQ-DI progression

Using the meta-analysis of the long term follow up the following pattern can be seen up to 132 weeks in the pooled TCZ 8mg/kg dose in combination with MTX. The trend is clearly for continued HAQ improvement over time whilst on treatment.

Figure 28: Mean HAQ score over time for patients in the DMARD-IR trials



DMARD-IR Jan 2009 follow-up

Week	Patient numbers	Mean HAQ score	95% CI	
24	873	0.9921	0.948	1.036396
36	792	0.9717	0.922896	1.0207
48	774	0.9272	0.878592	0.975612
60	768	0.9252	0.876788	0.973612
72	753	0.9082	0.858416	0.957788
84	751	0.8961	0.846904	0.945296
96	743	0.8762	0.82818	0.92422
108	705	0.8732	0.82224	0.923964
120	590	0.8382	0.782732	0.893472
132	445	0.7939	0.731768	0.856032
144	295	0.8117	0.73232	0.89108
156	189	0.8036	0.700896	0.906304
168	75	0.9033	0.735524	1.071272
180	7	0.7143	0.18314	1.24546

Tocilizumab in combination with DMARDs

The most commonly used DMARD in the pooled DMARD inadequate responder population was MTX (taken by 100% of patients in WA17822 and WA17823). This reflects the licensed indication for TCZ. In study WA18063, ongoing background

DMARD therapy included a range of commonly used DMARDs that were permitted by the protocol. Over 50% of patients were receiving TCZ in combination with background MTX; however, a sizeable subpopulation (≥ 50 patients per group) were receiving background therapy with leflunomide or a combination of DMARDs. As shown in an analysis of ACR20, ACR50 and ACR70 response at week 24, clinically relevant improvements were evident when TCZ 8 mg/kg was added to a broad variety of background DMARD regimens (Table below). Because of the similar outcomes seen when in combination with DMARDs (excl MTX) vs. in combination with MTX the ITT population has been retained within the pooled analysis.

Table 25: Summary of the Percentage of Patients with an ACR20 Response at Week 24 by Background DMARD Medication – WA18063 (ITT Population)

	Placebo + DMARD			TCZ 8 mg/kg + DMARD		
	N	**ACR20 Responders**	**% ACR20 responders**	**N**	**ACR20 Responders**	**% ACR20 responders**
No DMARD	5	0	0	9	5	55.6
One DMARD:						
MTX	224	56	25	456	269	59.0
Leflunomide	50	9	18	78	51	65.4
Sulfasalazine	16	0	0	35	23	65.7
Chloroquine/ Hydroxychloroquine	17	5	29.4	33	21	63.6
Azathioprine	4	0	0	12	4	33.3
Parenteral Gold	0	-	-	2	0	0
Two DMARDs	82	24	29.3	152	100	65.8
Three or more DMARDs	15	7	46.7	26	15	57.7
Total ITT population	**413**	**101**	**24.5**	**803**	**488**	**60.8**

Anti TNF IR population

It has not been possible to run a meta analysis in these patient populations due to there only being one study in each population. The methodology and outcomes have been described previously.

6.6 Indirect/mixed treatment comparisons

- When evidence is combined using indirect or mixed treatment comparison frameworks, trial randomisation must be preserved. Where this is not possible the data should be treated as observational.
- Provide a clear description of the methods of synthesis
- Provide a rationale for the identification and selection of the RCTs, including the rationale for the selection of treatment comparisons that have been included.
- Perform a statistical assessment of heterogeneity. The degree of, and the reasons for, heterogeneity should be explored as fully as possible
- The methods and results of the individual trials should be documented. If there is doubt about the relevance of a particular trial, sensitivity analysis should also be presented in which these trials are excluded.
- The heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies should be reported.
- Evidence from a mixed treatment comparison may be presented in a variety of ways such as in tables or diagrams.

Tocilizumab, an IL-6 inhibitor, has been tested in 3 placebo-controlled trials (TOWARD, OPTION & LITHE) and was efficacious in this patient group. Since no head-to-head studies have been conducted, an indirect comparison versus TNF-inhibitors, abatacept and rituximab was performed.

Methods

Identification of eligible studies and data extraction

A systematic literature search was performed to identify published results of RCTs that evaluated biologic agents used in the treatment of patients with RA. Medline and EMBASE databases were searched simultaneously using DATASTAR. Search terms included a combination of free-text and thesaurus terms relevant to RA agents. The search period was from 1990 through 2007 and fully published reports in English, German, French, and Dutch were reviewed (letters and abstracts were excluded). The search strategy used can be found in appendix 8.

Outcome measures of interest were the ACR 20, ACR 50, and ACR 70 response criteria as well as DAS28 clinical remission and the change in ACR core disease parameters from baseline to month 6. For example, the ACR criteria for 20% clinical improvement (ACR 20) are a 20% improvement in tender and swollen joint count and a 20% improvement in three of the following five core disease parameters: patient's global assessment of disease activity, physician's global assessment of disease activity, patient's assessment of pain, patient's assessment of physical disability (measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI), and level of acute-phase reactant.(10)

Two independent reviewers evaluated each study against the following selection criteria: (1) fully published RCT; (2) patients with a clinical diagnosis of RA; (3) treatment interventions with tocilizumab, adalimumab, etanercept, infliximab, abatacept, or rituximab; (4) outcome measures of ACR 20, ACR 50, ACR 70 response criteria and ACR core disease parameters; and (5) study duration of at least 6 months. For each selected study, reviewers extracted details of study design, patient population characteristics, treatment interventions, outcome measures, and length of follow-up. Consensus of both reviewers was required for studies to be included in the analysis.

Data analysis

A MTC is similar to a conventional meta-analysis in which multiple studies are used to obtain an estimate of the efficacy of a single agent. However, a MTC uses multiple studies of multiple agents to simultaneously estimate response rates for all pair-wise efficacy comparisons.(11-14) The underlying logic of the MTC is that the study populations in all included trials are similar. If this condition is met then responses from trials with common treatment interventions can be used to estimate a response rates (relative to placebo) for that treatment. Estimated response rates for each treatment intervention are the basis for treatment-to-treatment comparisons. In this analysis, we combined results of treatment interventions of interest from the selected studies using a Bayesian MTC. Multiple meta-analyses of pair-wise comparisons from the selected studies were performed simultaneously. Analyses were performed for patients with RA who had inadequate responses to DMARDs, including methotrexate (MTX).

Odds ratios for ACR 20, ACR 50, and ACR 70 responses (relative to the comparator response) from the selected publications were the effect measures and separate analyses of each ACR response level were conducted. Because our analysis focused on real-world medical decision making, we only used data from trial arms in which currently licensed doses of treatments of interest were evaluated. Results of the analysis are reported as the 'relative risk' (RR) of response for each biologic agent, compared with placebo, and the RR of response for tocilizumab, compared with each of the other biologic agents. Relative risks were also translated into response rates using the pooled placebo response as baseline.

Homogeneity at each ACR response level was assessed using standard statistical tests (Q-statistics). Fixed effects or random effects assumptions were used to calculate the precision of effect size estimates. The Q-statistics were used to assess the null hypothesis that a fixed effects estimation should be used for all ACR responses. The null hypothesis was rejected for ACR 20 and ACR 50 response

outcomes, but not for ACR 70 response outcomes. As a result, random effects methods were used to estimate ACR 20 and ACR 50 responses and fixed effects methods were used to estimate ACR 70 responses. Results of the Cochran's Q statistics are reported in the table below.

Table 26: Heterogeneity statistics

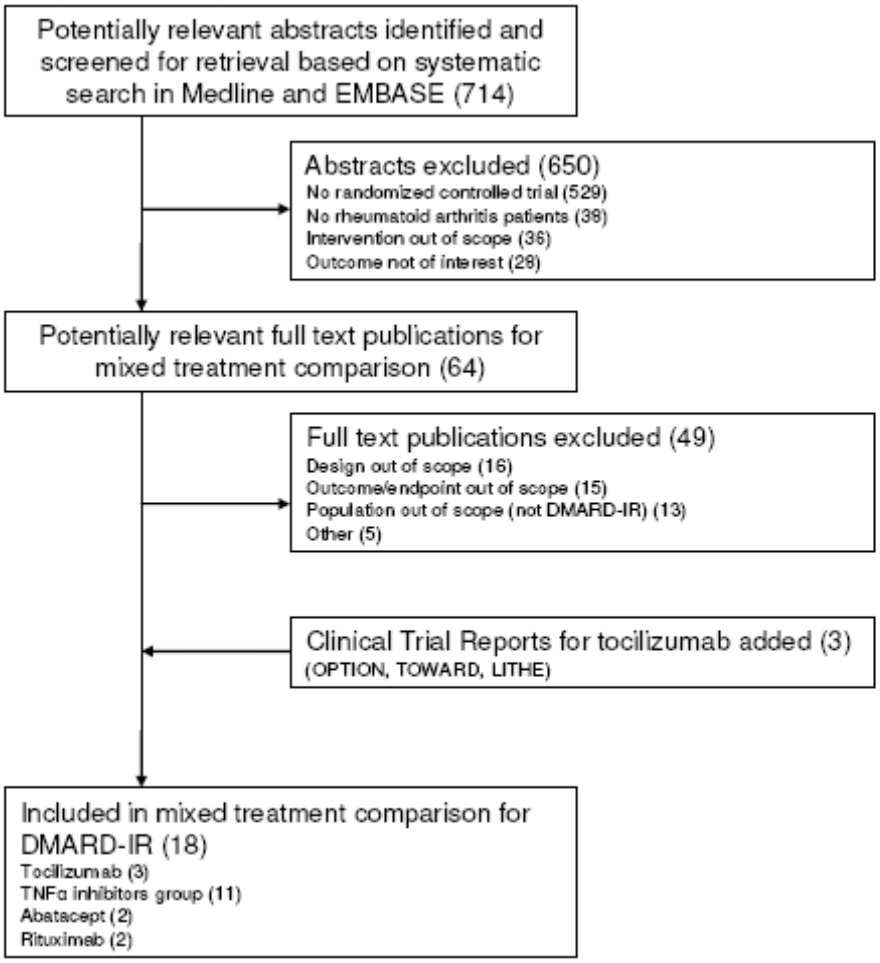
Overview of heterogeneity statistics			
	ACR20	ACR50	ACR70
Cochran's Q statistics			
Q	44.1857	41.6878	25.5752
p-value (two-tailed)	0.0002	0.0004	0.0603

Analyses were performed with WinBUGS 1.4 statistical software (MRC Biostatistics Unit, Cambridge, UK). Although WinBUGs provides estimates from a Bayesian perspective, the analysis was conducted with non-informative priors so that the results are equivalent to frequentist-based estimates. Results for TNF-alpha agents were pooled based on the lack of differentiation in efficacy of these agents as assessed by NICE (HTA 130 TNF assessment section 4.3.3) and published research (Hochberg, (2003)/Nixon, (2007) Results are presented with summary statistics for RR: a point estimate reflects the most likely value and 95% credibility intervals (95%CrI) reflect the range of true underlying effects with 95% probability. The probability of tocilizumab, compared with the other biologic agents or placebo, being the most effective treatment for patients with RA was also calculated. Scenario analyses were performed to assess the robustness of the base case results.

Results

The search strategy identified 714 potentially relevant studies. Of these studies, 650 did not meet inclusion criteria, mainly because they were not RCTs. The remaining 64 studies were subjected to full text review and data extraction. From those, another 49 studies were excluded for reasons such as absence of an ACR response measure, dose ranging focus, and focus on an early RA patient population. Fifteen studies remained as preliminary candidates for inclusion in our analysis. Three clinical trial reports for tocilizumab were added, resulting in 18 relevant studies in total. A summary of the study selection process is shown in Figure 29.

Figure 29: Selection of randomised controlled trials included in analysis



Among the 18 candidate studies we determined that no DMARD background treatment was provided in the Van de Putte trial(15), the Moreland trial(16),and in a subgroup in the Furst trial.(17) In addition, unlike all other trials in which combination therapy was defined as a biologic agent and MTX, the Combe(62) trial evaluated combination therapy with a biologic agent and sulfasalazine. Because treatment arms in these trials were fundamentally different from the remaining trials, they were not included in our initial analysis. However, they were included in the alternative scenarios tests to ensure that trial selection did not affect our results.

All studies were randomised, placebo-controlled, double-blind trials and included patients with persistent RA despite having been treated with MTX or other DMARDs. The trials included approximately 9,500 patients and were grouped as follows: tocilizumab (3)(18-20), TNF-α inhibitors (10)(21-30), abatacept (2)(31;32), and rituximab (2)(33;34). All trials had a follow-up period of either 24 or 30 weeks (appendix 8 Table A1). Patients included in the analysis were predominantly female (approximately 80%), older than 50 years of age, experienced more than 6 years

duration of RA, were previously treated on average with more than two DMARDs, and more than half of patients used NSAIDs or glucocorticoids concomitantly.

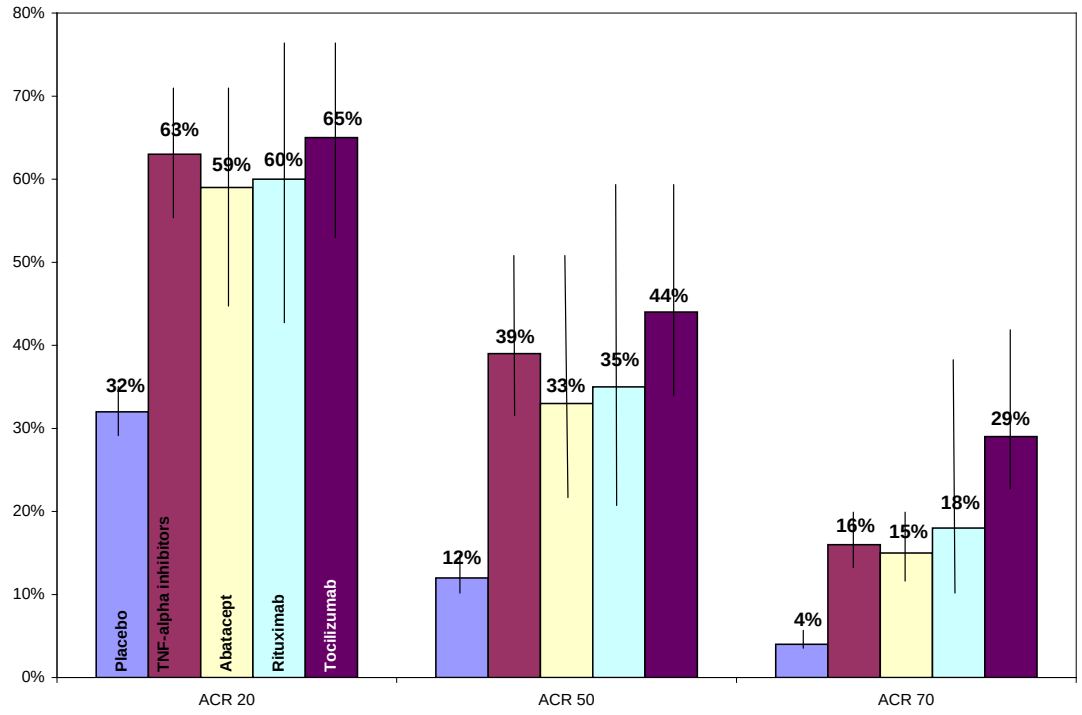
Baseline characteristics across the trials were comparable with respect to ACR core parameters (appendix 8 Table A2). The number of ACR 20/50/70 responders (r) and the sample size per treatment arm (n) from the full set of trials are reported in appendix 8 Table A3.

ACR 20/50/70 responses

As expected, all biologic agents, compared with placebo, had RRs of response significantly greater than 1, which indicated superiority (appendix 8 Table A4). Tocilizumab had a higher estimated RR of response than other biologic agents, compared with placebo, in all response categories. However, the differences in RRs of responses between tocilizumab and other biologic agents were smaller for ACR 20 and ACR 50 than they were for ACR 70. The ACR 70 RR of response for tocilizumab, compared with placebo, was 6.75, which was substantially higher than the RRs of response for TNF-α inhibitors (3.81), abatacept (3.42), and rituximab (4.33), compared with placebo.

The estimated RRs of response for tocilizumab, compared with other biologic agents, exceeded 1 in pairwise comparisons at all ACR response levels (appendix 8 Table A5). However, the credibility interval for these estimates did not exclude 1 at ACR 20 or ACR 50. Conversely, at ACR 70 the credibility intervals for RRs of response for tocilizumab, compared with TNF-α inhibitors and abatacept, excluded 1 (RR=1.77, CrI: 1.22 - 2.58; RR=1.98 CrI: 1.28 – 3.07, respectively). When these results were translated into response rates, based on the assumption of a common placebo response equal to the pooled placebo response from all trials, tocilizumab was estimated to have a 65% response rate at ACR 20 and a 44% response rate at ACR 50 (Figure 30). This is roughly comparable to the estimated response rates for TNF-α inhibitors. Conversely, tocilizumab was estimated to have a 29% response rate at ACR 70 while the rate for TNF-α inhibitors was 16%. The estimated response rate for tocilizumab was outside the 95% CrI for TNF-α inhibitors.

Figure 30: Expected responses for ACR 20, ACR 50, and ACR 70 in DMARD-IR patients adjusted for placebo differences across trials (base case analysis)



Direct calculation of the probabilities of response rate estimates, using Bayesian estimation techniques, showed that tocilizumab has only modest probabilities of being better than other biologic agents at achieving ACR 20 or ACR 50 responses (appendix 8 Table A5). However, tocilizumab has a 99% or greater probability of being better than TNF-α inhibitors at achieving an ACR 70 response.

Thus, compared with other biologic agents, treatment with tocilizumab is expected to result in a comparable proportion of patients with RA who achieve ACR 20 and ACR 50 responses. However, a higher proportion of patients who are treated with tocilizumab are expected to achieve ACR 70 responses than those who are treated with TNF-α inhibitors. Comparable ACR 70 responses are expected in patients who are treated with tocilizumab and the other biologic agents evaluated in this analysis.

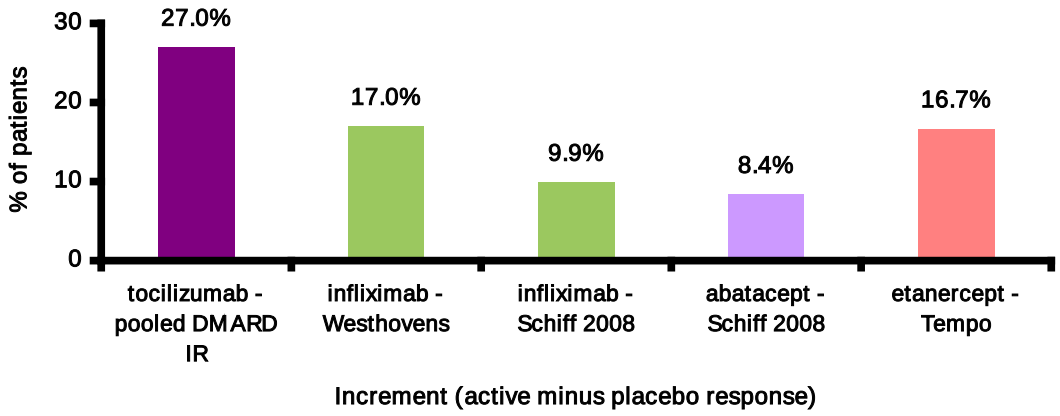
DAS-28 Clinical remission

Based on published clinical trial results tocilizumab offers patients the best chance of reaching a disease activity score (DAS-28) below 2.6 after accounting for the placebo effect. This score is the threshold used to define remission for patients with RA. An assessment of placebo adjusted remission rates using mixed treatment comparison indicates that this difference is statistically significant.

Published remission rates at 6 months (DAS28<2.6) for DMARD-IR patients are available for tocilizumab, etanercept, infliximab, and abatacept. In each trial, both placebo group and treatment group remission rates were reported. The success of a treatment is measured by its impact relative to placebo – the difference between the treatment group and placebo group remission rates.

Data from these studies show that Tocilizumab provided a 27 percentage point increment in remission (three studies combined) compared with its placebo group, while the closest anti-TNF inhibitor provided a 13 percentage point increment (infliximab – two trials combined) as shown in Figure 31.

Figure 31: Incremental remission (DAS28 < 2.6) with bDMARDs at 6 months in DMARD-IR patients



Source: Tocilizumab: pooled analysis; EMEA submission, infliximab: Westhovens et al. 2006, infliximab/abatacept: Schiff et al 2008, etanercept: van der Heijde et al 2006

Scenario Analyses

Three scenario analyses were performed to assess the robustness of the base case results. The alternative trial sets used in the scenario analyses were: (1) inclusion of data from the Van de Putte trial(35), the Moreland trial(36), and a sub-group of the Furst trial(37) that were excluded from the base case analysis; (2) exclusion of data from the Klareskog trial(38); and (3) inclusion of data from the Combe trial(39).

Results of the first scenario analysis (inclusion of the Van de Putte, Moreland, and a subgroup of the Furst trials) showed essentially the same results as described above in the base case analysis: tocilizumab had similar risk of achieving ACR 20 and ACR 50 responses as other biologic agents; in ACR 70, tocilizumab's relative risk of response (compared to TNF alpha inhibitors and abatacept) was greater than 1 with a credibility interval that excluded 1 (1.67 (1.15,2.43) TNF alpha inhibitors; 1.92 (1.23,3.02) abatacept). Adjusted ACR 70 response rates showed similarly showed superiority for tocilizumab with a response rate of 27% (95%CrI: 20%,37%). Both TNF alpha inhibitors and abatacept had response rate estimates below the lower bound of the credibility interval for tocilizumab.

For the second scenario analysis, exclusion of data from the Klareskog trial was considered relevant because the trial had high observed response rates in the control group, which was markedly different from control responses in the other studies (appendix 8 Table A3). Results from the second scenario were substantively the same as with scenario 1 with only minor changes in estimates relative risks and credibility intervals.

The Combe trial was excluded for the third scenario analysis because background treatment was with sulfasalazine, which is not defined as a DMARD in some countries. Results of this scenario analysis were similar to those reported above.

Overall, results from these alternative scenarios were consistent with initial findings and suggest that the base case results are robust.

Results of this MTC showed that tocilizumab may have efficacy similar to that of other biologic agents for achieving ACR 20/50 responses. However, analysis of ACR 70 outcomes suggested that tocilizumab may have improved efficacy relative to that of TNF-α inhibitors.

Biologic agents within the class of TNF-α inhibitors have been shown to have a comparable efficacy and safety profile,(40-44) and are currently considered the treatment of choice for patients with RA who do not adequately respond to DMARDs. Results of this analysis suggest that tocilizumab has at least comparable efficacy to TNF-α inhibitors and may provide an increased opportunity for achieving high hurdle responses, such as ACR 70.

These results are subject to several limitations. First, a MTC is only credible if the underlying trial data used in the analyses are adequately homogeneous. Our analysis was assiduous in our review of the included studies, thus ensuring consistency in patient population and treatment modality. Nevertheless, some variation in trial procedures and population may exist. We attempted to respond to these factors by using random effects-based estimations of precision where appropriate and varying the set of underlying trial data to ensure that the findings were not dominated by inclusion (or exclusion) of one or several trials.

The decision to include the Klareskog trial (45) in the base case analysis was based on factors that could be open to debate. The trial reported an exceptionally high ACR 20/50/70 placebo response rate, suggesting that it might not be comparable to the other trials in the base case analysis. Therefore, it could be reasonably argued that this trial should be excluded from that analysis. We decided to include the Klareskog trial in the base case analysis for two reasons. First, the study met all our predefined selection criteria. Excluding it would have meant post hoc rejection of our pre-defined study plan. Second, the baseline patient population and characteristics were similar to those in the other selected trials. Despite these reasons to include the Klareskog trial, we decided to estimate the MTC with results of the Klareskog trial excluded from the analysis. Statistical tests showed an increase in the homogeneity of trial results with Klareskog excluded and the overall study conclusions remained unchanged whether or not the base case was defined with this study included or excluded.

Another, and perhaps more important, limitation involves the selected study endpoints. Although responses at ACR 20, ACR 50, and ACR 70 have been the principal efficacy outcome measure in most recent RA clinical trials, they are nevertheless a binomial reduction (response or no response) built on a quasi-continuous underlying distribution of ACR_n scores. Optimally, we would want to compare treatments using all of the information available in a continuous response measure and compare the mean improvement (relative to placebo) of ACR_n scores for competing treatments. This comparison would eliminate the possibility of error resulting from the crudity of only three levels of response and non-uniform distributions within the response categories. Unfortunately, ACR_n results are not

available in most published studies and thus could not serve as an effect size measure. However, in order to test whether separate analyses for ACR response level were appropriate, we conducted a chi-square test to determine whether predicted response significantly varied by treatment. We translated the predicted responses as obtained with the MTC into an expected number of patients for each treatment into non-overlapping ACR response categories. Based on the total sample size of patients included in the studies, we performed a chi-square test to determine whether response distributions varied by treatment. The results were significant and showed that response distributions indeed varied by treatment, which supported the use of separate analyses by response level.

As in all studies (RCT or MTC), response rate estimates are subject to error. Statistical methods are used to estimate the size of the error and provide a basis for assessing the precision of the estimates. In a MTC, the precision of the effect size estimates may be calculated using a fixed effects or a random effects assumption. Under a fixed effects assumption, complete homogeneity in population and experimental procedures is assumed and variance across trials within treatment subsets is ascribed strictly to sampling variation. Under a random effects assumption, less than complete homogeneity is assumed and the standard error is increased to reflect these additional sources of variation. We used standard statistical tests (Q-statistics/Higgins I^2) to assess homogeneity in each ACR response level and thus, random effects estimation assumption was used for ACR 20 and ACR 50 responses and a fixed effects estimation assumption was used for ACR 70 responses.

In conclusion, an extensive clinical trial program has shown that tocilizumab is an effective treatment, compared with placebo, for patients with RA that is not well controlled by DMARDs. This MTC of reported trial results suggests that tocilizumab is likely to show similar efficacy to other biologic agents, based on the ACR 20/50 responses in DMARD-IR patients, but is likely to show greater efficacy than TNF-α inhibitors for achievement of an ACR 70 response. In addition tocilizumab offers patients the best chance of reaching a disease remission (DAS-28< 2.6).

The full report and the reference list can be found in Appendix 8.

6.7 Safety

The safety analysis is based on 3728 patients who received at least one dose of tocilizumab at either 4mg/kg or 8mg/kg

The long term open label extension studies included 2,562 patients who received tocilizumab 8 mg/kg with or without DMARDs.

The total exposure in the long term safety analysis was 3,685 patient years. The most commonly reported ADRs (occurring in ≥ 5% of patients treated with tocilizumab monotherapy or in combination with DMARDs) were upper respiratory tract infections, nasopharyngitis, headache, hypertension and increased ALT

Monitoring is required with tocilizumab however as co-treatment with MTX is expected to be used in the majority of patients, the monitoring for both tocilizumab and MTX can be combined

The safety analyses are based on data collected in 3728 patients who received at least one dose of TCZ. Of these, 2570 patients received treatment with the 8 mg/kg dose for at least 6 months, 1443 patients were treated for 12 months and 554 patients were treated for at least 18 months.
Safety analyses for the 24-week controlled clinical studies were performed on 2644 patients treated with double-blind TCZ. In these studies, the highest exposure was achieved in the TCZ 8 mg/kg + DMARD group (685 patient years), approximately half of which was contributed by patients in studies WA17822, WA17823 and WA18062 who received TCZ in combination with MTX and the remainder from patients in study WA18063 who received TCZ in combination with MTX and/or other conventional DMARDs. A total of 321 patient-years of exposure was accumulated in the TCZ 4 mg/kg + MTX group (studies WA17822, WA17823 and WA18062) and 126 patient-years was accumulated in the 8 mg/kg monotherapy group (study WA17824).

Long-term safety analyses were based on all patients who completed the 24-week controlled studies and received TCZ in the open-label extension studies. Data were summarized from the first dose of TCZ received in the extension study (for those patients treated with placebo/MTX in the core studies) or in the 24-week controlled studies (for all other patients). A total of 2439 patients completed the core studies and entered the extension studies providing, by the cut-off date (April 20, 2007), 2628 patient-years of exposure to TCZ in the long-term safety analysis. At the data cut, 2188/2439 patients (89.7%) had been receiving TCZ treatment for at least 24 weeks, 1507 patients (61.8%) had been receiving TCZ treatment for at least 48 weeks and 574 patients (24%) for 18 months.[56] The mean and median extent of

exposure to TCZ treatment from the first dose was 1.08 years. All together, this represents an acceptable safety database, both in number of patients and exposure time with this biologic therapy.

Overview of the Safety Profile

Comparison of data across the five controlled clinical studies demonstrates that treatment with TCZ is generally well tolerated with 20-30% of patients reporting no adverse effects (see Table 27 below). Overall, adverse effects associated with the mechanism of IL-6R inhibition were observed in all TCZ treatment groups. These adverse effects include transient hepatic transaminase elevations (IL-6R expressed on hepatocytes), asymptomatic elevations of indirect bilirubin, transient neutropenia (IL-6R expressed on neutrophils), and lipid elevations which appear to occur in association with marked decreases in acute phase proteins. In addition, serious infections occur associated with the immunomodulatory effects of TCZ, and were comparable to the incidence of serious infections with TNF-antagonists, as reported in long term follow-up and registry studies.[57,58]

Adverse events reported more frequently with TCZ 8 mg/kg monotherapy than in the MTX group were abdominal pain and discomfort, headache, dizziness, rash, pruritis and elevated blood pressure, neutropenia, leukopenia and hyperlipidemia events. Most of these events were mild and transient. Administration of TCZ in combination with established DMARD therapy for the treatment of RA was also generally well tolerated.

Of the events that appeared to be associated with TCZ treatment, mouth ulceration, stomatitis, transient elevations in blood pressure reported as hypertension, headache and dizziness did not substantially influence the tolerability of TCZ, as reflected in the low number of patients withdrawing from treatment. (see section 6.3.3)
In the controlled 24-week studies, the adverse event profile in the 4 mg/kg + MTX group was generally comparable with that observed in the 8 mg/kg + DMARD group, as evidenced by the similar proportion of patients with adverse events, whether serious or non-serious, and the proportion of patients withdrawn from treatment due to adverse events in trials comparing the 8 mg/kg and 4 mg/kg dose regimens (see Table 27 below). A PK/PD analysis performed to characterize the TCZ exposure-safety relationship supports the clinical data by demonstrating no apparent association between the occurrence of any type of adverse event or serious adverse event and the cumulative area under the curve up to the time of onset of adverse event or the closest C_{max} prior to the adverse event.

Table 27: Overview of Adverse Events and Deaths (6 Months Pooled Safety Population)

Number of patients (%)	Placebo + DMARD N=1170	MTX N=284	4 mg/kg + MTX N=774	8 mg/kg + DMARD N=1582	8 mg/kg N=288	All TCZ N=2644
Any AEs	733 (62.6%)	220 (77.5%)	547 (70.7%)	1134 (71.7%)	230 (79.9%)	1911 (72.3%)
AE rates per 100 patient years (95% CI)	377.34 (360.6,394.6)	449.70 (414.5,487.1)	472.24 (449.6,495.8)	462.37 (447.2,478.0)	491.73 (455.7,529.9)	468.44 (456.5,480.7)
Severe AEs	97 (8.3%)	19 (6.7%)	68 (8.8%)	138 (8.7%)	20 (6.9%)	226 (8.5%)
Any SAEs	62 (5.3%)	8 (2.8%)	46 (5.9%)	95 (6.0%)	11 (3.8%)	152 (5.7%)
SAE rates per 100 patient years (95% CI)	14.79 (11.6,18.5)	11.22 (6.3,18.5)	14.79 (11.0,19.5)	15.26 (12.6,18.3)	8.58 (4.4,15.0)	14.38 (12.3,16.7)
AEs leading to withdrawal	28 (2.4%)	15 (5.3%)	38 (4.9%)	74 (4.7%)	11 (3.8%)	123 (4.7%)
AEs leading to dose interruption	84 (7.2%)	63 (22.2%)	103 (13.3%)	194 (12.3%)	56 (19.4%)	353 (13.4%)
Deaths	4 (0.3%)	1 (0.4%)	-	2 (0.1%)	3 (1.0%)	5 (0.2%)

Of the five deaths in patients receiving treatment with the TCZ 8 mg/kg dose in the controlled 24-week studies, two of these (2/1582 [0.13%]) occurred in patients enrolled in trials comparing the 8 mg/kg and 4 mg/kg dose regimens and three occurred in trials evaluating the 8 mg/kg dose alone. Comparably, there were four deaths in patients receiving placebo infusions in the same studies (4/1170 [0.34%]). Causes of death were consistent with those reported among patients with moderate to severe RA and were broadly comparable between the TCZ (myocardial ischemia, cardiopulmonary arrest, stroke, postoperative infection, GI hemorrhage) and control groups (placebo + MTX: coronary artery thrombosis, pneumonia, intestinal obstruction, Wegener's granulomatosis; MTX alone: lung cancer).

An additional 11 patients died during treatment in the long-term safety analysis. The mortality rate in patients treated with TCZ was 0.51 per 100 patient-years of exposure. This is comparable to that in a study conducted to estimate the relative risk of overall mortality in RA patients in which the crude mortality rate was found to be 1.6 per 100 patient-years in patients receiving TNF-antagonist therapy compared with 3.5 per 100 patient-years in an age-matched RA population not treated with TNF-antagonists[59]. Therefore, the mortality rate observed to date within the TCZ program in adult RA patients is within the range expected for RA patients receiving a biologic therapy. Additionally, the reported causes of death were similar to those reported among RA patients receiving other therapies.

The frequency of serious adverse events was low (see Table 27 above) and the nature of events reflected the patient population enrolled. The most common serious adverse events in all treatment groups were infections. Serious infections were reported with a higher frequency in the TCZ 8 mg/kg monotherapy and 8 mg/kg + DMARD arms (1.4% and 2.4%, respectively) compared with their respective controls (0.7% and 1.5%, respectively), and in the TCZ 8 mg/kg + DMARD arm (2.4%) compared with the TCZ 4 mg/kg + MTX arm (1.7%), although the rates of serious infection per 100 patient years in the 8 mg/kg groups (see Table 28 below) were comparable to those seen with TNF-antagonists in registry studies. Few infections led to withdrawal (< 1%), and similar proportions of patients withdrew because of infections in each TCZ treatment group. Most patients with serious infection

temporarily interrupted dosing, with a minority temporarily reducing the dose from 8 mg/kg to 4 mg/kg. Case fatality rates in patients with serious infection appear to be no greater than would be expected in patients acquiring serious infections within the community and as expected, most of these patients had other risk factors contributing to a higher probability of a fatal outcome (age, comorbidities including diabetes, corticosteroid treatment).

Table 28: Rates of Serious Infections

	24-week pooled safety population					Long-term safety
	Placebo + DMARD N=1170	MTX N=284	4 mg/kg + MTX N=774	8 mg/kg + DMARD N=1582	8 mg/kg N=288	Pooled TCZ N=2439
Serious infection rates per 100 patient years (95% CI)	3.75 (2.26,5.85)	1.50 (0.18,5.41)	4.35 (2.44,7.18)	5.18 (3.68,7.08)	2.86 (0.78,7.32)	3.84 (3.12,4.67)
Deaths due to infection	1	-	-	1	-	5*

*Includes the patient who died due to diverticulitis complicated by diverticular perforation

Most of the withdrawals in the TCZ groups were due to hepatic transaminase elevations, which reflects the protocol-defined requirement to discontinue study treatment in the event of repeated elevations of ALT/AST ≥ 3x upper limit of normal (ULN) or a single elevation > 5x ULN. In no case were these abnormalities associated with hepatitis or hepatic dysfunction.

The dosage regimen in the extension studies was TCZ 8 mg/kg and, thus, the long-term safety profile of the 4 mg/kg regimen has not been established. The safety profile observed with TCZ 8 mg/kg in the controlled 24-week trials was consistent with that observed in the long-term analysis. The most common events were infections and infestations. There was no increase in the severity or frequency of adverse events with prolonged exposure to the 8 mg/kg dose.

Thus overall, TCZ was generally well-tolerated with 5% of patients discontinuing treatment because of adverse events or laboratory abnormalities. Once established on treatment, patients generally tolerated continued therapy well over the long-term.

6.8 Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available.

Inferences about relative treatment effects drawn from non-RCT evidence will necessarily be more circumspect than those from RCTs with properly controlled evidence. The bias that may be present in non-randomised data means the results should be interpreted cautiously. When possible, the use of more than one independent source of such evidence needs to be examined to gain some assurance of the validity of any conclusions drawn.

6.8.1 Details of how the relevant non-RCTs have been identified and selected

A search of the literature did not identify any non-randomised, controlled clinical trials, and none has therefore been selected for inclusion in this submission.

6.8.2 Summary of methodology of relevant non-RCTs

Not applicable

6.8.3 Critical appraisal of relevant non-RCTs

Not applicable

6.8.4 Results of the relevant non- RCTs

Not applicable

6.9 Interpretation of clinical evidence

6.9.1 **Provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.**

The data presented in Section 6 indicate the potential benefit of tocilizumab to treat signs and symptoms of RA. Tocilizumab has demonstrated consistent and robust effects on all primary and secondary endpoints in a broad range of RA patients with moderate to severe active RA either starting DMARD therapy de novo or requiring additional treatment following an inadequate response to previous treatment. When treated with the licensed dose, substantial numbers of patients achieve a 50% or better ACR response as well as DAS28 remission/low disease activity which reflect highly meaningful improvements in signs and symptoms of the disease. Additionally tocilizumab provided improvement in patient-reported outcomes relative to control treatment. The improvements in signs and symptoms are supported by significant improvements in markers of disease progression assessed by radiographs, thus tocilizumab can be seen to be disease modifying. The benefits of treatment are apparent rapidly following the start of TCZ therapy with the first evidence of clinically important responses e.g. ACR and DAS as early as week 2 (i.e., the first scheduled assessment). The magnitude of response continued to improve with duration of treatment.

The safety profile of tocilizumab has been evaluated as monotherapy, as a combination therapy (with DMARDs) in patients who have an inadequate response to established DMARD therapy and in those patients who have had an inadequate response to anti TNFs. In all patient populations studied, the most frequent AEs were infections. Compared with MTX, tocilizumab monotherapy was associated with a higher incidence of mild events of abdominal pain and discomfort, headache, dizziness, rash, pruritis, and elevated blood pressure, as well as infrequent events of neutropenia, leukopenia and hyperlipidemia. In patients with established DMARD therapy, addition of tocilizumab resulted in an increased frequency of mouth ulcerations and liver enzyme elevations. Few hypersensitivity reactions were reported with tocilizumab. No major differences in the safety profile were observed between the two doses studied in combination with MTX or DMARDs. There was no evidence that prolonged exposure to tocilizumab results in increased frequency or severity of AEs reported in association with tocilizumab treatment. The monitoring requirements for tocilizumab in terms of liver enzymes, lipids, platelets and neutrophils can be accommodated within the current monitoring requirements for methotrexate.

Overall tocilizumab can be considered an efficacious drug with an acceptable safety profile that is *additive* to the current portfolio of disease modifying drugs available to rheumatologists. There is a significant unmet need in both the DMARD IR and TNF IR patient populations which tocilizumab will go someway towards addressing.

6.9.2 **Identify any factors that may influence the applicability of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select suitable patients based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the Summary of Product Characteristics?**

The data presented in this submission formed the basis for the application for a marketing authorisation to allow the use of tocilizumab in the management of rheumatoid arthritis; as such 1873 out of 2652 received the licensed 8mg/kg dose. The marketing authorisation was granted on the 20th January. The licensed indication for tocilizumab is:

'Tocilizumab, in combination with methotrexate (MTX) is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists. In these patients, tocilizumab can be given as mono-therapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate'.

The clinical trials referred to in addressing the decision problem are broadly reflective of the population in which is licensed to be used in the UK and the study was carried out using the same dose and posology that has now been licensed for clinical practice. There are no unique criteria that would be used in identifying patients suitable for treatment over and above what is already employed clinically when assessing disease activity in rheumatoid arthritis patients. There are no identifiable sub groups of patients that benefit significantly over any other sub population. Tocilizumab use requires ongoing monitoring however this can be accommodated within the methotrexate monitoring and should place no extra burden on the clinical use of this technology.

7 Cost effectiveness

7.1 Published cost-effectiveness evaluations

7.1.1 Identification of studies

A systematic review was conducted to identify existing economic evaluations relevant to the submission's decision problem.

The review updated and extended the search from a recent comprehensive review of cost –effectiveness studies performed by the HTA programme[60]. The review itself and ten already identified studies from the HTA report were included in the present economic evaluation review (see details in **Table 29** in section 7.1.2).

Update of the search

Two published HTA search strategies (Appendix 5 and Appendix 6 of the HTA report[60]) were combined and adapted for use. Details of the complete search strategies are available in Appendix 3. Only articles in English were included. No time limits were applied, except for the pharmacologic agents covered by the review in Chen et al. 2006[60]. In the latter case, searches for adalimumab, etanercept and infliximab were limited to articles published from 2005 to present. Table 29 presents the applied time limits to the updated search.

Table 29: Time limits on the updated search

Intervention	Date span	Notes
Abatacept	No limit	Not considered in TA130
Adalimumab	2005 – present	
Etanercept	2005 – present	
Infliximab	2005 – present	
Golimumab	No limit	Not considered in TA130
Certolizumab pegol	No limit	Not considered in TA130
Rituximab	No limit	Not considered in TA130
Tocilizumab	No limit	Not considered in TA130

The following databases were searched;

- Medline
- Embase
- Medline (R) In-Process
- Health Technology Assessment Database
- NHS Economic Evaluation Database (NHS EED)
- Heath Economic Evaluations Database (HEED)

Similarly to the search strategy, the review inclusion criteria were replicated and modified here from Chen at all 2006[60];

Study design: Cost–consequence analysis, cost–benefit analysis, cost-effectiveness analysis, cost–utility analysis, cost studies (UK only)

Population: Adults with RA; other forms of arthritis are excluded

Treatment: abatacept, adalimumab, etanercept, infliximab, golimumab, certolizumab pegol, rituximab, and tocilizumab

Outcome Quality of life estimates, cost estimates, cost-effectiveness

Studies were included in the systematic review if they described an economic evaluation quantifying both costs and benefits. However, no restrictions were placed on the type of economic evaluation or outcomes presented, such that cost-utility analyses, cost-effectiveness analyses, cost-benefit analyses and cost-consequence analysis were all considered appropriate for inclusion. Review articles referring to studies already included as individual studies were excluded from this review. Data were extracted into a pre-specified table by one reviewer.

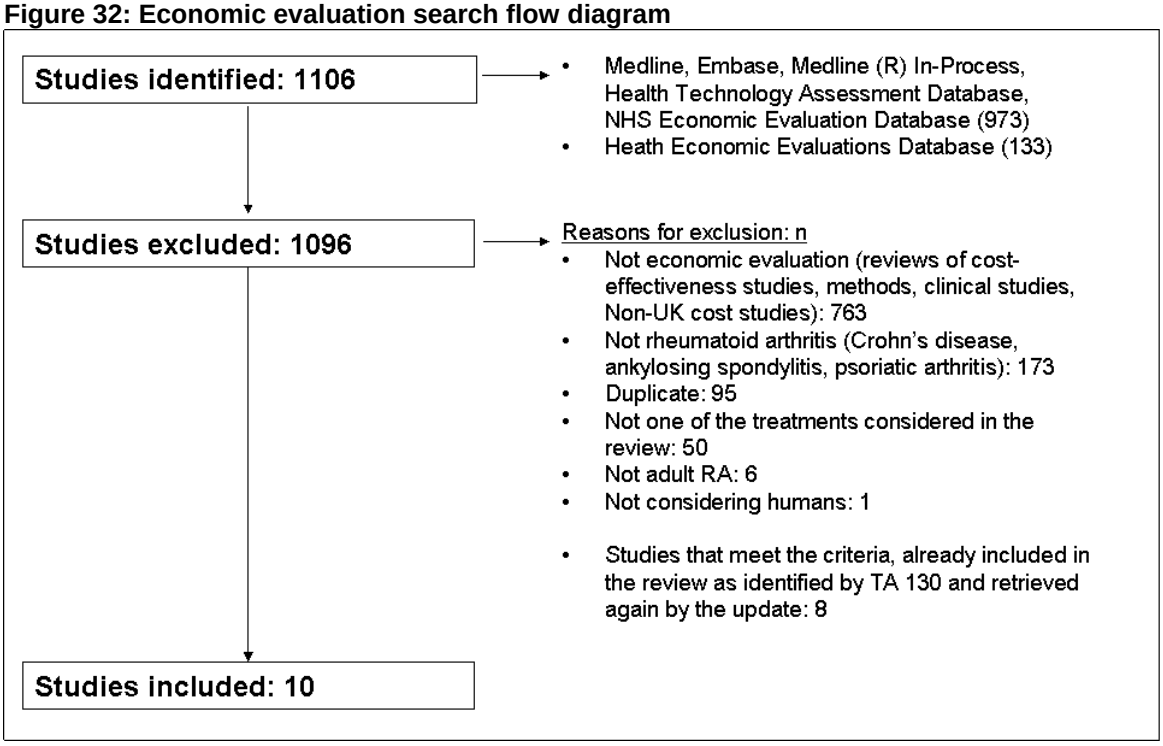
The database search was conducted in two phases;

1. All databases accessed by EMBASE, Cochrane library, and PubMed (973 articles)
- Medline
- Embase
- Medline (R) In-Process
- Health Technology Assessment Database
- NHS Economic Evaluation Database (NHS EED)

2. Heath Economic Evaluations Database (HEED) alone (133 articles)

A single electronic file of the literature search results comprising all records retrieved via the database searches was created by exporting records from the respective platforms and importing them into a Reference Manager database.
A total of 1106 references were identified from both search phases. Of the total references, 1088 articles were excluded based on the abovementioned criteria. Of the 18 eligible references 7 were already included in the review TA 130[60] and one was the review itself. The latter 8 studies were considered duplicates and excluded by the update of the review but summarised in the article appraisal (section 7.1.2).

Figure 32: Economic evaluation search flow diagram



7.1.2 **Description of identified studies**

Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. Where studies have been identified and not included, justification for this should be provided.

A total of twenty one studies are considered in the economic evaluation review. Eleven studies (10 + TA 130 which this review updates) were already identified by Chen et al. 2006[60] and ten studies were retrieved by updating the search. The identified articles are summarised below in **Table 30** and **Table 31** for studies included by TA 130 and for studies from the update, respectively.

The results of the published economic evaluations vary with most results falling within the generally acceptable cost-effectiveness range. However, a direct comparison of the results of the published studies is not possible because of the differences between the methods of the evaluations. In particular, the studies were different in:

- The modelling approach. Although the majority of the studies use a Markov or an individual simulation model, there is no consensus on the approach.
- The time horizon (from 6 months to lifetime). The selected time-horizon is well justified by the authors and primarily based on the available data. Nevertheless, when considering chronic conditions a lifetime horizon is more appropriate in order to capture all possible health related benefits.

- The comparator treatment (single treatment or multiple treatment sequences)
- The country setting (Japan, the Netherlands, Sweden, US and the UK).
- The cycle length (from 3 months to 1 year)
- The considered outcomes (QALYs, ACR 20, ACR 70 weighted response etc.)

The review did not identify any economic evaluations of tocilizumab and therefore a de novo analysis is required. The methods of some of the retrieved articles that are relevant to the decision problem were consulted for the development of the analysis (see setion 7.2).

Table 30: Summary of published studies as identified by TA 130

Study	Treatment considered	Form of economic analysis	Type of model	Time-horizon	Main results	Relevance to the decision problem
Bansback et al. 2005[2]	Etanercept, infliximab, adalimumab vs DMARD sequence	Cost-utility	Patient level simulation	Lifetime	ACR50/DAS28 good: €34,167 per QALY (adalimumab+MTX) €34,922 per QALY (adalimumab+MTX) €35,760 per QALY (etanercept + MTX) €48,333 per QALY (infliximab + MTX) €41,561 per QALY (adalimumab) €36,927 per QALY (etanercept) ACR20/DAS28 moderate: €40,875 per QALY (adalimumab+MTX) €44,018 per QALY (adalimumab+MTX) €51,976 per QALY (etanercept+MTX) €64,935 per QALY (infliximab+MTX) €65,499 per QALY (adalimumab) €42,480 per QALY (etanercept)	Relevance – Limited The economic study reflects the Swedish perspective. The methods of the economic evaluation can be useful for the design of the model. In particular the method of treatment withdrawal and the mapping of HAQ-QoL model.
Brennan et al. 2004[3]	Etanercept vs DMARD sequence	Cost-utility	Patient level simulation	Lifetime	£16,330 per QALY when etanercept used after failure of two traditional DMARDs	Relevance – Relevant Cost data reflect UK environment. The methods of the economic evaluation can be useful for the design of the model. Possible reporting error: the withdrawal probability cites the same source with Bansback et al. 2005, but a completely different value.
Chen et al. 2006[1]	Etanercept, infliximab, adalimumab vs base strategy of	Cost-utility	Patient level simulation	Lifetime	Adalimumab (no MTX): 3rd line (late RA) 140,000, last in strategy 40,000, 3rd line (early RA data) 35,000, first-line 53,000 Etanercept (no MTX): 3rd line (late RA) 47,000, last in strategy	Relevance –Relevant Developed by UK HTA program. Lifetime model approach is appropriate. Reflects UK environment. The methods of the economic evaluation can be

Study	Treatment considered	Form of economic analysis	Type of model	Time-horizon	Main results	Relevance to the decision problem
	DMARDs without TNF inhibitors				24,000, 3rd line (early RA data) 30,000, first-line 49,000 Adalimumab (with MTX): 3rd line (late RA) 64,000, last in strategy 30,000, 3rd line (early RA data) 30,000, first-line 170,000 Etanercept (with MTX): 3rd line (late RA) 50,000, last in strategy 24,000, 3rd line (early RA data) 28,000, first-line 78,000 Infliximab (with MTX): 3rd line (late RA) 140,000, last in strategy 38,000, 3rd line (early RA data) 30,000, first-line 650,000	useful for the design of the model.
Chiou et al. 2004[4]	Etanercept, infliximab, adalimumab vs anakinra	Cost-utility	Decision tree	1 year	US $13,387 per QALY (Etanercept alone) Adalimumab alone dominated US $7925 per QALY (etanercept + MTX) Adalimumab + MTX and infliximab + MTX dominated	Relevance – not directly relevant The comparator anakinra is not recommended for routine use in the NHS 1-year cycle modelling is very limiting. Considering the nature of the disease (chronic condition) a lifetime approach is more appropriate. The assumption that treatment will continue over this period with no switching of therapy is not appropriate.
Choi et al. 2002[5]	Etanercept vs methotrexate, sulfasalazine	Cost-effectiveness	Decision tree	6 months	US $41,900 per ACR20 (sulfasalazine) US $40,800 per ACR70 weighted response (methotrexate)	Relevance – not directly relevant 1-year cycle modelling is very limiting. Considering the nature of the disease (chronic condition) a lifetime approach is more appropriate. Did not calculate cost per QALYs
Jobanputra et al. 2002[6]	Etanercept infliximab vs. DMARD	Cost-utility	Patient level simulation	Lifetime	Pharma agents used 3rd in sequence £64,881 per QALY (etanercept) £89,973 per QALY (infliximab) £35,229 per QALY (etanercept vs	Relevance – Relevant Developed by UK HTA program. Lifetime model approach is appropriate.

Study	Treatment considered	Form of economic analysis	Type of model	Time-horizon	Main results	Relevance to the decision problem
	sequence				infliximab) Pharma agents used last in sequence £33,011 per QALY (etanercept) £43,584 per QALY (infliximab) £19,398 per QALY (etanercept vs infliximab)	Reflects UK environment. The methods of the economic evaluation can be useful for the design of the model.
Kobelt et al. 2003[7]	Infliximab vs methotrexate	Cost-utility	Markov	10 years	With 1 year of treatment: €34,800 per QALY With 2 years of treatment: €48,200 per QALY	Relevance –limited Modelling short-term treatment effect. Indirect cost included (societal perspective)
Kobelt et al. 2004[8]	Etanercept, infliximab vs cost and QoL at baseline	Cost-utility	NA	NA	After 3 months of treatment €43,500 per QALY After 6 weeks of treatment: €36,900 per QALY	Relevance – not directly relevant Analysis presents patient-level direct costs and effectiveness using data from a cohort of Swedish patients.
Kobelt et al 2005[9]	Etanercept vs methotrexate	Cost-utility	Markov	10 years	Etanercept monotherapy dominated In combination with MTX: Treatment for 2 years, extrapolation to 10 years: €37,331 per QALY Treatment for 2 years, extrapolation to 5 years: €54,548 per QALY	Relevance – limited The methods of the economic evaluation can be useful for the design of the model. In particular the method of cost per HAQ score functional capacity.
Welsing et al. 2004[10]	Etanercept vs usual treatment, leflunomide	Cost-utility	Markov	5 years	Etanercept monotherapy dominated Etanercept vs usual treatment: €163,556 per QALY for LEF–Etan €297,151 per QALY for Etan–LEF Etanercept vs leflunomide: €317,627 per QALY for LEF—Etan €517,061 per QALY for Etan–LEF	Relevance – not directly relevant The economic evaluation reflects the Dutch perspective. 5-year time horizon very limiting. Considering the nature of the disease (chronic condition) a lifetime approach is more appropriate.
Wong et al. 2002[11]	Infliximab vs methotrexate, placebo	Cost-utility	Markov	Lifetime	US $30,500 per QALY	Relevance –not directly relevant The economic evaluation reflects the US perspective.

***References are given as a separate list in section 9.3**

Table 31: Summary of published studies identified by the updated review

Study	Treatment considered	Form of economic analysis	Type of model	Time-horizon	Main results	Relevance to the decision problem
Barbieri 2005[12]	Infliximab vs methotrexate	Cost-utility analysis	Markov model	Lifetime	£33,618 per QALY (one year treatment) £23,936 per QALY (lifetime treatment) £36,616 per QALY (ITT – 2 year treatment) £5,111 per QALY (assuming radiographic stabilization of joint disease)	Relevance – Not directly relevant Short-term treatment (1 year) not realistic in current clinical practice. Assumption of maintained effect following treatment withdrawal not realistic. The study reflects the ARAMIS cohort (US and Canada).
Brennan et al. 2007[13]	TNF inhibitors vs traditional DMARDs	Cost-utility	Patient level simulation	Lifetime	£23,882 per QALY	Relevance – Relevant The study is based on data by the BSR, reflecting UK environment. The methods of the economic evaluation can be useful for the design of the model.
Kielhorn et al. 2008[14]	Rituximab as add on therapy vs. sequential use of DMARDs, methotrexate	Cost-utility	Patient level simulation	Lifetime	£11,601 (sequence) £14,690 (methotrexate)	Relevance – Relevant The economic evaluation reflects the UK environment. Use of NOAR data. The methods of the economic evaluation can be useful for the design of the model
Russell et al. 2008[15]	Abatacept vs anti-TNF strategies	Cost-effectiveness	Patient level simulation	2-year time	DMARD-IR population LDAS Abatacept–etanercept–infliximab–DMARDs : Dominant Etanercept–abatacept–infliximab–DMARDs: $12,514 Remission Abatacept–etanercept–infliximab–DMARDs: Dominant Etanercept–abatacept–infliximab–DMARDs: $16,829 TNF-IR population LDAS	Relevance –Not directly relevant The economic evaluation reflects the Canadian environment. Use of short term time-horizon. No QALYs were considered

Study	Treatment considered	Form of economic analysis	Type of model	Time-horizon	Main results	Relevance to the decision problem
					Etanercept–abatacept–infliximab–DMARDs: $20,377 Remission Etanercept–abatacept–infliximab–DMARDs: $26,400	
Spalding et al. 2006[16]	Adalimumab, etanercept, infliximab vs methotrexate	Cost-utility analysis	Markov model	Lifetime	$US 63,769 per QALY (adalimumab) $US 89772 per QALY (etanercept) $US 194,589 per QALY (adalimumab + methotrexate) $US 409,523 per QALY (infliximab and methotrexate)	Relevance – Not directly relevant The study reflects US environment This study aims to examine the cost effectiveness of using TNFalpha inhibitors (both as monotherapy and in combination with methotrexate) as first-line agents.
Tanno et al. 2006[17]	Etanercept as add on treatment vs standard DMARD treatment regime	Cost-utility analysis	Markov model Monte carlo simualtion	Lifetime	¥ 2.5 million per QALY	Relevance – Limited The study reflects the Japanese environment. The methods of the economic evaluation can be useful for the design of the model. The economic evaluation considers indirect cost such as lost productivity costs due to RA disability and premature mortality (societal perspective)
Vera-Llonch et al. 2008a[18]	Abatacept + methotrexate vs methotrexate	Cost-utility	Patient level simulation	10 years and lifetime	US$ 47,910 per QALY (10 years) US$ 43,041 per QALY (lifetime)	Relevance – Limited The study reflects the US environment.
Vera-Llonch et al. 2008b[19]	Abatacept + methotrexate vs methotrexate	Cost-utility	Patient level simulation	10 years and lifetime	US$ 50,576 per QALY (10 years) US$ 45,979 per QALY (lifetime)	Relevance – Limited The study reflects the US environment.
Wailoo et al. 2008[20]	Infliximab vs etanercept vs adalimumab vs anakinra	Cost-utility	Patient level simulation	Lifetime	Infliximab dominated by etanercept and adalimumab. US$ 216,513 per QALY (anakinra vs. infliximab) US$ 142,726 per QALY (adalimumab vs. anakinra) US$ 92,058 per QALY (etanercept vs.	Relevance – Limited The study reflects the US environment. The methods of the economic evaluation can be useful for the design of the model.

Study	Treatment considered	Form of economic analysis	Type of model	Time-horizon	Main results	Relevance to the decision problem
					adalimumab)	
Welsing et al 2006[21]	NA	Cost-utility analysis	Markov model	5-year	3.266 expected QALYs per patient over 5 years €6754 medical direct cost €12 641 total cost	Relevance –Not relevant The study although presents a decision model analysis, does not contain information on the economic evaluation of any RA treatment. It is an attempt to validate results from an economic model with real life data. Data reflect the Dutch environment.

***References are given as a separate list in section 9.3**

7.2 De novo economic evaluation(s)

In the absence of a relevant published economic evaluation, manufacturers or sponsors should submit their own economic evaluation. When estimating cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal'). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Element of health technology assessment	Reference case	Section in 'Guide to the methods of technology appraisal'
Defining the decision problem	The scope developed by the institute	5.2.5 & 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 & 5.2.6
Perspective costs	NHS and Personal Social Services	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 to 5.2.12
Synthesis of evidence on outcomes	Bases in a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12

HRQL, health related quality of life; NHS, National Health Service; QALYs, quality-adjusted life years

7.2.1 Technology

7.2.1.1 How is the technology (assumed to be) used within the economic evaluation? For example, give indications, and list concomitant treatments, doses, frequency and duration of use.

The technology (tocilizumab) is assumed to be used as indicated in its EU Summary of Product Characteristics (SPC). Tocilizumab is administrated by intravenous infusion (IV) in combination with methotrexate (MTX). The treatment regimen is the same for both indications; Disease-modifying antirheumatic drugs inadequate responders (DMARD-IR) and Anti-tumour Necrosis Factor Alpha inadequate responders (TNF-IR). Tocilizumab is assumed to be given to both treated populations for a minimum of 6 months. After 6 months only those patients achieving an ACR20 or higher are assumed to continue therapy. The duration of therapy is assumed to be as long as the patient is exhibiting a treatment effect. This is informed by historical data on biologic treatment duration described in further detail below. Tocilizumab is given as an infusion within the hospital setting every 4 weeks.

The assumed doses for each drug used in the treatment sequences are described in the table below.

Table 32: Drug dose and frequency included within in the economic models for DMARD-IR and TNF-IR

Drug	DMARD-IR dose	TNF-IR dose
Tocilizumab (IV)	8mg/kg every 4 weeks	8mg/kg
Etanercept (SC)*	50mg; every week	N/A
Methotrexate (SC)*	7.5–20mg; every week	7.5–20mg; every week
Rituximab (IV)	N/A	1000mg; Administered on day 1 and day 15; then repeated every 6-12 months (assumed to be 9)
Leflunomide (oral)	15.2 mg per day	15.2 mg per day
Ciclosporin (oral)	2.5-4mg/kg per day	2.5-4 mg/kg per day
Gold (Intramuscular)	25-50mg; every 2-4 weeks	25-50mg; every 2-4 weeks
Included in the scenario analysis		
Infliximab (IV)	3 mg/kg at weeks 2 and 6 after the first infusion then	N/A

	every 8 weeks thereafter	
Adalimumab (SC)*	40mg every other week	N/A

*SC: subcutaneous injection

7.2.1.2 Has a treatment continuation rule been assumed? Where the rule is not stated in the SmPC this should be presented as a separate scenario, by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- the costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required)
- the robustness and plausibility of the endpoint on which the rule is based
- whether the 'response' criteria defined in the rule can be reasonably achieved
- the appropriateness and robustness of the time at which response is measured
- whether the rule can be incorporated into routine clinical practice
- whether the rule is likely to predict those patients for whom the technology is particularly cost effective
- issues with respect to withdrawal of treatment from non-responders and other equity considerations.

The model assumes that all patients receive tocilizumab for a minimum of 6 months, consistent with both the phase III tocilizumab trials and existing NICE guidance on TNF inhibitors. At 6 months, providing patients have achieved a response that is greater or equal to ACR 20, patients will continue therapy. For these responding patients, therapy is assumed to continue for as long as the clinician is satisfied a treatment benefit is being achieved, These exact probabilities of treatment continuation, based upon rates observed for TNF inhibitor therapy, is described in further detail below.

For patients that fail to achieve ACR 20, ACR 50 or ACR 70 at 6 months, treatment with tocilizumab is stopped and patients move onto the next medication in the treatment sequence. Achieving an ACR 20 response is the continuation criterion in both DMARD-IR and TNF-IR indications.

An ACR 20 response, defined as a 20% improvement in tender and swollen joint counts and 20% improvement in 3 of the 5 remaining ACR-core set measures[i], is the primary endpoint in the phase III RCTs and a widely accepted indication of minimal treatment

[i] Patient and physician global assessments, pain, disability, and an acute phase reactant

success Roche is mindful that existing NICE guidance for RA biologic therapies define response and stopping rules according to DAS. However this outcome is not publicly reported for the other comparator drugs and therefore was not considered a practical endpoint upon which to define stopping rules within the model. Previous submissions to NICE for RA biologic treatments have focused on ACR response endpoints.

Assessment of the response to tocilizumab treatment is assumed to take place after the 1st cycle of the model. Each cycle in the model is 6 months. RA patients are routinely monitored in normal clinical practice and therefore their assessment 6 months after treatment initiation is not assumed to incur any additional cost.

Patients that do respond to tocilizumab treatment are assumed to stop treatment due to lack of efficacy. After withdrawal, patients progress to the next pre-defined treatment and their response is evaluated again in the next cycle in the same manner (by ACR responses).

Discontinuation of current treatment can be determined by one of two alternative assumptions within the model:

- Constant probability of withdrawal
- Mean time on treatment

Either method of withdrawal is subject to different underlying assumptions and is described separately below.

Constant probability of withdrawal

This method (the base case) assumes a constant 6-month withdrawal rate from treatment and applies to the economic model a constant probability of withdrawal. Data extracted from Geboreck et al. (2002)[61] on etanercept and infliximab suggest that the withdrawal rate is 8% and 12% respectively. These estimates agree with similar data presented by Bansback et al. (2005)[62]. The economic model assumes the same withdrawal rate for all bDMARDs[ii] equal to the average of the two estimates for etanercept and infliximab. The SE is estimated assuming the number of events is that of the infliximab observations from Geboreck et al. (2002) (τ=33.75). The economic model assumes the same probability of withdrawal for all tDMARDs[iii] (Bansback et al.; 2005). The SE is assumed to be proportionally the same as that of the bDMARDs.

Table 33: Constant probability of withdrawal

Treatment	Withdrawal rate		Probability of withdrawal		Source
	Mean	SE	Mean	SE	
Etanercept	0.08	0.0135	NA	NA	Withdrawal rate extracted by Geboreck et al. 2002
Infliximab	0.12	0.0207	NA	NA	Withdrawal rate extracted by Geboreck et al. 2002

[ii] bDMARD: biological DMARD
[iii] tDMARD: traditional DMARD

bDMARD	0.10	0.0172*	0.095	0.0156**	Assume average of the two extracted rates
tDMARD	NA	NA	0.270	0.0442***	Bansback et al. 2005

*Assume number of events τ=33.75 (infliximab)
**Estimated by the CI of the withdrawal rate
***Assume the same proportion of mean / SE in bDMARDs
****bDMARDs are adalimumab, etanercept infliximab, rituximab, and tocilizumab; tDMARDs are ciclosporin, gold and leflunomide

Mean time on treatment

This method assumes that individuals who respond to a treatment continue for a predetermined period of time equal to actual estimates of mean time on treatment. This period of time includes the time individuals spend at the initial cycle before their response is evaluated. This assumption is consistent with the Roche economic model submitted as part of the rituximab in RA NICE STA in 2006.

The model is structured so that each treatment can have a different mean time on treatment if data are available or become available in the future. The model tested in a scenario analysis assumes that the time on treatment for all bDMARD therapies is the same. Figure 1 from Brocq et al. (2007)[63] suggests that the median time on a biologic for RA patients is 39 months or 3.25 years. Since the data from Brocq et al. (2007) are incomplete an estimate of the mean time on treatment requires assumptions about an underlying survival distribution and then extrapolation, both subject to error. We have made the simplifying assumption that the median estimate of time on treatment from Brocq et al. (2007) is approximately equal to the mean time on treatment.

The base case analysis estimates assume a constant probability of withdrawal.

7.2.2 Patients

7.2.2.1 What group(s) of patients is/are included in the economic evaluation? Do they reflect the licensed indication? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem?

The assumed patient cohorts are consistent with both the license and populations observed within the tocilizumab phase III studies. Two patient cohorts are analysed in the model and subsequently 2 separate ICERs are estimated. The **first cohort** includes moderate to severe RA patients who have had an inadequate response to one or more traditional disease-modifying antirheumatic drugs (tDMARDs). The **second cohort** includes moderate to severe RA patients who have had an inadequate response to one or more anti-tumour necrosis factor (aTNF) drugs.

The two cohorts analysed consistent with the SmPC that recommends use of tocilizumab in both patient populations. The population analysed in the DMARD-IR indication reflects 3 out of the 5 registration trials for Tocilizumab; WA17822 (OPTION), WA17823 (LITHE) and WA18063 (TOWARD). Although the population of the OPTION and LITHE trials had a methotrexate inadequate response where as the population in the TOWARD study had a DMARD inadequate response, it has been assumed that these two populations are the same in terms of clinical characteristics (see section 6.3.2). The population analysed in the TNF-IR indication reflects the fourth registration trial for tocilizumab; WA18062 (RADIATE). This is the only trial that investigated the clinical efficacy of tocilizumab among TNF-IR patients.

The pooled percentage of women in the DMARD-IR trials (82%) and the percentage of women in the TNF-IR trial (82%) is assumed in the gender ratio in the economic model. Other patient baseline characteristics have been considered to be the same as the ones in the DMARD-IR pooled trial analysis and the RADIATE TNF IR trial and are tabulated below.

Table 34: Baseline patient characteristics within the economic model

Demographics	DMARD-IR analysis		TNF-IR analysis	
	Values	Reference	Values	Reference
Females	82%	DMARD-IR pooled analysis (includes LITHE, OPTION and TOWARD registration trials)	82%	RADIATE registration trial
Males	18%		18%	
Mean age	52.5		53.7	
Baseline HAQ	1.51		1.70	

7.2.2.2 Was the analysis carried out for any subgroups of patients? If so, how were these subgroups identified? If subgroups are based on differences in relative treatment effect, what clinical information is there to support the biological plausibility of this approach? For subgroups based on differences in baseline risk of specific outcomes, how were the data to quantify this identified? How was the statistical analysis undertaken?

To date there are no known factors that predict response to a particular treatment in RA. The lack of prognostic factors and therefore subgroups was reinforced by the multivariate analysis carried out in the pooled DMARD analysis and the anti-TNF analysis. No subgroups were identified therefore no separate analysis has been performed in the economic analysis.

7.2.2.3 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Refer to the subgroups identified in the scope.

As outlined in the final scope for this appraisal and consistent with previous RA appraisals, no subgroups were identified.

7.2.2.4 At what points do patients 'enter' and 'exit' the evaluation? Do these points differ between treatment regimens? If so, how and why?

In the DMARD-IR analysis patients 'enter' the evaluation after failing one or more tDMARDs. Patients on the tocilizumab arm of the analysis receive tocilizumab and methotrexate as their first treatment. Patients on the tocilizumab non-containing arm receive the first therapy in the sequence, which in the base-case is etanercept and methotrexate. Due to the long-term nature of the disease patients 'exit' the evaluation when they die. Death has been assumed to be the absorbing state.

In the TNF-IR analysis patients 'enter' the evaluation after failing one or more anti-TNFs (bDMARDs). Patients on the tocilizumab arm of the analysis receive tocilizumab and methotrexate as their first treatment. Patients on the tocilizumab non-containing arm receive the first therapy in the sequence, which in the base-case is rituximab and methotrexate. Again due to the long-term nature of the disease patients 'exit' the evaluation when they die. Death has been assumed to be the absorbing state.

7.2.3 Comparator technology

What comparator(s) was/were used and why was it/were they chosen? The choice of comparator should be consistent with the summary of the decision problem (Section A).

The choice of the comparator treatment regimens in both DMARD-IR and TNF-IR indications are consistent with the decision problem. The most appropriate comparator was not considered to be a single treatment but a "treatment sequence" reflecting the real life practice within RA of cycling through different treatment options as all patients eventually inadequately respond to therapy. It is assumed tocilizumab will not be replacing any existing treatment from within this treatment, but will be additive to the existing treatment strategies. The assumed treatment sequences have been verified by clinical consultation in a Roche NICE advisory board and do not assume that multiple TNF inhibitors will be used. Furthermore the addition to, rather than the replacement of any existing treatment options is consistent with the methodology utilised in previous NICE appraisals in RA.

The two intervention treatment sequences and the two comparator sequences for the DMARD IR and TNF IR populations are summarised in the table below.

Table 35: Summary of economic comparators

DMARD-IR indication		**TNF-IR indication**	
Intervention	Comparator	Intervention sequence	Comparator sequence

sequence	sequence		
viii. Tocilizumab + MTX ix. TNFα inhibitor (etanercept assumed most commonly used) x. Rituximab xi. Leflunomide xii. Gold xiii. Cyclosporine xiv. Palliative care	vii. TNFα inhibitor (etanercept assumed most commonly used) viii. Rituximab ix. Leflunomide x. Gold xi. Cyclosporine xii. Palliative care	vii. Tocilizumab + MTX viii. Rituximab ix. Leflunomide x. Gold xi. Cyclosporine xii. Palliative care	vi. Rituximab vii. Leflunomide viii. Gold ix. Cyclosporine x. Palliative care

Therefore in both analyses the incremental cost and QALYs of adding tocilizumab to the existing, NHS treatment strategy, according to its licensed indication, is evaluated.

7.2.4 **Study perspective**

If the perspective of the study did not reflect NICE's reference case, provide further details and a justification for the approach chosen.

The perspective on costs and outcomes employed in the analysis is consistent with the reference case as outlined by the National Institute for Health and Clinical Excellence, (NICE). The perspective taken when estimating costs in the economic evaluation is that of the NHS and personal social services (PSS) in England and Wales. All relevant healthcare costs are evaluated. The health outcomes measured in the economic model are calculated from the perspective of the patient.

7.2.5 **Time horizon**

The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared.

What time horizon was used in the analysis, and what was the justification for this choice?

The economic evaluation estimates costs and health benefits over the full life-time of each individual. This time horizon is necessary for the main health outcomes and resource use to be fully explored since we are concerned with the therapy of a chronic disease. A time horizon less than the full life-time of the patient population would not be sufficient to capture the true benefits and costs of treatment.

7.2.6 Framework

The purpose of this section is to provide details of the framework of the analysis. Section a) below relates to model-based evaluations, and section b) below relates to evaluations conducted alongside clinical trials. Please complete the section(s) relevant to the analysis.

a) Model-based evaluations

7.2.6.1 Please provide the following.

- A description of the model type.

The design of the economic analysis follows guidelines set by the OMERACT (Outcome Measures in Rheumatoid Arthritis Clinical Trials) Economics Working Group[64, 65]. The structure is developed to closely represent real practice, by allowing the user to perform analysis of sequential RA treatment.

At the centre of the economic analysis is an individual sampling model (ISM) designed in MS Excel® with the use of visual basic for applications (VBA). In this case, the individual simulation assumes a homogenous cohort at the start of the model and does not include any variability in the baseline patient characteristics. The ISM is used to track the characteristics of the individuals and maintain a record of the "history" after the start of the model and during the simulation process. This approach is deemed appropriate as the accrued health benefits and costs depend upon a large or conceptually infinite number of values of the model's key parameter (HAQ score).

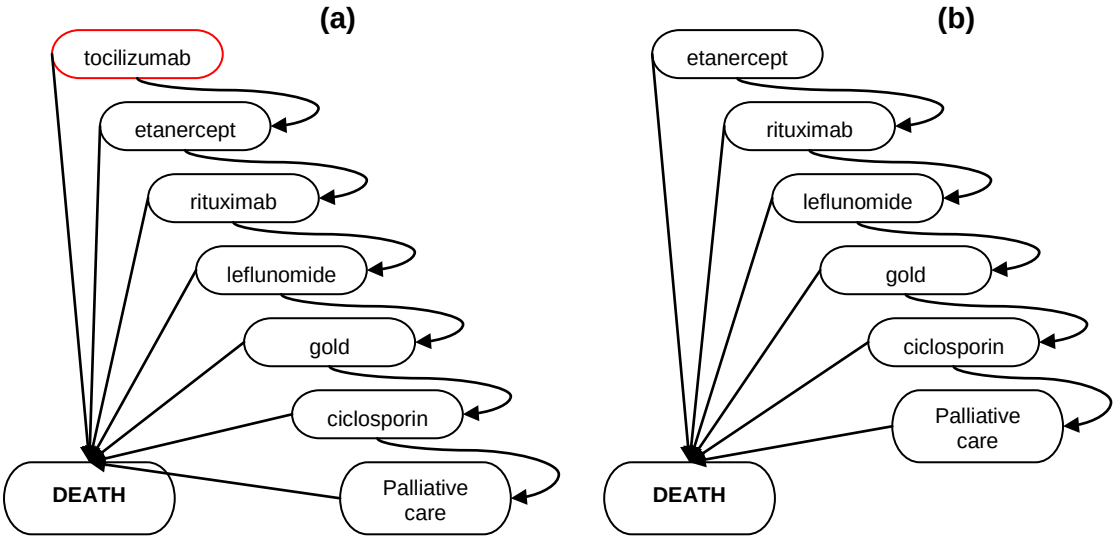
The model algorithm is presented below:

Start the simulation
For patients *i=1, 2, …, n*, cycles *k=1, 2, …, n* a random number drawn by a continuous uniform distribution *θ~U[0,1]*, and the relevant risk (probability) factor *p.*
Determine the path of patient *i* through the model by $\theta_{i,k} \leq p_k$
Determine cost c_i and utility u_i for individual *i*
End the simulation
Estimate the mean cost and utility *E[(C, U)]* by

$$\hat{a}_n = \frac{1}{n}\sum_{i=1}^{n}(c_i, u_i)$$

- A schematic of the model. For models based on health states, direction(s) of travel should be indicated on the schematic on all transition pathways.

Figure 33: Schema of individual patient flow showing the treatment sequences in the DMARD-IR indication with (a) and without (b) tocilizumab



In the DMARD-IR indication all patients enter the model after failing one or more traditional DMARDs (tDMARDs) and at the start of their next treatment option. In the tocilizumab sequence, tocilizumab+MTX is the first line of treatment consistent with both its licensed indication and the associated phase III trials. Patients either stay on tocilizumab if they respond after 24 weeks from treatment initiation or move to the next option (etanercept+MTX) as shown in **Figure 33(a)**. If patients respond to tocilizumab+MTX, they stay on treatment and withdraw due to lack of efficacy with a constant probability of withdrawal, as specified in 7.1.2.1.

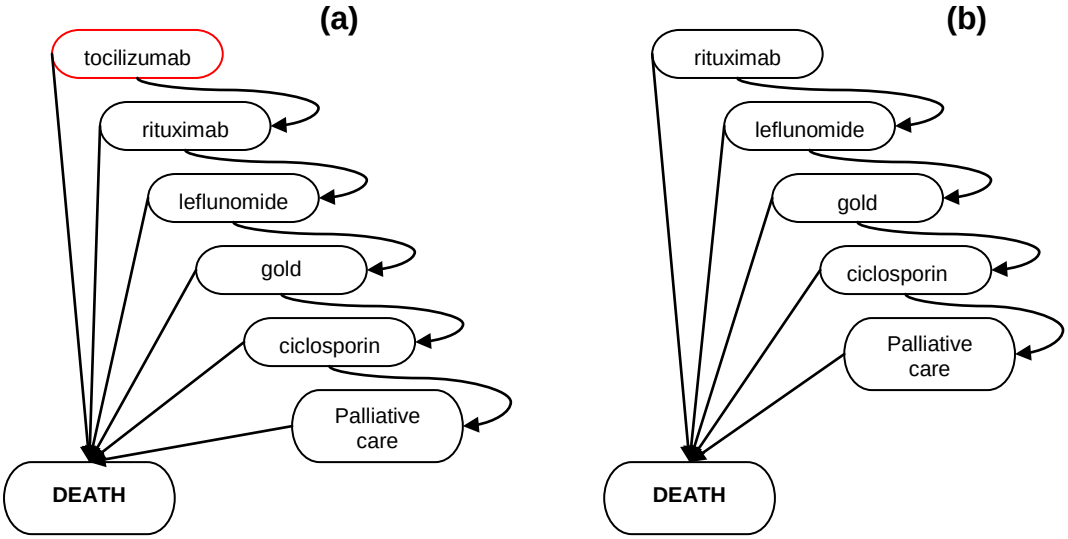
The same process is repeated for all the treatment options in the pathway until patients withdraw from ciclosporin (the last treatment option) and enter the palliative care state. Patients stay in this state until they die. At any point on this treatment pathway, patients can die from a background RA specific mortality rate.

The treatment pathway is the same for the comparator treatment pathway apart from the exclusion of tocilizumab, hence etanercept+MTX is the first treatment option as shown in

Figure 33(b).

In TNF-IR indication all patients enter the model after failing one or more anti-TNFs. In the tocilizumab containing sequence, tocilizumab+MTX is assumed to be the first treatment, consistent with both its license and the population of the RADIATE study. . Patients either stay on tocilizumab if they respond after 24 weeks from treatment initiation or move to the next option (rituximab+MTX) as shown in **Figure 34(a)**. The process is repeated and the last state is again palliative care where patients stay until they die. The pathway is the same for the comparator sequence, but patients start with rituximab+MTX treatment(**(b)**) as currently recommended by NICE. At any point on this treatment pathway, patients can die due to natural causes not directly related to RA.

Figure 34: Schema of individual patient flow showing the treatment sequences in the TNF-IR indication with (a) and without (b) tocilizumab

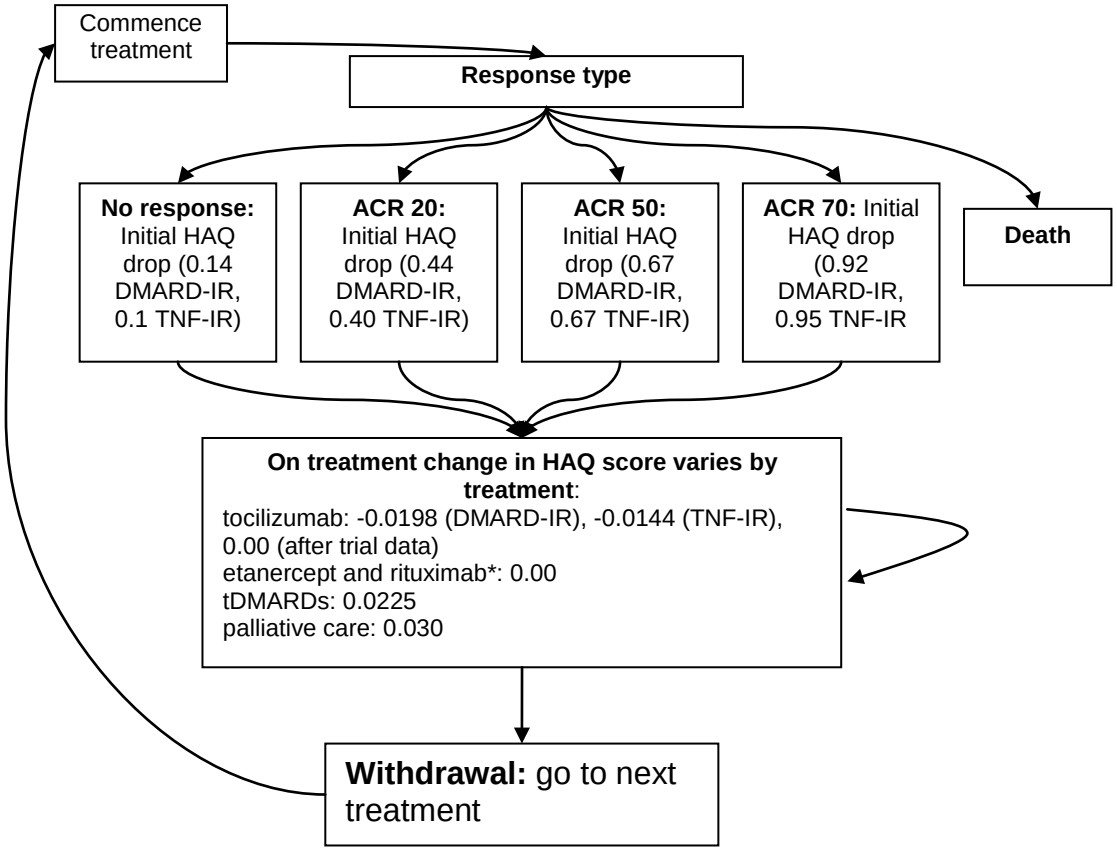


In both indications and in all treatment options, patients may respond to one of the three ACR response categories (ACR 20, ACR 50, and ACR 70). The probability of response in each category is taken from the MTC (section 6.6), the RADIATE trial and published data. Patients are then allocated a pre-defined drop in HAQ according to the ACR response they achieved. This reduction in HAQ conditional on response category was derived from the DMARD IR and TNF IR patient level trial data in the relevant tocilizumab trials. The relationship between ACR response and initial HAQ drop is assumed to be generic and applicable to all interventions. Further details on this calculation are provided in section “ACR model inputs” below.

Patients who respond are then subject to a constant risk of withdrawal from the specified treatment due to the lack of efficacy. This risk is represented through a constant probability of withdrawal, as explained in 7.1.2.1.

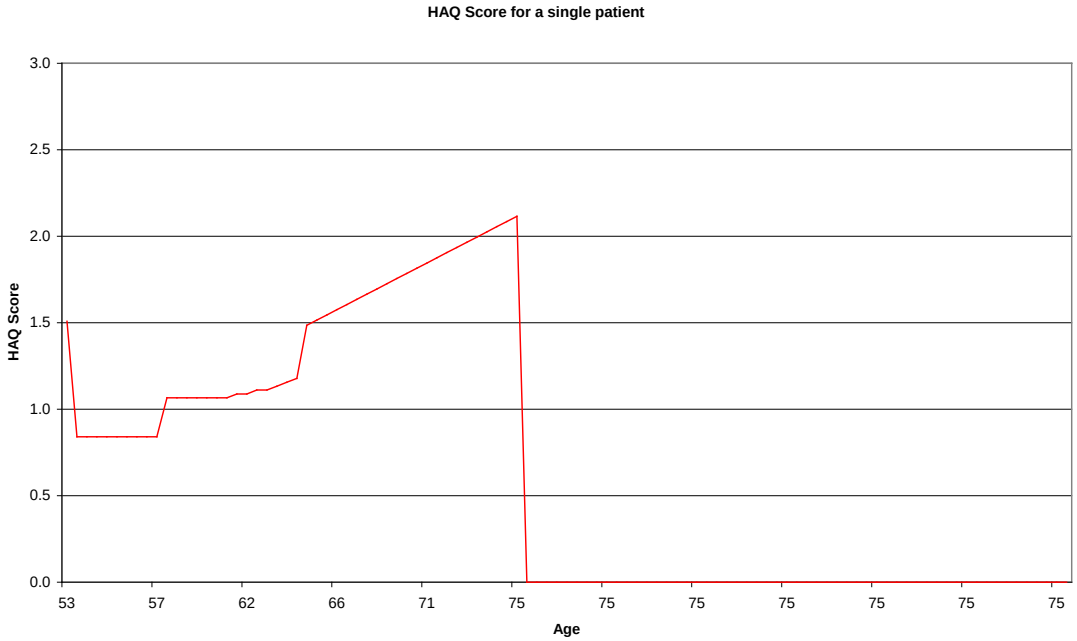
For responding patients, following the initial HAQ drop at 6 months a change in HAQ score is assumed during a patient's remaining time on treatment. The specific assumption and derivation of this rate is described in further detail below. At the point of treatment failure the patient is assumed to experience an increase in HAQ (rebound effect), before commencing the next pre-defined treatment within the sequence, where the above process starts again as shown in **Figure 35**: At every cycle in the model patients are subject to an age, sex and RA adjusted risk of death. The model is assigned six monthly cycles.

Figure 35: A detailed schematic representation of the possible transition states in each treatment of the model



An example of the predicted disease progression for a single patient within the microsimulation is illustrated in the figure below (**Figure 36**).

Figure 36: Predicted HAQ score



- A list of all variables that includes their value, range (distribution) and source.

All major variables included within the model are both listed and discussed in more detail below. Additional statistical details on the associated ranges and distributions for selected variables are provided in the probabilistic sensitivity analysis section below:

ACR model inputs

There are four different categories of response within the model: non-responder, ACR 20 responder, ACR 50 responder and ACR 70 responder. These response rates differ by treatment. The proportion of patients who fall within each response category is obtained by adjusting the reported response rates in order to ensure the categories are non-overlapping.

Response to treatment is defined by the ACR response rates;

- patients who demonstrate an estimated response higher than ACR 20 are considered responders
- patients that demonstrate an estimated response lower than ACR 20 are considered non-responders and progress to the next treatment

The economic model uses ACR response rates as the primary measure of response for each therapy. Due to lack of head to head clinical data between bDMARDs and variation in the observed performance of the respective control arms, a mixed treatment comparison (MTC) was performed to more accurately measure the relative treatment effect of the various biologic therapies and methotrexate in the DMARD-IR and TNF IR

populations. The ACR efficacy assumptions utilised within the economic model are reported in section 6.6 above.

The term "adjusted response rates" is used to refer to the output of the mixed treatment comparison. **Table 36** and **Table 38** present the adjusted response rates for the DMARD-IR and TNF-IR indication respectively. Consistent with published reports the rates are reported as 'overlapping' response rates where the percentages are cumulative. The model utilizes a simple re-expression of these rates in non-overlapping categories for both DMARD-IR and TNF-IR patients. To obtain the final ACR inputs and avoid the double-counting of patients, the following method was utilised: Taking the DMARD-IR tocilizumab response rates as an example; The ACR 70 response is identical. The ACR 50 response rate was calculated by subtracting 29% (ACR 70 response rate) from 44% (>ACR 50 response rate), producing 15%. The final ACR 20 response rate was calculated by subtracting 44% (>ACR 50 response rate) from 65% (>ACR 20 response rate), producing 21%. The subsequent ACR transition probabilities utilised within the economic model are illustrated in **Table 37** (DMARD-IR indication) and **Table 39** (TNF-IR indication).

Table 36: ACR adjusted response rates in DMARD-IR

Treatment	ACR 20	ACR 50	ACR 70	Source
Tocilizumab	0.65	0.44	0.29	Indirect comparison base case analysis: excl. van de Putte, Moreland and subgroup Furst
Rituximab (TNF-IR)	0.46	0.23	0.14	Indirect comparison TNF-IR analysis
anti-TNFα	0.63	0.39	0.16	Indirect comparison base case analysis: excl. van de Putte, Moreland and subgroup Furst
tDMARD	0.15	0.04	0.01	Indirect comparison TNF-IR analysis
Palliative care	0.15	0.04	0.01	Indirect comparison TNF-IR analysis

*anti-TNFα are adalimumab, etanercept, and infliximab; tDMARDs are ciclosporin, gold and leflunomide

The ACR response rates for tDMARDs in the DMARD-IR analysis have not been taken from the MTC because these were taken from the response rates of the placebo arm in the trials. The ACR rates from the trials do not reflect what the response rate would be to a tDMARD once a patient has had an inadequate response to aTNF and rituximab therapy. The ACR response rates for the DMARD-IR analysis have been taken from the TNF-IR MTC as these reflect better the response to a tDMARD when a patient has been treated with an aTNF and rituximab. These ACR response rates may even present an overestimation as they reflect patients that have only been treated with an aTNF and not rituximab. The ACR response rates once patients have had an inadequate response to rituximab are expected to be even lower.

Table 37: DMARD-IR transition probabilities (ACR response rates: non-overlapping, adjusted) – economic model inputs

Treatment	ACR 20	ACR 50	ACR 70	No Response
Tocilizumab	0.21	0.15	0.29	0.35
Etanercept	0.24	0.23	0.16	0.37
Rituximab (DMARD-IR)	0.25	0.17	0.18	0.40
Leflunomide	0.11	0.03	0.01	0.85
Gold	0.11	0.03	0.01	0.85
Ciclosporin	0.11	0.03	0.01	0.85
Palliative care	0.11	0.03	0.01	0.85
Adalimumab	0.24	0.23	0.16	0.37
Infliximab	0.24	0.23	0.16	0.37

Table 38: ACR adjusted response rates in TNF-IR

Treatment	ACR 20	ACR 50	ACR 70	Source
Tocilizumab	0.62	0.31	0.12	Indirect comparison TNF-IR analysis
Rituximab	0.46	0.23	0.14	Indirect comparison TNF-IR analysis
tDMARDs	0.15	0.04	0.01	Assume same as placebo: Indirect comparison TNF-IR analysis
Palliative care	0.15	0.04	0.01	Assume same as placebo: Indirect comparison TNF-IR analysis

*anti-TNFα are adalimumab, etanercept, and infliximab; tDMARDs are ciclosporin, gold and leflunomide

Table 39: TNF-IR transition probabilities (ACR response rates: non-overlapping, adjusted) – economic model inputs

Treatment	ACR 20	ACR 50	ACR 70	No Response
Tocilizumab	0.31	0.19	0.12	0.38
Rituximab (DMARD-IR)	0.23	0.09	0.14	0.54
Leflunomide	0.11	0.03	0.01	0.85
Gold	0.11	0.03	0.01	0.85
Ciclosporin	0.11	0.03	0.01	0.85
Palliative care	0.11	0.03	0.01	0.85

The unadjusted ACR response rates were derived from the corresponding trials and the transition probabilities for both indications and are provided in appendix 6. The base-case analysis utilises the adjusted response rate. The impact of using unadjusted rates however, is examined in the scenario analyses.

ACR response degradation adjustment

The adjustment method is based on data from Anderson et al. (2000)[66]; a study that explores predicting factors of response to treatment in rheumatoid arthritis (RA). This option is included within the model if it is considered a more reasonable basecase to assume some degradation in response rates as one moves the treatment option down the treatment sequence.

The paper suggests that disease duration is one of the most important factors predicting response. Anderson (2000) analysed primary trial data from randomised control trials of drugs or devices in RA, and found that the disease duration effect on odds of response was 0.98 per extra year of disease duration. This is translated to **Equation 1**

$$OR_{t+1} = \frac{\frac{P_{t+1}}{1-P_{t+1}}}{\frac{P_t}{1-P_t}} = 0.98$$

Where P_t is the response rate at time t, P_{t+1} is the response rate the following year, OR_{t+1} the odds ratio per extra year of disease duration, and t reflects years. If we assume two equal odds ratios OR_α and OR_β for the biannual response rates then we obtain;

Equation 2

$$OR_\alpha = \frac{\frac{P_{t+1/2}}{1-P_{t+1/2}}}{\frac{P_t}{1-P_t}}$$

And

Equation 1

$$OR_\beta = \frac{\frac{P_{t+1}}{1-P_{t+1}}}{\frac{P_{t+1/2}}{1-P_{t+1/2}}}$$

then from **Equation 1**, **Equation 2**, and **Equation 3** we obtain;

Equation 2

$$OR_\alpha \cdot OR_\beta = OR_{t+1} = 0.98$$

and since assumed parity between OR_α and OR_β we obtain the odds of response per extra 6-months of disease duration;

$$OR_\alpha = OR_\beta = \sqrt{OR_{t+1}} = \sqrt{0.98}$$

Solving **Equation 1** for P_{t+1} we obtain;

Equation 3

$$P_{t+1} = \frac{OR_{t+1}\frac{P_t}{1-P_t}}{1+OR_{t+1}\frac{P_t}{1-P_t}}$$

and similarly for the biannual

$$P_{t+½} = \frac{OR_{\alpha}\frac{P_t}{1-P_t}}{1+OR_{\alpha}\frac{P_t}{1-P_t}}$$

which defines the response rate for the next increment of time, given the odds ratio and the initial response rate.

The base-case assumes no degradation adjustment of the ACR response rates.

HAQ score drop for ACR responses

The model assumes that response to treatment has an impact on disease severity (as measured by individual HAQ score). Data from four tocilizumab phase III clinical trials (OPTION, TOWARD, LITHE and RADIATE) were analysed to estimate the relationship between ACR response and individual HAQ score for the first 24 weeks. A separate DMARD IR and TNF IR relationship was estimated. The data from the first 24 weeks of the studies suggest that the higher the observed ACR response the greater the drop in HAQ score. **Table 40** and **Table 41** present the individual HAQ score drop per ACR response and the corresponding standard errors (SEs) for the DMARD-IR and TNF-IR population, respectively. For every response to a new treatment, the model applies the corresponding HAQ score reduction to every simulated individual during the first cycle on treatment (first six months). The model assumes that the relationship between ACR response and initial HAQ reduction is a generic relationship and thus is the same regardless of treatment.

Table 40 DMARD-IR HAQ score drop for ACR response

ACR response	Mean	SE	Source
No response	0.13572	0.01679	DMARD-IR pooled analysis(includes OPTION, TOWARD and LITHE registration trials)
ACR 20	0.44266	0.01831	
ACR 50	0.66795	0.0261	
ACR 70	0.92257	0.03201	

Table 41: TNF-IR HAQ score drop for ACR response

ACR response	Mean	SE	Source
No response	0.09788	0.02162	RADIATE registration trial
ACR 20	0.40455	0.03412	
ACR 50	0.6704	0.05794	
ACR 70	0.94945	0.06424	

Long-term HAQ progression while on treatment

The evolution of HAQ scores while on treatment is clinically important and also plays a very important role in the economic analysis of RA therapies. The long-term HAQ progression data used in the economic model has been derived from published sources, previous NICE appraisals and the tocilizumab clinical trials. It is important to stress that the change in HAQ scores relate to **responding patients only** who remain on treatment and not to the entire population. **Table 42** summarises the HAQ inputs utilised within the model.

Table 42: HAQ progression while on treatment after the initial 24 week period

Treatment	DMARD-IR analysis	TNF-IR analysis
Tocilizumab (using trial data)	-0.0198	-0.0126
Tocilizumab (beyond trial data)	0.0000	0.0000
Etanercept	0.0000	N/A
Rituximab (TNF-IR)	0.0000	
Leflunomide	0.0225	
Gold	0.0225	
Ciclosporin	0.0225	
Palliative care	0.0300	
Infliximab	0.0000	N/A
Adalimumab	0.0000	N/A

Previous assessments by NICE have used differing assumptions about on treatment clinical change, assessed via HAQ. A summary and critique of these previous assumptions can be found in Appendix 5. Roche has performed a thorough assessment of previous evidence for this key model parameter to understand the strengths and weaknesses of previous long term HAQ assumptions. As a consequence Roche has attempted to improve the quality of the existing evidence base by utilizing patient level data from the extensive tocilizumab phase III development program. Furthermore, specifically for the purposes of the NICE submission, Roche performed a special analysis of latest available evidence from ongoing Phase III extension trials (December 2008) to ensure that the longest possible follow-up of HAQ data was utilized to inform this parameter and to minimize uncertainty.

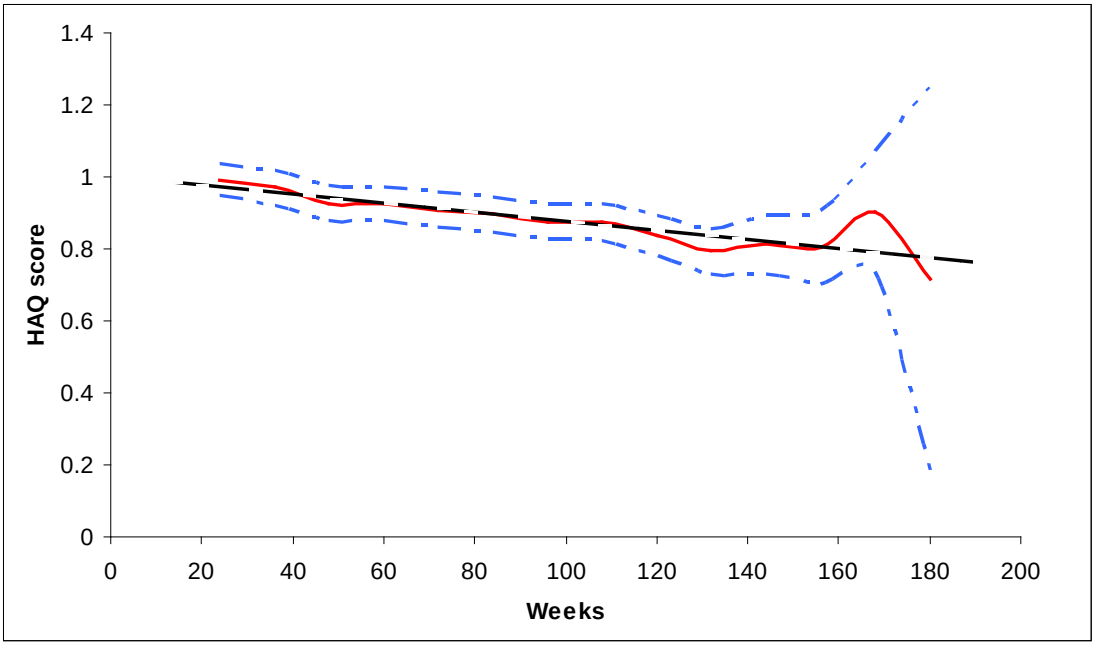
Since the tocilizumab phase III studies demonstrate a reduction in HAQ scores beyond the initial 6 month period after treatment initiation, contrary to previous NICE modelling assumptions, it is important to highlight how the long-term progression HAQ data was derived, what data was used in the analysis and how this disease progression is reflected in the model.

In order to obtain an estimate of the average rate at which patients' functional status changes while on tocilizumab treatment for the DMARD IR population, a mixed model of HAQ scores was estimated. The data for the mixed model consisted of all observations in tocilizumab extension trials (WA18695 and WA18696) for patients continuing on treatment. Data were available from week 24 up to week 180 (3.50 years post-baseline and 3.0 years subsequent to trial endpoint) from the DMARD-IR trials and from week 24 up to week 144 (2.75 years post-baseline and 2.25 years subsequent to trial endpoint) from the TNF-IR trial. Observations prior to week 24 were excluded since this was

estimated separately (initial HAQ drop described above) and represents a different model input.

The long term trial follow-up data for mean HAQ scores, beyond 6 months, are presented in the figures below.

Figure 37: Mean HAQ score over time for patients in the DMARD-IR trials



It is important to highlight that the HAQ slopes remain negative for the duration of the trial follow-up in both indications for patients remaining on treatment. The figure above illustrates the actual trial data (red line), 95% CI (blue dashed lines) and the fitted regression line (black line). Patient numbers mean HAQ scores and 95% CI are summarised in **Table 43** and **Table 44** for the two indications respectively.

Table 43: DMARD-IR mean HAQ scores, patient numbers and 95% CI from the DMARD-IR registration and extension trials (including January 2009 follow-up)

	DMARD-IR Jan 2009 follow-up			
Week	**Patient numbers**	**Mean HAQ score**	**95% CI**	
24	873	0.9921	0.948	1.036396
36	792	0.9717	0.922896	1.0207
48	774	0.9272	0.878592	0.975612
60	768	0.9252	0.876788	0.973612
72	753	0.9082	0.858416	0.957788
84	751	0.8961	0.846904	0.945296
96	743	0.8762	0.82818	0.92422
108	705	0.8732	0.82224	0.923964
120	590	0.8382	0.782732	0.893472
132	445	0.7939	0.731768	0.856032
144	295	0.8117	0.73232	0.89108

156	189	0.8036	0.700896	0.906304
168	75	0.9033	0.735524	1.071272
180	7	0.7143	0.18314	1.24546

As seen in the figure and table above there is strong evidence that HAQ score has a negative slope while patients receive tocilizumab treatment in the DMARD-IR indication. There was no censoring done in the analysis. All patients remaining on treatment in the extension study at every available time point were included. The mean HAQ uniformly declines from week 24 through week 132 and the mean score at week 156 is smaller than the mean score at week 132. Since these data are the latest extract from an ongoing extension study, the number of observations late in the series (week 168 and week 180) has far small number of observations which introduce substantial uncertainty into the means estimated at those time points. It should be noted that the overall trendline described in figure 37 above is within the 95% confidence interval of the estimated mean at that time.

A separate completer analysis, consisting of the 189 patients who completed the study to week 156 was conducted and also showed a decline in HAQ. This suggests that the decline in HAQ was not likely to be a product of patient dropout.

All patient observations (including observations at week 180) were utilised to inform the mixed model described below. However due to the uncertainty in the tail of the data, the estimated slope was only applied in the model up to 3 years (week 156) after treatment initiation. This is because there is clear uncertainty as to the actual trend of the slope beyond week 156. No extrapolation is done beyond the period adequate data are available. After this period (week > 156), for the remaining time that a patient may be on tocilizumab treatment, the slope is ‘increased’ to zero – parity to anti-TNF inhibitors.

Figure 38: Mean HAQ score over time for patients in the TNF-IR trial

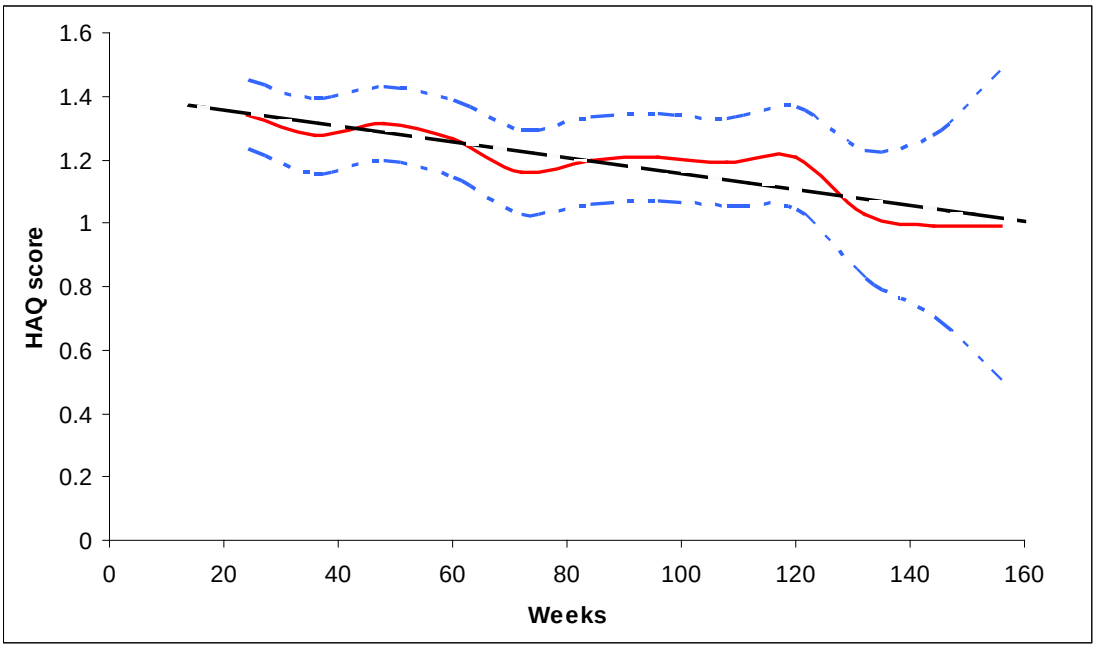


Table 44: TNF-IR mean HAQ scores, patient numbers and 95%CI from the TNF-IR registration and extension trial (including January 2009 follow-up)

	TNF-IR Jan 2009 follow-up			
Week	**Patient numbers**	**Mean HAQ score**	**95% CI**	
24	146	1.343	1.232064	1.45374
36	137	1.2746	1.155628	1.393768
48	132	1.3131	1.198244	1.427956
60	123	1.2663	1.142232	1.390172
72	118	1.16	1.027112	1.292692
84	113	1.1974	1.06216	1.33264
96	106	1.207	1.068232	1.345964
108	106	1.1922	1.053824	1.330772
120	77	1.207	1.044908	1.369092
132	49	1.0281	0.828376	1.227628
144	26	0.9904	0.702476	1.278324
156	13	0.9904	0.501576	1.479224

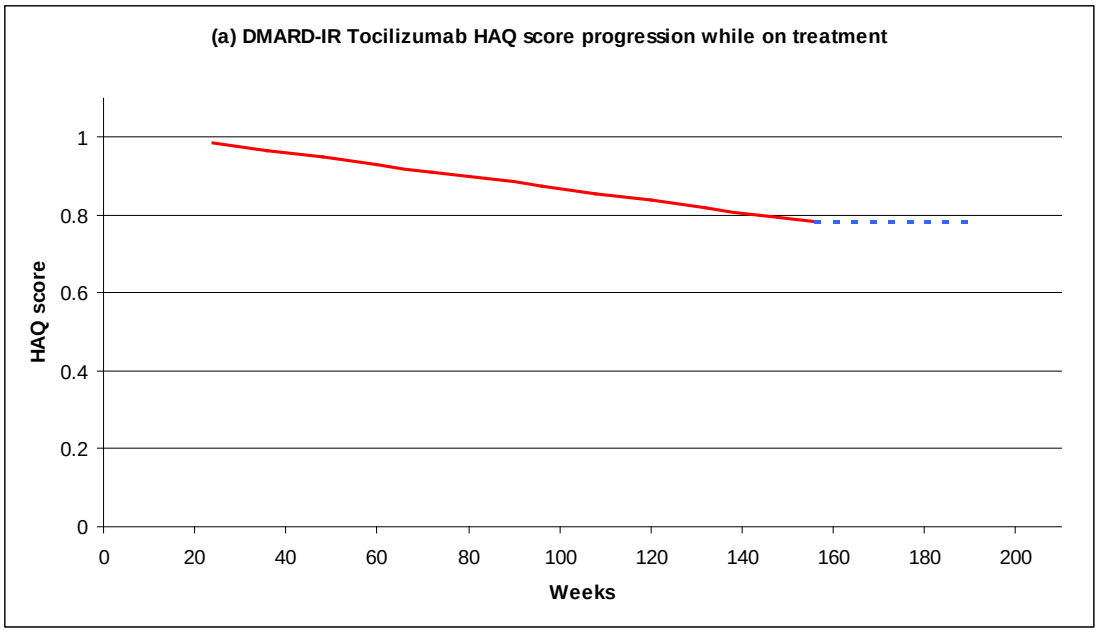
The negative slope of mean HAQ scores can also been observed in patients in the TNF-IR indication. The patient numbers are lower than in the DMARD-IR indication because only responding patients in the RADIATE trial (and its extension) are included. Nevertheless there is strong evidence to conclude that the HAQ slope is negative for the length of the follow-up data available. For the same reasons, due to potential uncertainty as in the DMARD-IR indication, the negative slope derived from the mixed model is only applied for a limited period after treatment initiation (2.5 years).

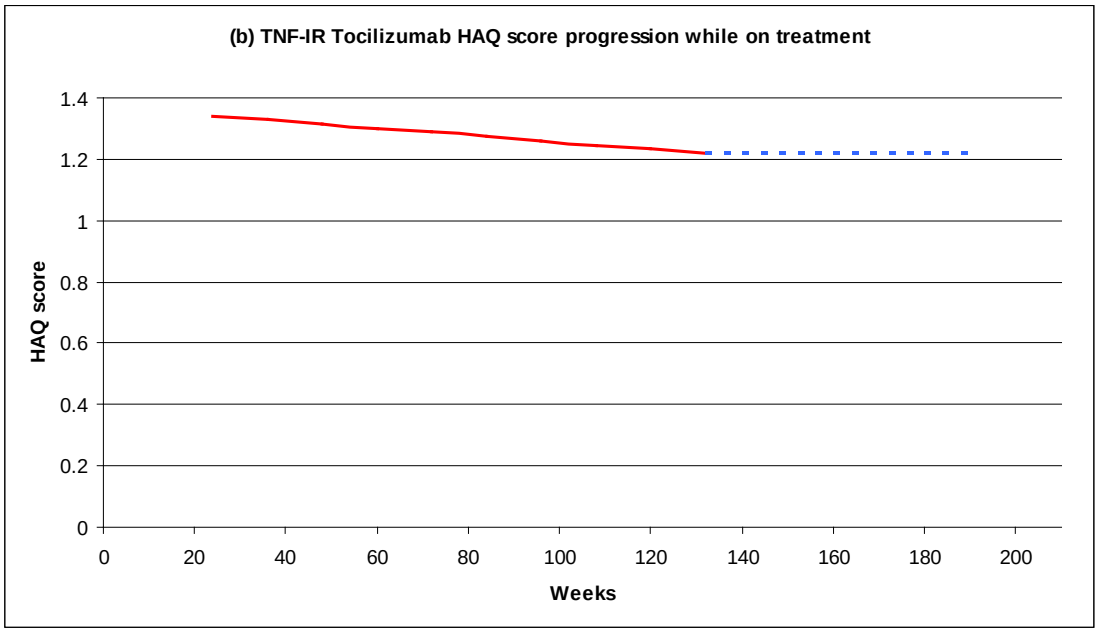
The actual estimates of the slope of HAQ change were made from patient level mixed regression models of trial data from both the DMARD IR and TNF IR trials. Separate models were estimated for DMARD-IR and TNF-IR patients because of significant differences in their baseline clinical status. The mixed model used patient as a random effect in order to control for correlation over time in individual patient HAQ scores. The estimated slope derived by the DMARD-IR HAQ progression model was -0.00011 per day (p-value < 0.0001). As the model uses a 180 day cycle this slope was multiplied by 180 to give the estimated HAQ slope progression of -0.0198.

The estimated slope derived by the TNF-IR HAQ progression model was -0.00007 per day (p-value = 0.0211). Again this value was multiplied by 180 to give the estimated slope per 180 day cycle. The resulting tocilizumab TNF-IR slope was -0.0126.

The above rates of HAQ progression for responding patients derived from the tocilizumab trial data have been utilised in the economic model **only** for the period that Roche has follow up data in both indications. The assumed tocilizumab HAQ slope after that point has been assumed to be the same as other bDMARDs and is equal to 0.0000 (no deterioration-no improvement) This is consistent with the HAQ progression assumption utilised by NICE in the appraisal of TNF inhibitors. A schematic representation of the utilised HAQ progression whilst on treatment can be seen in the figure below (**Figure 39a** and **Figure 39**b).

Figure 39: Schematic representation of the tocilizumab HAQ progression while on treatment within follow-up period (solid line) and after follow-up period (dashed line) derived from the pooled DMARD-IR analysis (a) and the RADIATE trial analysis (b)

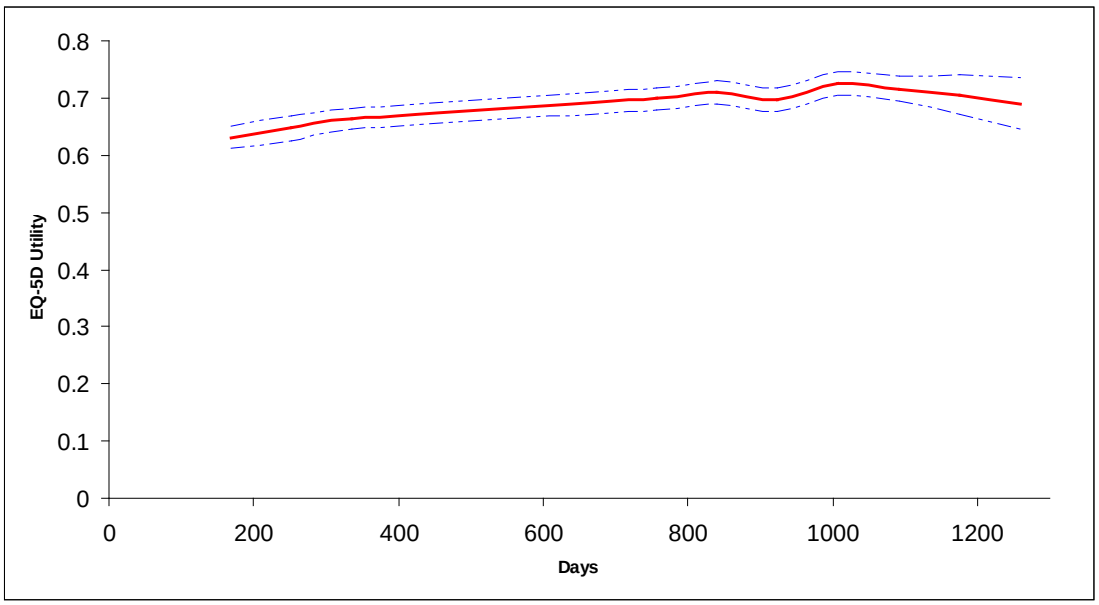




Validation of improving utility whilst on treatment

The assumption of a negative HAQ slope and subsequent improving utility score for the duration of the trial follow-up can be validated when observing the EQ-5D data collected directly from the phase III tocilizumab trials. This allows a unique opportunity to validate this key assumption within the economic model. The EQ-5D data was transformed into utility scores using the UK tariffs from Dolan et al[67].

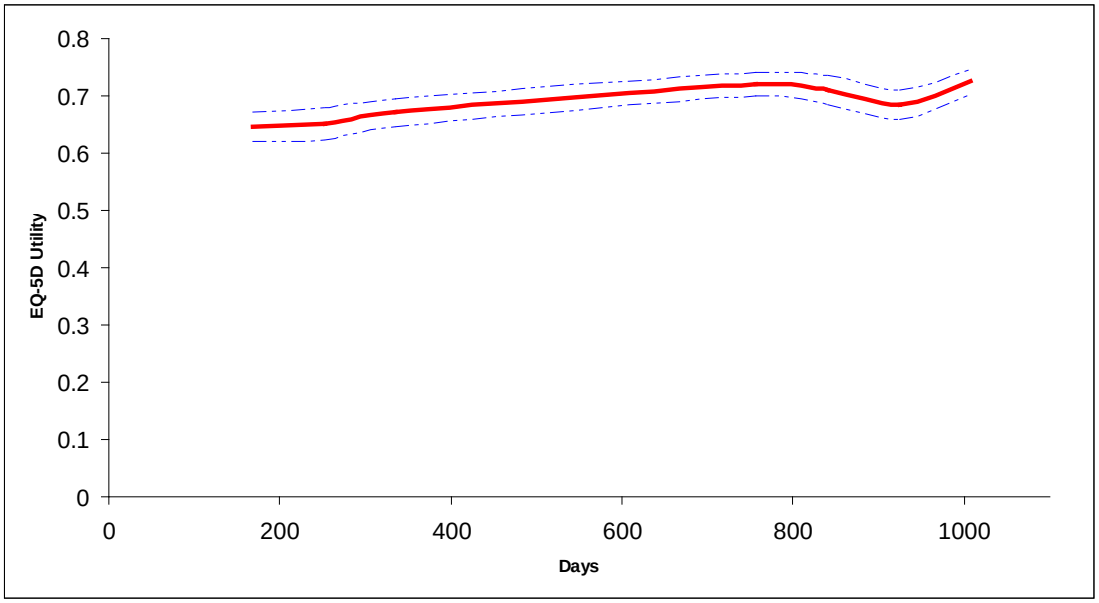
Figure 40: EQ-5D utility over time for patients originally on study WA17822 (OPTION*). The red line denotes trial EQ-5D data; Blue dashed lines denote +/- SE



*EQ-5D data available for responding patients in OPTION and extension trials

Day	168	252	336	756	840	924	1008	1092	1176	1260
Nr of Patients	193	167	167	152	151	140	102	81	44	6

Figure 41:
EQ-5D utility over time for patients originally on study WA17823 (LITHE*). The red line denotes trial EQ-5D data; Blue dashed lines denote +/- SE



*1 year EQ-5D data available for responding patients in LITHE

Day	168	252	336	756	840	924	1008
Nr of Patients	97	86	88	93	96	95	97

As the figures above illustrate, there is still a positive slope post 6 months after treatment initiation, consistent with the negative HAQ slope included within the model. EQ-5D data was only collected in the OPTION and LITHE studies.

In summary, to estimate long term HAQ progression for responding patients, the Roche tocilizumab economic model utilises the available clinical trial data for as long as such data are available. No extrapolation of this parameter is made to time periods beyond the data. Immediately after clinical trial data are unavailable the conclusion reached in NICE Guidance TA 130 on TNF alpha inhibitors, that HAQ change is zero while on treatment with TNF alpha inhibitors, is applied to tocilizumab patients. When objectively evaluating the previous data sources used to inform long term HAQ progression in the TNF, rituximab and abatacept appraisals (see appendix 5)

Roche considers its multiple phase III trial HAQ change data an improvement in the quality of the estimation of this crucial parameter and consistent with an evidence based approach.

- **A separate list of all assumptions and a justification for each assumption.**

Mortality risk

A time-dependent transition probability linked to a life table determines the transition to death. The life table is populated by data from the UK Government Actuary's department (GAD 2007).

The standard probability of death from the life table is adjusted for the disability of RA patients. The adjustment consists of an RA risk multiplier related to each simulated individual's HAQ score at any cycle. Wolfe and colleagues (1994) studied the relationship between HAQ score and early mortality and concluded on a relative risk of 1.33 (CI 1.099 – 1.61). The formula for the mortality risk adjustment (1.33^{HAQ}) is derived from Barton et al. (2004)[68].

Rebound effect

Little evidence exists on the long-term sustained benefit of treatment after patients withdraw due to lack of efficacy. Evidence from etanercept suggests that a "rebound" occurs when therapy is withdrawn[69]. Based on this data, HAQ worsening, equal to the initial HAQ improvement (see section 0), has been assumed to occur immediately at the point of withdrawal for all treatments. The deterioration in an individual's condition is modelled by an increase in HAQ score (rebound effect).

The base case analysis assumes 100% rebound/loss of the initial benefit. Sensitivity analysis applies a 50% rebound effect.

Gold and Ciclosporin efficacy

As there were no published results for gold and ciclosporin efficacy in this patient group, it is assumed the response rates of these therapies are equivalent to MTX (palliative care) and was considered reasonable by expert clinical opinion.

HAQ long-term progression following observed tocilizumab trial data

All tocilizumab registration and extension studies are ongoing. This means that the HAQ progression, whilst on treatment data, is restricted to 3 years (DMARD-IR) and 2.5 years (TNF-IR) after treatment initiation. Due to the lack of data it has been assumed that the long-term HAQ progression, whilst on tocilizumab treatment, is the same with the other biological DMARDs in the period following the trial data. The same assumption has been applied in both the DMARD-IR and TNF-IR indication analysis.

Withdrawal from treatment rate

As explained in 7.2.1.2.

7.2.6.2 Why was this particular type of model used?

The model used was a Markov model using micro-simulation, operating at a patient level. By using micro-simulation of 10,000 hypothetical RA patients, patient history is

being kept in memory and cost and utility values are assigned to each individual at each cycle.

The particular type of model was utilised in order to 'track' the health benefits that individual patients will exhibit while they go through the different treatment options in the model. There are an infinite number of individual pathways and the model ISM is attempting to capture enough of these in order to extract robust results and draw comprehensive findings.

7.2.6.3 What was the justification for the chosen structure? How was the course of the disease/condition represented? Please state why any possible other structures were rejected.

The structure model adopted has been widely used in previous RA NICE technology appraisals. The course of the disease has been represented with the HAQ scores; a surrogate health outcome for utility measurements. The chosen structure of the model effectively captures the progression of HAQ scores for each individual patient in the microsimulation process. ACR response rates were used as a measurement of response to treatment as these are readily available from the tocilizumab registration trials as well as for the RCTs of the other therapies in the treatment sequences. Alternative measures of response such as DAS are not commonly reported for other treatments within the sequence and as such a robust indirect analysis of efficacy would not be possible.

7.2.6.4 What were the sources of information used to develop and inform the structure of the model?

See above – 7.2.6.1

7.2.6.5 Does the model structure reflect all essential features of the condition that are relevant to the decision problem? If not, why not?

The model captures the progression of disease severity by modelling HAQ score over time. Secondly, the impact of response and non-response to treatment is included within the model structure, including the relative efficacy of subsequent treatments. Increased risk of mortality experienced by RA patients is included along with the recognised rebound effect experienced upon treatment failure within this disease area. The time horizon of the model captures the long term chronic nature of this condition.

7.2.6.6 For discrete time models, what was the model's cycle length, and why was this length chosen? Does this length reflect a minimum time over which the pathology or symptoms of a disease could differ? If not, why not?

The model cycle length was 6 months which is consistent with the time period to assess drug efficacy (ACR response rate) in all randomised control trials utilised in the economic evaluation.

7.2.6.7 Was a half-cycle correction used in the model? If not, why not?

Half-cycle correction was used in the economic model.

7.2.6.8 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer-term difference in effectiveness between the technology and its comparator?

Long term effectiveness is measured in the model via the HAQ progression assumption. The HAQ progression of tocilizumab in both the DMARD-IR and TNF-IR indications has been taken directly from the trial data for the period data are available (3.0 years and 2.5 years respectively). It has been assumed that the HAQ change for patients on treatment with tocilizumab is equal to zero after the period data are available. This is consistent with the most recent NICE assessments of TNF-alpha inhibitors.

b) Non-model-based economic evaluations

7.2.6.9 Was the evaluation based on patient-level economic data from a clinical trial or trials?

Not Applicable.

7.2.6.10 Provide details of the clinical trial, including the rationale for its selection.

Not Applicable.

7.2.6.11 Were data complete for all patients included in the trial? If not, what were the methods employed for dealing with missing data for costs and health outcomes?

Not Applicable.

7.2.6.12 Were all relevant economic data collected for all patients in the trial? If some data (for example, resource-use or health-related utility data) were collected for a subgroup of patients in the trial, was this subgroup prespecified and how was it identified? How do the baseline characteristics and effectiveness results of the subgroup differ from those of the full trial population? How were the data extrapolated to a full trial sample?

Not Applicable.

7.2.6.13 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about any longer-term differences in effectiveness between the technology and its comparator?

Not Applicable.

7.2.7 Clinical evidence

7.2.7.1 How was the baseline risk of disease progression estimated? Also state which treatment strategy represents the baseline.

The comparator sequence HAQ progression represents the baseline risk of disease progression. This is based on the various HAQ progression assumptions for each treatment within the sequence (see Table 42 above).

7.2.7.2 How were the relative risks of disease progression estimated?

No relative risks of disease progression were estimated.

7.2.7.3 Were intermediate outcome measures linked to final outcomes (such as patient survival and quality-adjusted life years [QALYs])? If so, how was this

relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

The patient's HAQ score over time represented an intermediate outcome within the model and was linked to the final outcome of quality adjusted life years by means of applying a mapping equation. In the base case the methodology has been derived by using data from the tocilizumab trials. Further details on the methodology utilised to derive the mechanism of converting HAQ scores to utility are given in 7.2.8.3.

The derived mechanism to map QALYs from a disease severity measure (HAQ score) is incorporated in the model. The underlining basis of this calculation is that we accept HAQ score as an indication of the severity of the condition and therefore, it can be claimed to be reliable to link it with QALY values. It should be noted that this is a standard practice in most RA published models to date and has been endorsed by NICE in the appraisal of the anti-TNFs, rituximab and abatacept in RA.

The model improves upon previous mapping techniques by utilising the EQ-5D instrument direct from the relevant phase III studies.

7.2.7.4 Were the health effects or adverse effects associated with the technology included in the economic evaluation? If not, would their inclusion increase or decrease the estimated cost effectiveness of this technology?

Adverse events observed in the trials were not included in the economic evaluation as the ones that were associated with tocilizumab treatment are assumed to generate an insignificant burden in the quality of life of the patients. In addition the treatment of the adverse events observed is unlikely to utilise a significant amount of medical resources or costs to the NHS. Adverse events have not previously been considered in NICE technology appraisals of RA for these reasons. However additive monitoring requirements for safety reasons have been included.

7.2.7.5 Was expert opinion used to estimate any clinical parameters? If so, how were the experts identified, to which variables did this apply, and what was the method of elicitation used?

No clinical expert opinion was utilised to estimate clinical variables in the model

7.2.7.6 What remaining assumptions regarding clinical evidence were made? Why are they considered to be reasonable?

It has been assumed that the tDMARDs within the model have efficacy (ACR response rates) equal to MTX.

It was assumed that the long-term HAQ deterioration rate when patients are in palliative care is equal to 0.06 per annum (NICE TA130; 2007).

7.2.8 Measurement and valuation of health effects

7.2.8.1 If health effects were not expressed using QALYs, what health outcome measure was used and what was the justification for this approach?

Health outcomes were expressed in QALYs.

7.2.8.2 Which health effects were measured and valued? Health effects include both those that have a positive impact and those with a negative impact, such as adverse events.

Patient's disease severity was measured. This was measured with the HAQ. The baseline HAQ of the population and the HAQ drop relative to the ACR response category were taken directly from the pooled analysis for the DMARD-IR indication and the RADIATE clinical trial for the TNF-IR population. HAQ for responding patients whilst on treatment was then taken from the literature for the tDMARDs and previous assumptions utilised by NICE for the anti-TNFs and rituximab (listed above in section 7.2.6.1). HAQ progression whilst on tocilizumab treatment was taken directly from the observed long-term follow-up data availability from the tocilizumab registration trials. At the end of follow-up the same assumptions applied to the other biologic DMARDs were applied to tocilizumab.

7.2.8.3 How were health effects measured and valued? Consideration should be given to all of the following:

- State whether the EQ-5D was used to measure HRQL or provide a description of the instrument/s used.

EQ-5D scores from tocilizumab trial data were mapped to HAQ scores using a linear regression model (described in section below). The mapping equation was then used to convert HAQ scores to EQ-5D scores during each model cycle. Previous assessments of RA biologic products reviewed by NICE have used this technique of mapping HAQ to

a utility measure. The model we submit is the first to use EQ-5D as the underlying utility measure.

- Provide details of the population in which health effects were measured. Include information on recruitment of sample, sample size, patient characteristics and response rates.

The population in which health effects were measured was the population of the registration trials as well as the long-term extension studies (WA18696 and WA18695) of tocilizumab (see section 6.3.2).

- Were the data collected as part of a RCT? Refer to section 5.3 as necessary and provide details of respondents.

Both HAQ and EQ-5D data was collected during the registration RCTs and subsequent extension study for both indications. Consequently the HAQ to utility mapping was based directly on the tocilizumab trials and utilising the reference case EQ-5D. Roche considers this a significant improvement in the evidence base to inform the mapping of HAQ to utility when compared to those mapping methods previously used in RA NICE appraisals.

- How were health effects valued? If taken from the published literature, state the source and describe how and why these values were selected. What other values could have been used instead?

Health effects were valued using the utility scores derived from the EQ-5D. The UK EQ-5D utility data was derived by mapping the EQ-5D to TTO coefficients using the University of York tariff (Dolan et al. 1995).

- Was a mapping mechanism (or 'cross-walk') generated to estimate health-related utilities of patients in the trials? Provide details of the rationale for the analysis, the instruments used, the sample from which the data were derived and the statistical properties of the mapping mechanism.

A mechanism of mapping utility from patient HAQ score is utilised within the model. This technique is similar to previously published cost-utility studies and reimbursement submissions of biologic treatments in RA (Bansback et al. 2005, Brennan et al. 2004). The method utilised within this submission attempts to improve upon the existing

evidence and methods utilised in previous RA appraisals by firstly utilising the patient level data directly from the tocilizumab's registration clinical trials to inform the estimate. Secondly HAQ is mapped directly to the EQ-5D to derive utility scores as both instruments were collected in the phase III studies. This avoids the use of non-reference case instruments such as the SF-36 or HUI-3, as relied upon by previous NICE RA appraisals. Finally both a linear and non-linear model is estimated with a non-linear model more intuitively and accurately estimating the relationship between HAQ and utility.

The mapping equation used in the previous RA appraisals was based on a regression analysis of pooled adalimumab trial data (n=1970) reported at ACR in 2002 (Boggs et al. 2002[70]).

The equation used in the cost effectiveness analyses was

Equation 1 (existing NICE mapping):

HUI3 = 0.76 - 0.28 * HAQ score + 0.05 (if female).

Boggs reported that the above model was not optimal and that models which included non-linear terms had superior fit;

"The basic estimated cross-sectional model was: HUI3=0.76-0.28*HAQ+0.05*FEMALE, ($p<0.0001$ for each regressor, Adj. $R2=0.49$). However, the relationship between HUI3 and HAQ appears to be nonlinear: coefficients for HAQ-squared and HAQ-cubed were significant ($p=0.013$ and $p=0.003$, respectively) when added to the regression."

However, the coefficients for these non-linear specifications were not reported and have not been used in subsequent cost effectiveness analyses.

EQ-5D and HAQ data were available from two tocilizumab trials (OPTION and LITHE, N=1800). HAQ scores were regressed on EQ-5D utility data using a linear mixed model. All available observations from these trials (treated and comparator groups) were included in the estimations. LITHE results extended through year 1 and OPTION results extended through month 6. The significance of coefficients for HAQ and the square of HAQ were tested and the fit of strictly linear and non-linear models were compared. EQ-5D data was not available from the RADIATE study and therefore a TNF-IR specific mapping mechanism could not be derived. It has been assumed that the mapping of HAQ to utility is independent of indication.

Results showed that a linear model generated coefficient estimates similar to those reported by Boggs:

Equation 4 (tocilizumab pooled trial – linear):

EQ5D = 0.89 – 0.28 * HAQ
(p-value < 0.0001)

Consistent with Boggs, inclusion of a model term for the square of the HAQ score resulted in an improved fit and a significant coefficient for the non-linear term.

Equation 5 (tocilizumab pooled trial – non-linear):

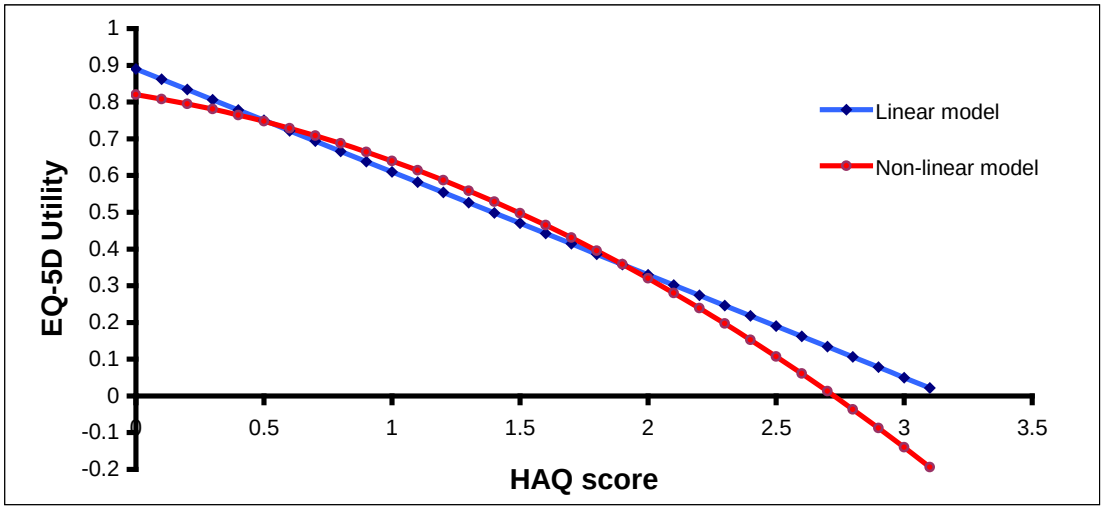
$$EQ5D = 0.82 - 0.11*HAQ - 0.07 * HAQ^2$$
(p-value < 0.0001; for both coefficients)

The mapped utility values from the two models differ (Figure 42). This suggests that results of cost effectiveness analyses will differ as a function of the mapping equation used.

From the mixed model output report the log likelihood chi square for the model with the linear and squared term is 2462.0 (non-linear) while the chi square for the bivariate model (linear) is 2141.9. This yields a difference of 320.1. The p value for chi square distributed variable with 1 degree of freedom [chidist (320.1,1)] is 1.38*e-71. This strongly suggests that the model with the squared term model has a better 'fit' and hence was selected to inform the basecase model.

An additional analysis that included age as a covariate in the non-linear model was performed. The coefficient estimates were found to be essentially unchanged. This suggests that there is little correlation between the variables. Assuming that age is entered into the model as years, the coefficient for age is .0008 which means that 1 year increase in age is projected to change the HAQ by 8/10,000. The 20 year lifespan of a patient in the model is then projected to produce a .0160 change in HAQ. Therefore the model used in the base-case model does not include age as covariate.

Figure 42: Tocilizumab HAQ score and EQ-5D mapping



The base-case analysis reflects recommendations by NICE to use EQ-5D utility scores where available. Moreover, it adopts the suggestion by Boggs and colleagues that a non-linear model produces a better fit. This assumption by Boggs was subsequently confirmed by the analysis of the tocilizumab trial data.

In some cases when patients progress to very high HAQ score levels the model can result in negative QALYs. This indicates that the patient's condition is rated to be worse than death. In the base case analysis, the model allows this assumption. Sensitivity analysis evaluated the impact of not permitting negative utility values and replacing these with a value of zero.

- Were health states directly valued? If so, provide details of the rationale for the analysis, the HRQL measures that were valued, the population who produced the values and full details of the methods used. Explain the rationale for the analysis and the choice of instruments used.

The HAQ scores derived from the trials were used as a surrogate endpoint to calculate utility measurements.

7.2.8.4 Were any other generic or condition-specific preference based measures used in the clinical trials? Provide a description of the data below. The results should be considered in a sensitivity analysis (see Section 6.2.11).

Consistent with most phase III RA trials a large variety of physician and patient reported instruments were collected. For a full list of generic or condition-specific preference based measures used in the trials see section **6.2.11**. HAQ has been used to evaluate utility values in all the previous RA NICE appraisals and it was therefore chosen as the health measure on which this economic analysis was based.

7.2.8.5 Were any health effects excluded from the analysis? If so, why were they excluded?

See section **7.2.7.4**.

7.2.9 Resource identification, measurement and valuation

7.2.9.1 What resources were included in the evaluation? (The list should be comprehensive and as disaggregated as possible.)

The table below summarises the resource utilisation and costs for all the treatments in the model. The same costs were applied in the analysis in both indications.

Table 45: Unit costs of resources used in the valuation

Treatment	Average acquisition cost per year	Description	Reference
Tocilizumab	£9,295	8mg/kg; 70kg patient; 13 infusion per year	Tocilizumab SmPC; BNF 56
Rituximab	£4,890	1000 mg by IV infusion followed by a second 1000 mg IV infusion two weeks later; repeat every ~9 mos (5 year average)	Rituximab SmPC; BNF 56
Etanercept	£9,295	2 times 25mg; every week	Etanercept SmPC; BNF 56
Leflunomide	£472	100mg days 1,2 and 3, 15mg per day thereafter	Kremer et al. 2002; BNF 56
Gold (Myocrisin)	£200	30mg every 3 weeks	ACR Guidelines For The Management Of Rheumatoid Arthritis: 2002 Update; BNF 56
Ciclosporin (Neoral)	£1,735	225mg every day	ACR Guidelines For The Management Of Rheumatoid Arthritis: 2002 Update; BNF 56
Methotrexate	£37	15mg; every week	ACR Guidelines For The Management Of Rheumatoid Arthritis: 2002 Update; BNF 56
Palliative Care (MTX)	£37	Same as MTX	ACR Guidelines For The Management Of Rheumatoid Arthritis: 2002 Update; BNF 56
Infliximab	£8,812*	3mg/kg at weeks 0, 2 and 6, every 8 weeks thereafter (4 year average)	Infliximab SmPC; BNF 56
Adalimumab	£9,857	40mg every other week	Adalimumab SmPC; BNF 56

*minimum dosage of infliximab. Average price of infliximab ranges from £5,875 to £11,749 based on 2-4 vials used per patient for an average 7 administrations (NICE costing template TA130; 2008).

Table 46: Administration and monitoring cost of treatments

Treatment	Average administration/monitoring cost per year	Description	Reference
Tocilizumab	£1,843	13 infusions per year costing £142 each; Infusion costs are assumed to include routine monitoring.	Used in BRAM model (inflated from the 2004 £124/administration to 2008 value - £142 per IV infusion. Also utilised in Abatacept appraisal
Rituximab	£536	3.78 infusion per year costing £142 each; Infusion costs are assumed to include routine monitoring	Used in BRAM model (inflated from the 2004 £124/administration to 2008 value - £142 per IV infusion
Etanercept	£271	104 injections per year; Assumed 10% of subcutaneous injections performed by a district nurse; Refer to appendix 7 for monitoring assumptions	Curtis et al.[71] 2008; Unit costs of Health and Social Care (PPSRU 2008). Refer to appendix 7 for monitoring assumptions
	£1,268		
Leflunomide	Oral therapy		
	£3,389	Refer to appendix 7 for monitoring assumptions	
Gold	£313	Injected by an inpatient nurse every 3 weeks	Curtis et al. 2008; Unit costs of Health and Social Care (PPSRU 2008). Refer to appendix 7 for monitoring assumptions
	£6,528		
Ciclosporin	Oral therapy		
	£3,728	Refer to appendix 7 for monitoring assumptions	
Methotrexate in combination		Oral therapy	
	Monitoring excluded to avoid double-counting		
Palliative Care (MTX)	Oral therapy		
	£1,896	Refer to appendix 7 for monitoring assumptions	Assumption
Infliximab	£992	7 infusions per year costing £142 each; Infusion costs are assumed to include pre-medication and monitoring.	Used in BRAM model (inflated from the 2004 £124/administration to 2008 value - £142 per IV infusion
Adalimumab	£68	26 injections per year; Assumed 10% of subcutaneous injections performed by a district nurse; Refer to appendix 7 for monitoring assumptions	Curtis et al. 2008; Unit costs of Health and Social Care (PPSRU 2008)
	£1,268		

An important factor in determining the total treatment cost is the routine monitoring and surveillance of RA patients. Monitoring has been assumed to take place during the administration visit for all IV therapies. The process of monitoring patients, receiving non-IV therapies involves an outpatient visit (OPV) or a general practitioner visit (GPV) and certain examinations and tests such as: full blood count (FBC); erythrocyte sedimentation (ESR); C-reactive protein (CRP); liver function test (LFT); chest X-ray (CXR); urea, electrolytes and creatinine (U&E). Appendix 7 presents the frequency of monitoring visits or examinations that a patient would be subject to for the first 6 months and for subsequent time. The typical resources and associated frequencies assumptions were obtained from NICE TA126.

For etanercept, adalimumab and infliximab we assumed that before treatment, patients would make at least one visit and would have at least one of all the tests / examinations tDMARDs would have the same profile but would not necessarily have a U&E examination at the pre-treatment phase. The assumed average time on treatment for each therapy, was incorporated into the analysis for the calculation of the final monitoring cost. The average time on treatment was derived by taking the average time patients spend in each therapy from the model estimates.

Table 47: Hospital and personnel costs

	Cost	Reference
Personnel costs		
District nurse	£26 per hour	Unit costs of Health and Social Care (PPSRU 2008)
Inpatient nurse	£36 per hour	Unit costs of Health and Social Care (PPSRU 2008)
Hospital costs		
Inpatient stay per day	£284 per day	Unit costs of Health and Social Care (2002 price - inflated to reflect 2008 costs)
Outpatient visit costs	£109 per visit	NHS Reference costs 2006/2007 (Rheumatology Consultant lead follow-up ;FU410)

RA related Inpatient costs

As in TA126 and other NICE appraisals it was assumed that patients often require inpatient care associated with RA in addition to the NHS resources utilised for drug administration and routine patient monitoring. Inpatient costs were calculated using the Norfolk Arthritis Register (NOAR database) as utilised in the previous NICE appraisal of rituximab. As previously stratified, inpatient hospital utilisation was grouped by HAQ band.

The method to incorporate resource utilisation in this analysis follows Kobelt et al[72,73]. Patient HAQ score is grouped into six categories:

1. 0.0< HAQ score < 0.5
2. 0.6 < HAQ score < 1.0
3. 1.1 < HAQ score < 1.5
4. 1.6 < HAQ score < 2.0
5. 2.1 < HAQ score < 2.6
6. 2.6 < HAQ score < 3.0

Each of these categories represents a class of disease severity. Data on mean days in hospital over a 12 month period were applied in the economic evaluation (e.g 1.86 days per annum for patients in HAQ category 5, that is 2.1 < HAQ score < 2.6).

Table 48: Inpatient Visits by HAQ score

HAQ Band at Registration	Patients in band *N*	Patients with inpatient stay		Number of days in hospital in the following 12 months			
		n	%	Mean	Median	IQR	Range
1	326	7	0.02	0.26	0	0-0	0-26
2	800	16	0.02	0.13	0	0-0	0-21
3	386	11	0.03	0.51	0	0-0	0-83
4	229	12	0.05	0.72	0	0-0	0-25
5	127	25	0.13	1.86	0	0-0	0-48
6	148	31	0.21	4.16	0	0-0	0-50

Each HAQ score category is assigned an inpatient cost. (£284 per day) The source for this cost is reported in **Table 47** above. These cost values are multiplied with the utilisation factor corresponding to each HAQ score category. The resulting inpatient resource utilisation values used in the analysis is summarised in the table below:

Table 49: Inpatient resource values by HAQ score

HAQ scores	0<0.5	0.6<1	1.1<1.5	1.6<2.0	2.1<2.6	2.6<3.0
Band	1	2	3	4	5	6
Inpatient cost (£) per cycle	74	37	145	205	528	1,182

7.2.9.2 How were the resources measured?

Drug costs were estimated according to recommended dose from their respective SPCs.

Medical resource utilisation, drug administration and monitoring costs were measured through synthesis of published data sources, including assumptions endorsed in previous NICE appraisals and expert clinical opinion. The reference for these costs and how they were derived can be found above in 7.2.9.1.

7.2.9.3 Were the resources measured using the same source(s) of evidence as the baseline and relative risks of disease progression?

No measurement of medical resource utilisation was included in any of the registration trials of tocilizumab. Therefore resource use was not derived from the respective trials.

7.2.9.4 Were resources used to treat the disease/condition included for all relevant years (including those following the initial treatment period)? Provide details

and a justification for any assumptions that were made (for example, assumptions regarding types of subsequent treatment).

All costs including drug acquisition, drug administration, monitoring and medical resource utilisation were included for all the years that patients stayed in the model. This period in most cases includes the treatment period after the trial period.

7.2.9.5 What source(s) of information were used to value the resources? Were alternative sources of information available? Provide a justification for the preferred source and explain any discrepancies between the alternatives.

Drug acquisition costs were taken from the British National Formulary (BNF 56). Personnel costs were taken from the Unit costs of Health and Social Care 2008 (PPSRU 2008). Outpatient visit and inpatient costs were taken from the NHS reference costs 2006/2007.

7.2.9.6 What is the unit cost (excluding VAT) of the intervention(s) included in the analysis? Does this differ from the (anticipated) acquisition cost reported in section 1? If price discounts are presented in sensitivity analyses provide details of formal agreements regarding the discount including the period over which the discount is agreed and confirmation of national organisations with which the discount has been agreed for the whole of the NHS in England and Wales.

The NHS list price for tocilizumab has not been set. The provisional price which should be used for the purposes of this appraisal is £1.28 per mg or £9,295 per annum.

Tocilizumab will be available in 3 vial sizes. The three vials will be linearly priced.

80 mg vial – £102.1
200 mg vial – £255.4
400 mg vial – £510.7.

This has been calculated by using NICE's historical precedence of assuming that an average UK RA patient weighs 70kg (Barton et al. 2004; NICE TA130 2007; NICE TA141 2007).

Roche acknowledges this could be viewed as a simplification of the likely real world average cost due to the following factors influencing the acquisition cost of tocilizumab:

1. SPC stated minimum dose requirement
2. Wastage
3. Dose modification

However when all these factors are fully accounted for there is actually a very minimal net effect on the assumed acquisition cost of £9,295 per annum, as some of the factors may increase the acquisition cost and some may reduce the acquisition cost. Then impact these 3 factors may have upon the assumed annual cost of £9,295 are described further below:

SPC minimum dose requirement

According to the licence, tocilizumab should be given at the 8mg/kg dose to all patients apart from the patients that weigh less than 60kgs were a minimum dose of 480mg should be administered. The annual average cost is therefore increased by this caveat within the SPC.

Wastage

Tocilizumab comes in three different vial sizes 80mg, 100mg and 200mg and combinations of them will minimise wastage for most patient weights hence the impact of wastage upon cost is limited. As tocilizumab is an IV biologic drug, some wastage is expected for patients whose weight requires them to receive only a part of a vial. For example, a patient weighing 73kg will require 584 mgs at the licensed dose. The full dose can be given by combining three 200mg vials giving a total of 600mg. 16mg will therefore be wasted if no vial sharing is assumed. Consequently the annual average cost will be increased through wastage.

To estimate the impact of wastage an assumption on the distribution of patient weight is required. As the number of UK patients in the tocilizumab phase III trial programme was limited, the EU weight distribution was considered a reasonable proxy to utilise for this exercise. The individual patient weights were taken from the DMARD-IR trials and TNF-IR trial separately and dosages were calculated based on the resulting distributions. These distributions were considered more representative of the expected UK RA patient weight when compared to including the US population within the trials.

Accounting for wasted vials and the 480mg minimum dose the average cost is increased by £616 per annum per patient (in the DMARD-IR indication and £552 pa per patient in the TNF-IR indication).

Dose modification

The 2 factors mentioned above increase the annual cost, however not all patients on average within the phase III studies received 8mg/kg due to missed doses. According to both the DMARD-IR pooled analysis and the TNF-IR RADIATE trial, patients received only 93% of the planned doses. If this is applied to the 13 infusions that an average patient will receive per annum, the average number of infusions received is decreased to 12.1 infusions per annum. Furthermore the SPC permits dose reductions to 4mg/kg in certain circumstances which was not permitted in the phase II studies, therefore in the

real world setting this may reduce the 8mg/kg observed in the phase III trials. Finally some clinicians may consider it appropriate to slightly reduce a dose as opposed to wasting a vial. For example in the 73kg patient example illustrated above, instead of administering the required 584mgs a clinician may administer 580mg which generates no wastage.

Consequently the net impact of accounting for these 3 factors that may influence the real-world dose/cost of tocilizumab is estimated to be minimal. A net effect of **-£78** in the DMARD-IR indication and **-£137** for TNF-IR per annum when compared to a 70kg patient average of £9,295 per annum.

Therefore Roche considers the annual cost assumption of £9,295 to be a reasonable cost assumption after a full evaluation of the influencing factors listed above.

7.2.9.7 Does the technology require additional infrastructure to be put in place? Provide details of data sources used to inform resource estimates and values.

No additional infrastructure would be required for the administration of tocilizumab.

7.2.9.8 Were the resources measured and valued in a manner consistent with the reference case? If not, how and why do the approaches differ?

Yes, the resources were measured and valued in a manner consistent with the reference case.

7.2.9.9 Were resource values indexed to the current price year?

Where costs were not available for the current year, prices and costs were inflated to the 2008 prices using the HCHS “Pay and Prices Index” from the latest Unit Costs of Health and Social Care (PSSRU 2008).

7.2.10 Time preferences

Were costs and health benefits discounted at the rates specified in NICE’s reference case?

Cost and benefits were discounted at the 3.5% per year rate according to NICE guidelines.

7.2.11 Sensitivity analysis

7.2.11.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated including a description of alternative scenarios included in the analysis.

The list of parameters evaluated via both one-way, scenario and probabilistic sensitivity analysis is provided in questions 7.2.11.2 and 7.2.11.3.

7.2.11.2 Which variables were subject to sensitivity analysis? How were they varied and what was the rationale for this?

In order to assess the robustness of the results and explore how sensitive the model is when underlying assumptions are changed, the following scenario analyses were carried out in both indications.

Scenario analysis

1 Negative utility scores are equal to 0

Scenario to assess the model sensitivity around the assumption that quality of life can be worse than death.

2 Withdrawal from treatment after a predefined time period

This scenario assesses the model's sensitivity around the basecase assumption that patients withdraw from treatment subject to a standard probability of withdrawal. Under this scenario, patients withdraw from treatment after a fixed time period as explained in 7.2.1.2, consistent with the previous Roche RA NICE model for rituximab.

3 Infliximab used instead of etanercept (DMARD-IR indication only)

Although infliximab is not considered to be the standard of care, the treatment replaced etanercept in the treatment sequence in order to assess the model's sensitivity around the assumption that etanercept is the standard of care in DMARD-IR patients.

4 Adalimumab used instead of etanercept (DMARD-IR indication only)

Although adalimumab is not considered to be the standard of care, the treatment replaced etanercept in the treatment sequence in order to assess the sensitivity around the assumption that etanercept is the standard of care in DMARD-IR patients.

5 Using cycle-by-cycle ACR efficacy adjustment

This is an option within the model and can be turned off or on by the user. How this option affects the model is explained in 7.2.1.2. For the scenario analysis degradation in ACR response rates is assumed.

6 Using the unadjusted ACR response rates from the MTC

As described in 7.2.6.1 and 6.6. This scenario uses the reported ACR response rates directly from the trials, without modifying these via a MTC.

7 Using the Hurst et al[74]. HAQ-utility mapping equation

The scenario assesses the model's sensitivity around the HAQ-utility mapping model utilised in the base case. In this scenario the Hurst et al. equation is utilised.

The equation derived by Hurst et al. is: QoL=0.862 – 0.327*HAQ

8 Using the Bansback et al. HAQ-utility mapping equation

The equation used by Bansback, based on HUI-3 utilities and lacking a non-linear term, was used as an alternate scenario.

The equation derived by Bansback et al. is: QoL=0.76-0.28*HAQ+0.05*Female

9 Assumed HAQ slope of 0 following ACR response

In this scenario a HAQ slope equal to 0 has been assumed for tocilizumab for all the subsequent cycles following ACR response (Initial HAQ drop).

10 Assumed positive HAQ slope post last trial follow-up

In this scenario a positive HAQ slope of 0.012 per cycle has been assumed for tocilizumab for patients that stay on treatment beyond 3 years (DMARD-IR) and 2.5 years (TNF-IR), the latest follow up in the RCT trials. The positive slope replaces the slope equal to zero assumed for tocilizumab and all other bDMARDS in the base case. The slope of all other bDMARDs has been kept equal to zero in this scenario.

11 Assumed negative HAQ slope post last trial follow-up

In this scenario a positive HAQ slope of the negative observed in the trials HAQ slopes (-0.0198 for DMARD-IR and -0.0144 for TNF-IR) have been assumed for tocilizumab for patients that stay on treatment beyond 3 years (DMARD-IR) and 2.5 years (TNF-IR).

The negative slope replaces the slope equal to zero assumed for tocilizumab and all other bDMARDS in the base case. The slope of all other bDMARDs has been kept equal to zero in this scenario.

12 Additional costs incurred for the monitoring of lipid levels according to tocilizumab's licence

The scenario assumes an incremental cost of £4.20 per test thus £54.6 per year on treatment for the monitoring of patients on tocilizumab. The monitoring of lipids will occur once every time patients have their infusion and monitoring. The cost of lipid testing has been derived from DoH's report on "Vascular Checks: risk assessment and management" (2008).

7.2.11.3 Was probabilistic sensitivity analysis (PSA) undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated; including the derivation and value of 'priors'.

Probabilistic sensitivity analysis was undertaken. The table below summarises the parameters included in the PSA along with their assumed distributions and assumed standard error or range.

Table 50: Parameters and their distributions as tested in PSA

Parameter			Distribution	Parameters
ACR response rates			Dirichlet	Use N=alpha of the one parameter Gamma distribution for each ACR category
Probability of withdrawal	bDMARD		Beta	Alpha = 33.67, Beta= 320.147
	tDMARD		Beta	Alpha= 26.97, Beta= 72.92
Long- term deterioration while on treatment	Tocilizumab DMARD-IR (trial data)		Normal	Mean= -0.0198, SE= 0.00432
	Tocilizumab TNF-IR (trial data)		Normal	Mean= -0.0144, SE= 0.00666
	bDMARD		Normal	Mean= 0, SE = 0.00432
	tDMARD		Triangular	Mode= 0.0225, Min= 0.015, Max=0.03
	Palliative care		Triangular	Mode= 0.03, Min= 0.0225, Max=0.0375
HAQ score response for ACR response category	DMARD-IR	Non responder	Normal	Mean= 0.1357, SE= 0.01679
		ACR20-49	Normal	Mean= 0.44266, SE= 0.01831
		ACR50-69	Normal	Mean= 0.66795, SE= 0.0261
		ACR70+	Normal	Mean= 0.92257, SE= 0.03201
	TNF-IR	Non responder	Normal	Mean= 0.09788, SE= 0.02162
		ACR20-49	Normal	Mean= 0.40455, SE= 0.03412
		ACR50-69	Normal	Mean= 0.6704, SE= 0.05794
		ACR70+	Normal	Mean= 0.94945, SE= 0.06424
Mortality rate for RA patients			LogNormal	Mean= 1.33 (CI 1.099 – 1.61); Trimmed for values >1
Inpatient cost			Gamma	Mean= 284.1, SE= 16.855, beta=1
Administration cost			LogNormal	Mean= 141.7 (CI 99.2 – 184.2)
Monitoring cost first attendance (OPV FA)			LogNormal	Mean= 183 (CI 128.1 – 237.9)
Monitoring cost follow-up (OPV FU)			LogNormal	Mean= 109 (CI 76.3 – 141.7)

* the standard error is derived the same regression model in which the slope was estimated. It is based on all available current data.

A lognormal distribution was fitted to the economic model to reflect uncertainty around monitoring cost parameters. The measure of dispersion for these parameters is unknown. The distribution was fitted to the cost of an outpatient visit, a range of +/- 30% from the mean was assumed to define the 95% confidence interval, and the cost of the first 6 months was sampled independently from the cost on subsequent cycles. All other parameters (GPV, FBC, ESR, CRP, LFT, CXR, U&E) that define the total monitoring cost are assumed to keep the same proportional difference with the cost of the outpatient visit.

7.2.12 Statistical analysis

7.2.12.1 How were rates or probabilities based on intervals transformed into (transition) probabilities?

See section **7.2.1.2** for the transformation of ACR response rates to transition probabilities and the derivation of the withdrawal from treatment probability.

7.2.12.2 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

ACR response rates may vary over time as a patient moves down the treatment sequence. A scenario analysis that looks at a cycle-by-cycle adjustment/degradation of the relative responses of treatment has been performed.

Life tables account for the increasing risk of death over time.

A constant risk of stopping treatment is assumed. No strong evidence to inform or suggest an increasing or decreasing risk is more appropriate.

For the basecase, HAQ progression has 3 discrete time periods for tocilizumab, where the rate of progression is assumed to vary, primarily informed by the clinical trial evidence:

- first 6 months
- trial follow-up period
- post trial follow up

7.2.13 Validity

Describe the measures that have been undertaken in order to validate and check the model.

The economic model was validated by an independent reviewer not involved in the development of the economic model in October 2008. The validation involved four different steps:

1. Source verification (validate the sources of the inputs)
2. Excel programming reference verification (validate the excel file programming)

3. Visual basic application verification (validate the VBA programming)
4. Model results verification (test face validity of the results)

7.3 Results

7.3.1 **Base-case analysis**

7.3.1.1 What were the results of the base-case analysis?

The base-case model results are presented below for the two indications.

DMARD-IR

Table 51: Total average costs and benefits for the two treatment sequences (including and excluding tocilizumab; DMARD-IR-indication)

	Sequence including Tocilizumab	Sequence excluding Tocilizumab
Life years	26.24	25.69
Discounted Life years	16.50	16.29
QALYs	8.946	7.775
Total Direct Medical Cost (£)	100,485	77.231
Total Drug Therapy Cost (£)	97,830	73,718
Incremental Direct Medical Cost (£)	23,253	
Incremental QALYS	1.17	
ICER	**£19,870**	

As illustrated above in **Table 51**, the addition of tocilizumab+MTX in the treatment sequence can be considered a cost effective treatment option in rheumatoid arthritis in the DMARD-IR indication. The treatment sequence that includes the tocilizumab-methotrexate combination generates an incremental 1.17 QALYs. Its addition also generates an incremental direct NHS cost of £23,253 per patient. The resulting incremental cost effectiveness ratio is **£19,870/QALY**.

TNF-IR

Table 52: Total average costs and benefits for the two treatment sequences (including and excluding tocilizumab; TNF-IR indication)

	Sequence including Tocilizumab	Sequence excluding Tocilizumab
Life years in the model	24.10	23.63
Discounted Life years in the model	15.63	15.42
QALYs	6.591	5.381
Total Direct Medical Cost (£)	77,232	50,592
Total Drug Therapy Cost (£)	72,878	45,007
Incremental Direct Medical Cost (£)	26,640	
Incremental QALYS	1.210	
ICER	**£22,003**	

As illustrated above in **Table 52**, the addition of tocilizumab+MTX in the treatment sequence can be considered a cost effective treatment option in rheumatoid arthritis in the TNF-IR indication. The treatment sequence that includes the tocilizumab-methotrexate combination generates an incremental 1.210 QALYs. Its addition also generates an incremental direct NHS cost of £25,640 per patient. The resulting incremental cost effectiveness ratio is **£22,003/QALY**.

As demonstrated above adding tocilizumab-methotrexate combination not only improves quality of life but also is a cost effective treatment option in both its licensed indications.

7.3.2 Subgroup analysis

7.3.2.1 What were the results of the subgroup analysis/analyses if conducted?

No subgroup analysis was undertaken.

7.3.3 Sensitivity analyses

7.3.3.1 What were the main findings of the sensitivity analyses?

DMARD-IR POPULATION

Scenario analysis

The ICERs derived from the scenario analyses in the DMARD-IR indication are summarised below.

Table 53: Scenario analyses and corresponding ICERs in the DMARD-IR indication

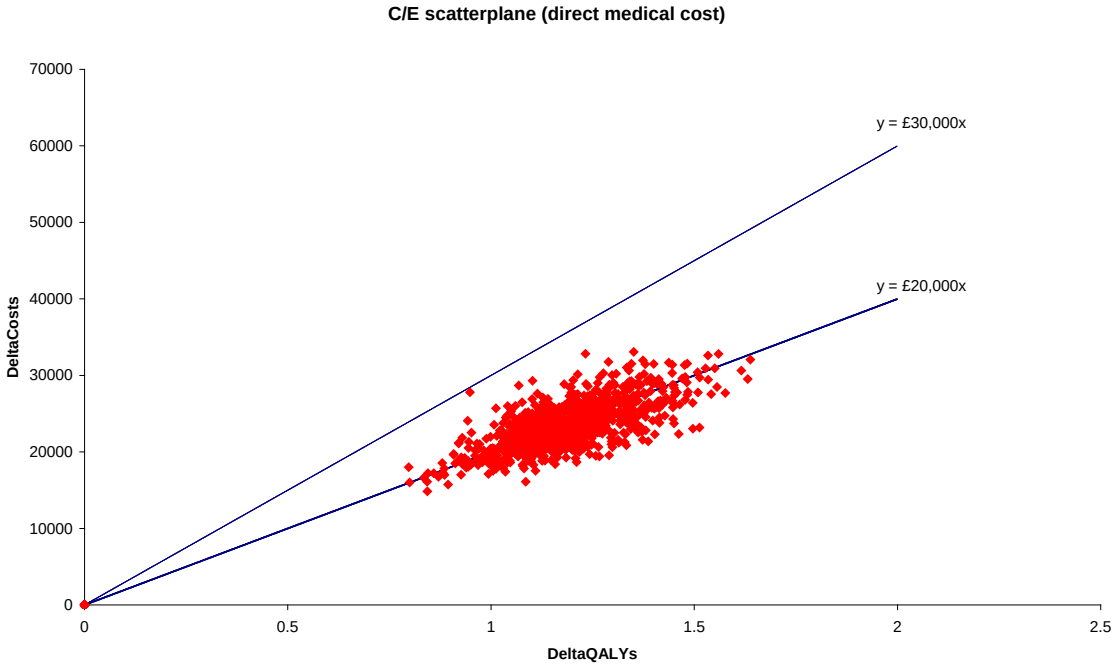
Scenario		Resulting ICER
1	Negative utility scores are equal to 0	£20,214/QALY
2	Withdrawal from treatment after a predefined duration	£15,878/QALY
3	Infliximab used instead of etanercept	£20,433/QALY
4	Adalimumab used instead of etanercept	£19,674/QALY
5	Using cycle-by-cycle adjustment	£19,484/QALY
6	Using unadjusted ACR response rates	£21,111/QALY
7	Using the Hurst et al. HAQ-utility mapping equation	£18,994/QALY
8	Using the Bansback et al. HAQ-utility mapping equation	£21,907/QALY
9	Assumed zero HAQ slope following ACR response	£24,905/QALY
10	Assumed positive HAQ slope for tocilizumab post latest follow up	£23,000/QALY
11	Assumed negative HAQ slope for tocilizumab post latest follow up	£16,507/QALY
12	Additional costs incurred for the monitoring of lipid levels according to tocilizumab's licence	£20,029/QALY

It is demonstrated in the results of the scenario analysis that the base-case ICER in the DMARD-IR indication is robust and in all the examined cases well within the £30,000/QALY threshold.

Probabilistic Sensitivity Analysis

In order to assess the model's sensitivity to simultaneous change of the base-case parameters, PSA was undertaken and the scatter plot of resulting ICERs shown in the figure below for the DMARD-IR indication. The cost-effectiveness plane in the example presented below (assumption: 1,000 patients running individually through the model) shows the distribution of incremental cost per QALY ratios in relation to an assumed willingness to pay (WTP) ceiling ratio of £30,000 per QALY (blue line). This shows that tocilizumab's incremental cost per QALY values always, with a few exceptions, lie below the threshold in the DMARD-IR indication. The cost effectiveness acceptability curve CEAC is also presented (**Figure 44**) showing the likelihood of the tocilizumab containing treatment being cost-effective at different WTP per QALY thresholds.

Figure 43: Scatter plot of cost per QALY for the DMARD-IR treatment sequence including tocilizumab+MTX versus the treatment sequence that does not contain tocilizumab (example: 1,000 Monte Carlo simulations)



56.2% of the estimated ICERs in the PSA are under the £20,000/QALY and 100% of the ICERs fall below a threshold of £30,000/QALY as shown in the figure below.

Figure 44: CEAC for the DMARD-IR treatment sequence including tocilizumab+MTX versus the treatment sequence that does not contain tocilizumab (example: 1,000 Monte Carlo simulations)

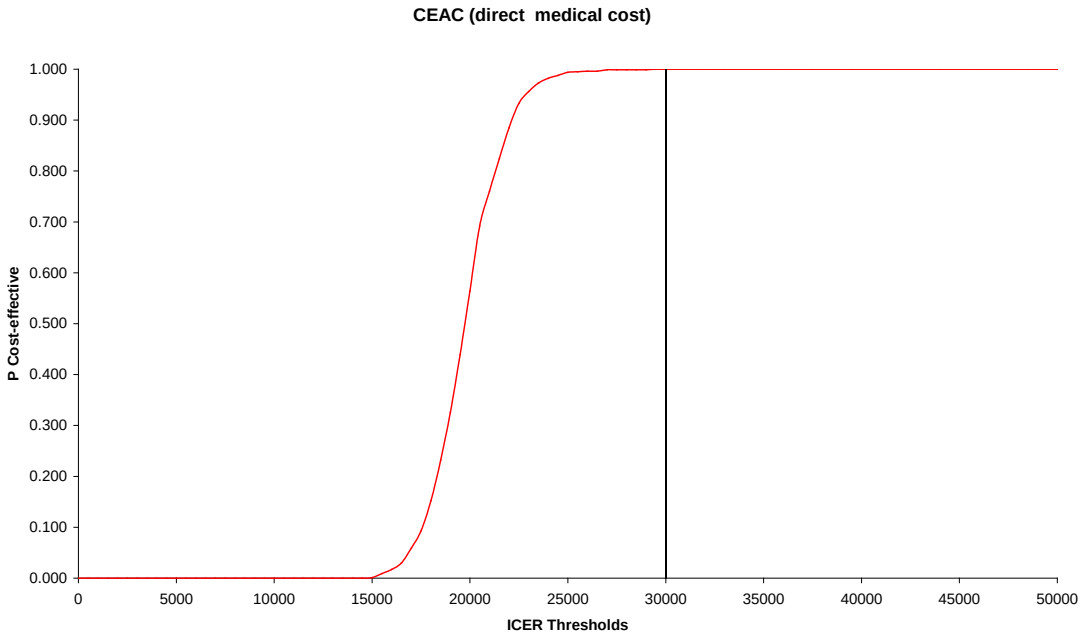


Table 54: Mean probabilistic Cost Effectiveness results for tocilizumab containing sequence versus tocilizumab not-containing sequence (1000 runs); DMARD-IR indication

Cost-utility results	Tocilizumab containing sequence	Tocilizumab not containing sequence	Incremental
Mean QALYs	8.96	7.77	1.19
Mean Total Cost	£101,840	£78,377	£23,462
Cost per QALY Gained (£)			**£19,766**
	Percentage of CE PSA results		
≤ £20,000/QALY	**56.4%**		
≤ £30,000/QALY	**100.0%**		

TNF-IR POPULATION

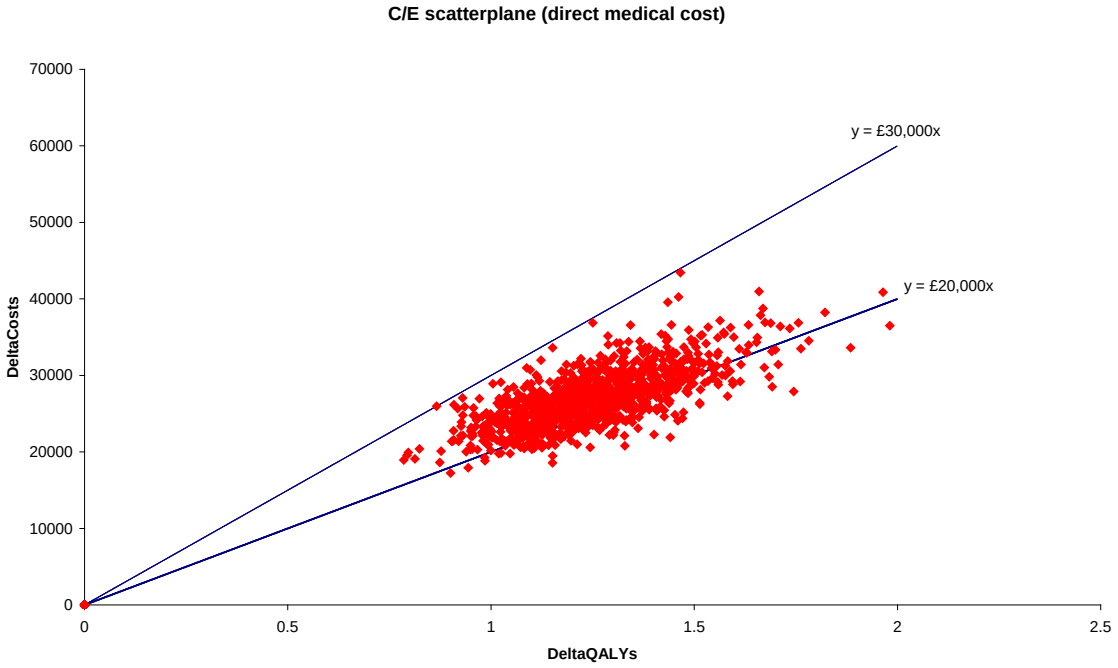
The ICERs derived from the scenario analyses in the TNF-IR indication are summarised below.

Table 55: Scenario analyses and corresponding ICERs in the TNF-IR indication

Scenario		Resulting ICER
1	Negative utility scores are equal to 0	£22,901/QALY
2	Withdrawal from treatment after a predefined duration	£19,185/QALY
5	Using cycle-by-cycle ACR adjustment	£22,609/QALY
6	Using unadjusted ACR response rates	£21,125/QALY
7	Using the Hurst et al. HAQ-utility mapping equation	£23,803/QALY
8	Using the Bansback et al. HAQ-utility mapping equation	£27,435/QALY
9	Assumed zero HAQ slope following ACR response	£24,739/QALY
10	Assumed positive HAQ slope for tocilizumab post latest follow up	£26,112/QALY
11	Assumed negative HAQ slope for tocilizumab post latest follow up	£19,026/QALY
12	Additional costs incurred for the monitoring of lipid levels according to tocilizumab's licence	£22,152/QALY

In order to assess the model's sensitivity to simultaneous change of the base-case parameters, PSA was undertaken and the scatter plot of resulting ICERs shown in the figure below for the TNF-IR indication. This showed that tocilizumab's incremental cost per QALY values always, with a few exceptions, lie below the threshold in the DMARD-IR indication. The cost effectiveness acceptability curve, CEAC, is presented in **Figure 46** showing that the likelihood of the tocilizumab containing treatment is cost-effective at different WTP per QALY thresholds.

Figure 45: Scatter plot of cost per QALY for the TNF-IR treatment sequence including tocilizumab+MTX versus the treatment sequence that does not contain tocilizumab (example: 1,000 Monte Carlo simulations)



Similarly to the DMARD-IR indication, the scenario analysis (**Table 55**) illustrates that the base-case ICER in the TNF-IR indication is robust and in most cases well within the £30,000/QALY threshold. 99.9% of the PSA resulting ICERs are under the £30,000/QALY threshold. 22.4% are under the £20,000 threshold

Figure 46: CEAC for the TNF-IR treatment sequence including tocilizumab+MTX versus the treatment sequence that does not contain tocilizumab (example: 1,000 Monte Carlo simulations)

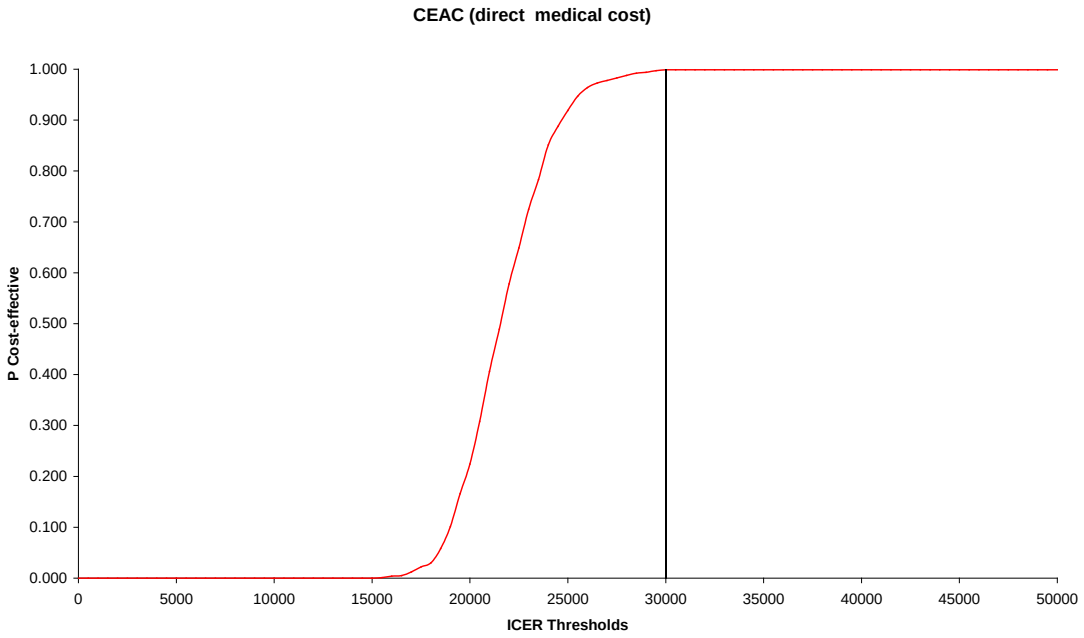


Table 56: Mean probabilistic Cost Effectiveness results for tocilizumab containing sequence versus tocilizumab not-containing sequence (1000 runs); TNF-IR indication

Cost-utility results	Tocilizumab containing sequence	Tocilizumab not containing sequence	Incremental
Mean QALYs	6.62	5.37	1.25
Mean Total Cost	£78,315	£51,368	£26,946
Cost per QALY Gained (£)			**£21,601**
	Percentage of CE PSA results		
≤ £20,000/QALY	**22.4%**		
≤ £30,000/QALY	**100.0%**		

7.3.3.2 What are the key drivers of the cost effectiveness results?

The 2 key drivers of the model identified from the sensitivity analysis are the long-term HAQ slope while on treatment and the HAQ-utility mapping method selected. The ICERs in both indications remain under the £30,000/QALY under most scenarios tested (apart from when the Hawthorn mapping model was utilised).

The cost effectiveness of treating patients with tocilizumab in the DMARD-IR and TNF-IR indications is reinforced by the extensive PSA performed and the resulting uncertainty around the deterministic values.

7.3.4 **Interpretation of economic evidence**

7.3.4.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

To date there have been no published abstracts, conference posters or full manuscripts on the cost effectiveness of adding tocilizumab+MTX in the standard of care treatment sequence. Therefore no comparison can be made between the results presented here and published results.

However the current NICE endorsement of TNF inhibitors within the DMARD-IR indication and associated analysis allows a crude validation of the tocilizumab results. NICE considered that adding a TNF inhibitor to an existing treatment strategy is cost effective in the DMARD-IR setting. Tocilizumab has an identical drug acquisition cost to Etanercept and Adalimumab and ACR response rates appear broadly similar. Therefore when adding tocilizumab to the existing treatment strategy it is reasonable to expect similar cost effectiveness conclusions.

Key differences in the economic evaluations of TNFs compared to tocilizumab that may be expected to affect the ICER, include:

- drug administration costs from an IV infusion
- slightly different ACR 70 response rates
- negative HAQ slope for year 0.5 to 2.5-3.0 years within the model
- non-linear mapping of utilities.

Apart from the addition of drug administration costs, these other differences increase the estimated health gain for tocilizumab, given the observed ACR responses and thus helps to explain why the estimated ICERs are slightly lower than those previously reported for the TNF inhibitors.

7.3.4.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology?

Yes, the economic evaluation is relevant to all groups who could potentially use the technology.

7.3.4.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

Strengths

- Multiple phase III studies. The clinical evidence utilised in the economic modelling is supported by 3 phase III trials in the DMARD-IR indication and 1 within the TNF-IR indication.

- Model structure previously endorsed by NICE. The model structure utilised in the cost effectiveness analysis is very similar to models endorsed by NICE in previous RA appraisals.

- Long-term phase III trial HAQ data. Long-term HAQ progression while on tocilizumab treatment is a key driver of the model. The rates and subsequent slopes have been derived by analysing actual patient data of the phase III and extension studies for as long as possible at the time of submission..

- HAQ-EQ5D mapping. The mapping mechanism has been derived by analysing patient level data from the tocilizumab OPTION and LITHE phase III clinical trials. The non-linear model used in the base-case analysis has been proven to be the best-fitting model, consistent the findings of Boggs et al. Secondly it maps directly to the reference case EQ-5D quality of life instrument.

- Improving HAQ / utility score assumption up to 2.5-3.0 years within the model has been validated by EQ-5D data collected directly in the phase III trial, as recommended by the NICE guide to methods.

- All major model parameters are included within the PSA providing a robust illustration of the uncertainty surrounding the deterministic values of the ICER for tocilizumab.

Weaknesses

- Due to the lack of head-to-head comparison of tocilizumab with other bDMARDs, ACR response rates had to be informed via indirect analysis utilising the NICE recommended method of an MTC.

7.3.4.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

- A comparative RCT that would compare ACR rates, probability of withdrawal and long tem EQ-5D/utility progression while on treatment for all biologic DMARDS in RA.
-
- A longer follow-up of the HAQ progression data from the ongoing tocilizumab extension studies toreduce uncertainty around longer term HAQ progression..
- A UK specific HAQ-EQ5D mapping estimation
- A resource utilisation study capturing the resource requirements and consequent health care costs of RA patients aside from routine monitoring and administration, improving upon the existing NOAR data.
- Resource utilisation study of administering infusible RA agents including tocilizumab in a real-world UK clinical setting. This would help understand the actual marginal costs involved in administering tocilizumab in greater detail.
- Real world UK data on the actual dose administered to tocilizumab patients to inform the drug acquisition cost estimates.
- A tocilizumab specific estimate of the mean treatment duration for responding patients.

8 Assessment of factors relevant to the NHS and other parties

8.1 What is the estimated annual budget impact for the NHS in England and Wales?

Assuming a staggered additional uptake of 5%, 10%, and 15% per annum over the next three years respectively the estimated budget impact of the addition of tocilizumab to the current treatment sequence for the treatment of moderate to severe RA patients is £16,381,923 in the 1st year, £45,159.052 in the 2nd year and £85,284,974 in the 3rd year. All the above figures include administration costs and VAT.

The budget impact estimates presented above represent the maximum possible cost to the NHS during the first three years following positive NICE guidance in both the DMARD-IR and TNF-IR indications.

8.2 What number of patients were assumed to be eligible? How was this figure derived?

According to the expected licence, tocilizumab will be prescribed to moderate to severe RA patients requiring treatment who have either had an inadequate response to one or more tDMARDs or had an inadequate response to one or more anti-TNF.

Two sub-populations were identified.

- Incident DMARD-IR population
- Incident TNF-IR population
- Prevalent DMARD-IR population
- Prevalent TNF-IR population

The Incidence of RA in 2007 was 0.0254% (NICE TA126; 2007). The prevalence of RA was derived from Symmons et al. (2002)[75] and it has been assumed to be 0.88%. Both the incidence and prevalence rates were assumed to remain constant. The total population of England and Wales is estimated to be 54,895,969 in 2009 (first year of tocilizumab marketing authorisation), 55,319,249 in 2010 and 55,744,028 in 2011 (GAD 2008)

The RA incidence rate of 0.0254% will result in 13,943 new RA patients in 2009, 14,051 in 2010 and 14,158 in 2011. The RA prevalence rate of 0.88% means that there will be 483,084, 486,809 and 490,547 RA patients in the years 2009, 2010 and 2011 respectively. Of all these patients only 59.6% are diagnosed and will be considered to receive treatment (Datamonitor 2006). 92.6% will actually receive treatment.

In the incident population it has been assumed that in the first year of treatment the treated population will receive a tDMARD. 25.62% will respond inadequately to

treatment and therefore will be eligible to tocilizumab treatment. 5% (2009), 10% (2010) and 15% (2011) of these patients has been assumed that will be treated with tocilizumab. The rest will be treated with a bDMARD. Of these patients 24.65% (Derived from Grove M.L. et al. 2002[76]) will respond inadequately to the aTNF and will also be eligible for tocilizumab treatment. Again 5% (2009), 10% (2010) and 15% (2011) of these patients has been assumed that will receive tocilizumab treatment. The assumptions, calculations used and the resulting total number of incident patients treated with tocilizumab are summarised in **Table 57**.

Table 57: Incident population of RA and calculation of tocilizumab eligible patients in both the DMARD-IR and TNF-IR for the 3 years following positive NICE guidance

Incident Population				
Year	Assumption	2009	2010	2011
Population England & Wales		54,895,969	55,319,249	55,744,028
% Incidence of RA in adults	0.0254%	13,943.58	14,051.09	14,158.98
% diagnosed (adults)	59.60%	8,310.37	8,374.45	8,438.75
% treated with tDMARD	92.60%	7,695.40	7,754.74	7,814.29
% DMARD-IR	25.62%	1971.56	1986.76	2002.02
% prescribed tocilizumab		5.00%	10.00%	15.00%
Number of patients on toc		98.58	198.68	300.30
Number treated with aTNF		1872.98	1788.09	1701.72
%TNF-IR	24.65%	461.69	440.76	419.47
% prescribed tocilizumab		5.00%	10.00%	15.00%
Number of patients receiving tocilizumab		23.08	44.08	62.92
Total number of incident population treated with tocilizumab		121.66	242.75	363.22

A significant prevalent population is currently treated for severe to moderate RA. It has been assumed that the prevalence of RA in the UK is 0.88%. Of the total prevalent population only 59.6% will be diagnosed with the condition and therefore around 92.6% will get treated. 31% will receive a tDMARD as treatment where as 12.54% will receive an anti-TNF. 25.62% of the patients treated with a tDMARD will respond inadequately to treatment and therefore will be eligible to tocilizumab treatment. 24.65% will respond inadequately to the aTNF and will also be eligible for tocilizumab treatment. Again 5% (2009), 10% (2010) and 15% (2011) of all eligible patients has been assumed that will

receive tocilizumab treatment. The assumptions, calculations used and the resulting total number of incident patients treated with tocilizumab are summarised in **Table 58**.

Table 58: Prevalent population of RA and calculation of tocilizumab eligible patients in both the DMARD-IR and TNF-IR for the 3 years following positive NICE guidance

Prevalent Population				
Year	Assumption	2009	2010	2011
Population England & Wales		54,895,969	55,319,249	55,744,028
% prevalence of RA	0.88%	483,084.53	486,809.39	490,547.45
% diagnosed (adults)	59.60%	287,918.38	290,138.40	292,366.28
% treated	92.60%	266,612.42	268,668.16	270,731.17
Number treated with DMARD	31%	82,649.85	83,287.13	83,926.66
% DMARD-IR	25.62%	21,174.89	21,338.16	21,502.01
% prescribed tocilizumab		5.00%	10.00%	15.00%
Number of patients on tocilizumab		1,058.74	2,133.82	3,225.30
% existing RA patients on aTNF	12.54%	33,433.20	33,690.99	33,949.69
%TNF-IR	24.65%	8,241.28	8,304.83	8,368.60
% prescribed tocilizumab		5.00%	10.00%	15.00%
Number of patients on tocilizumab		412.06	830.48	1,255.29
Total number of prevalent population treated with Tocilizumab		1,470.81	2,964.30	4,480.59

The total eligible population for 2009, 2010 and 2011 is 1,592, 3,207 and 4,843 respectively. As tocilizumab is given until the therapy shows lack of efficacy. The total population initiating treatment will continue to receive treatment for the subsequent years. Based on the trial data 35% of DMARD-IR patients and 38% of TNF-IR patients will show an inadequate response within the first 6 months and will therefore be withdrawn from treatment. An additional 10% withdrawal rate has also been assumed to occur for each year subsequent to the first year of treatment. The total number of patients receiving treatment is altered accordingly.

For example, 435 patients TNF-IR will start treatment in 2009. 38% will show an inadequate response and will stop treatment giving a total 269 that will remain on treatment in 2010. At the end of 2010 243 (269 -10%) patients will be still on treatment. At the end of 2011 only 218 (243 -10%) will still be on treatment.

Applying a half-cycle correction to account for the 6 months for which withdrawn patients will not be receiving treatment, the total number of patients receiving tocilizumab in 2009 will be **1,307**, **3,603** in 2010 and **6,806** in 2011.

8.3 What assumption(s) were made about current treatment options and uptake of technologies?

The use of tocilizumab in the treatment of RA patients will be an addition to standard treatment sequence. Therefore tocilizumab is not expected to displace any treatment regimen currently prescribed to RA patients.

8.4 What assumption(s) were made about market share (where relevant)?

Given that tocilizumab is a new treatment option it is expected that will not have a rapid uptake by clinicians within the NHS. Therefore a 5% uptake has been assumed in the first year of licensed use, with further increases to 15% by year 3.

8.5 What unit costs were assumed? How were these calculated?

Three vial sizes of tocilizumab will be available:

1: Single-use vial containing tocilizumab 80 mg priced at £102.1
2: Single-use vial containing tocilizumab 200 mg priced at £255.4
3: Single-use vial containing tocilizumab 400 mg priced at £510.7

The standard dose stated in the SmPC is 8 mg per kg. An average patient weighing 70 kgs will require 540 mg of tocilizumab for each infusion. To minimise wastage a combination of vials can be used to achieve the required dose; 1 x 400 mg vial and 2 x 80 mg vial. These will cost £510.7 and 204.3 respectively. The total cost per annum for 13 infusions is £9,295.

8.6 In addition to drug costs, consider other significant costs associated with treatment. What is the recommended treatment regime – for example, what is the typical number of visits, and does treatment involve daycase or outpatient attendance? Is there a difference between recommended and observed doses? Are there likely to be any adverse events or a need for other treatments in combination with the technology?

When tocilizumab is added to the current RA treatment sequence will be administered during hospital outpatient visits. The cost of such a visit has been determined to be £141.7 per visit.

Therefore, the maximum potential additional cost of the attendances to allow 13 IV tocilizumab infusions is £1,842 per patient per annum.

8.7 Were there any estimates of resource savings? If so, what were they?

Treatment with tocilizumab is not associated with any direct resource savings.

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Even though the addition of tocilizumab in the current treatment RA therapy strategy sequence is not associated with any direct, short-term resource savings, its use will generate cost offsets in the long-term as health outcomes, such as the increase in patients HAQ scores and hence disability will be delayed.

9 Appendices

9.1 Appendix 1

Supplied separately

9.2 Appendix 2: search strategy for section 6

The following information should be provided.

9.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Appendix 2, Section 9.2

The following databases were searched via DataStar

1. EMBASE (EMYY and EMBA)

No.	Database	Search term	Info added since	Results
1	EMYY	atlizumab.MJ.	unrestricted	58
5	EMYY	rheumatoid-arthritis.MJ.	unrestricted	24281
6	EMYY	1 AND 5	unrestricted	36
7	EMYY	6 AND CLINICAL-TRIAL# AND HUMAN=YES	unrestricted	30
8	EMYY	6 AND REVIEW=YES	unrestricted	10
9	EMYY	7 NOT 8	unrestricted	21

Saved: 20-Jan-2009 18:02:53 MET

No.	Database	Search term	Info added since	Results
1	EMBA	tocilizumab	unrestricted	11
2	EMBA	rheumatoid ADJ arthritis	unrestricted	612
3	EMBA	1 AND 2	unrestricted	8
4	EMBA	3 AND PT=REVIEW	unrestricted	2
5	EMBA	3 NOT 4	unrestricted	6

Saved: 20–Jan–2009 18:09:56 MET

2. MEDLINE (MEYY and MEIP)

No.	Database	Search term	Info added since	Results
2	MEYY	ANTIBODIES–MONOCLONAL.DE.	unrestricted	80692
4	MEYY	tocilizumab	unrestricted	105
5	MEYY	2 AND 4	unrestricted	76
6	MEYY	ARTHRITIS–RHEUMATOID.DE.	unrestricted	28077
7	MEYY	5 AND 6	unrestricted	43
8	MEYY	7 AND PT=CLINICAL–TRIAL# AND HUMAN=YES	unrestricted	7

Saved: 20–Jan–2009 14:00:27 MET

No.	Database	Search term	Info added since	Results
1	MEIP	tocilizumab	unrestricted	17
2	MEIP	rheumatoid ADJ arthritis	unrestricted	1513
3	MEIP	1 AND 2	unrestricted	6

Saved: 20–Jan–2009 14:30:12 MET

3. COCHRANE Library

Free text search using the terms 'tocilizumab', 'atlizumab' and 'rheumatoid arthritis'

Search date: 20 January 2009

4. EULAR – Abstracts from the Annual Meeting of EULAR, 2002-2008

Search term 1: 'tocilizumab' (in title field)
Search term 2: 'rheumatoid arthritis' (in any field)

Search date: 21 January 2009

5. ACR – Abstracts from the Annual Meeting of ACR, 2002-2008

Free text search using the terms: 'tocilizumab', 'atlizumab' and 'rheumatoid arthritis'

Search Date: 21 January 2009

9.2.2 The date on which the search was conducted.

20th and 21st January 2009

9.2.3 The date span of the search.

Embase and Medline: 1993 to present

EULAR and ACR: 2002 to 2008

COCHRANE: unlimited

9.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

See Section 9.2.1

9.2.5 Details of any additional searches, for example searches of company databases (include a description of each database).

Internal study reports and regulatory submission documents accessed through company databases

9.2.6 The inclusion and exclusion criteria.

For the systematic review, the following Inclusion and Exclusion Criteria were applied:

Inclusion criteria

Published papers or abstracts which evaluated the following were included:

- Tocilizumab (or atlizumab prior to 2005) was the major focus of the paper.
- Rheumatoid arthritis was a major focus of the paper.
- Patient population consisted of patients who had responded inadequately or who were intolerant to one or more DMARDs or TNF antagonists, to be consistent with the EU licence for tocilizumab, including dose
- Controlled clinical studies
- Documents relating to humans

Exclusion criteria

Published papers or abstracts which evaluated the following were excluded:

- Any papers providing a review, update or commentary on data published elsewhere were excluded
- Any papers which only mentioned tocilizumab within a discussion of treatments for rheumatoid arthritis were excluded
- Papers covering the use of tocilizumab in Castleman's disease, juvenile idiopathic arthritis, other autoimmune diseases or other off-licence indications were excluded
- Clinical studies conducted in Japanese patients were not included, as data generated in this patient population was not considered sufficiently relevant to European patients.

- Animal studies or *in vitro* research
- Case reports

9.2.7 The data abstraction strategy.

To identify all published papers or abstracts which included tocilizumab as a treatment for rheumatoid arthritis in at least one arm of a randomised, controlled clinical trial, in a patient population applicable to the UK, and at the dose included in the marketing authorisation.

9.3 Appendix 3: search strategy for section 7

The following information should be provided.

9.3.1 The specific databases searched and the service provider used.

The following databases were searched:

- EMBASE + MEDLINE
  - *Period Covered:* EMBASE records from 1974 to present plus MEDLINE records from 1966 to present
  - *Platform:* EMBASE.com[iv]
  - *Last Updated:* 23 December 2008 *Date of Search:* 24 December 2008
  - *Search Strategy:* see Table 9.3.1.T1 below.
- NHS Economic Evaluation Database (NHS EED)
  - *Platform:* The Cochrane Library via Wiley InterScience Web site
  - *Last Updated:* 2008 Issue 4
  - *Date of Search:* 24 December 2008
  - *Search Strategy:* see Table 9.3.1.T2 below

[iv] EMBASE.com combines EMBASE and MEDLINE content into a single, Web-accessible platform (http://www.embase.com), with duplicate citations removed. The single EMBASE.com platform means that EMBASE and MEDLINE can be searched simultaneously

- Health Technology Assessment Database (HTA)
    - *Platform:* The Cochrane Library via Wiley InterScience Web site
    - *Last Updated:* 2008 Issue 4
    - *Date of Search:* 24 December 2008
    - *Search Strategy:* see Table 9.3.1.T2 below
- MEDLINE In-process and Other Non-indexed Citations (PubMed)
    - *Platform:* Entrez PubMed Web site
    - *Last Updated:* 23 December 2008
    - *Date of Search:* 24 December 2008
    - *Search Strategy:* see Table 9.3.1.T4 below
- Health Economic Evaluation Database
    - *Platform:* HEED Web site
    - *Last Updated:* 05 January 2009
    - *Date of Search:* 06 January 2009
    - *Search Strategy:* see Table 9.3.1.T5 below

Table 9.3.1.T1a. – EMBASE.com base search

EMBASE.com Session Results

No.	Query	Results
#1	**'rheumatoid arthritis'**/exp AND [1995-2009]/py	**47,683**
#2	**'rheumatoid arthritis'**:ti,ab OR **'rheumatic arthritis'**:ti,ab	**67,234**
#3	**'arthritis deformans'**:ti,ab OR **'arthrosis deformans'**:ti,ab	**287**
#4	**'chronic *3 polyarthritis'**:ti,ab OR **'chronic *3 poly arthritis'**:ti,ab	**1,647**
#5	**'chronic *3 rheumatism'**:ti,ab OR **'inflammatory *3 rheumatism'**:ti,ab	**523**
#6	**'inflammatory *3 polyarthritis'**:ti,ab OR **'inflammatory *3 poly arthritis'**:ti,ab	**271**
#7	**'beauvais disease'**:ti,ab OR **rheumarthritis**:ti,ab	**2**
#8	**#1** OR **#2** OR **#3** OR **#4** OR **#5** OR **#6** OR **#7**	**87,556**
#9	**'cost benefit analysis'**/de	**49,189**
#10	**'cost effectiveness analysis'**/de	**57,693**

#11	'cost minimization analysis'/de	1,454
#12	'cost utility analysis'/de	2,445
#13	'economic evaluation'/de	4,436
#14	'economics'/de	170,692
#15	'cost'/de	44,701
#16	'cost control '	34,067
#17	'cost of illness'/de	9,304
#18	'health care cost'/exp	135,194
#19	'socioeconomics'/de	88,609
#20	'health economics'/de	26,548
#21	'medical fee'/de	8,752
#22	'hospital charge'/de	1,902
#23	'hospital costs'/de	9,207
#24	'pharmacoeconomics'/exp	119,724
#25	'fee'/de	12,800
#26	'capitation fee'/de	3,544
#27	cost:ti,ab OR costs:ti,ab OR costed:ti,ab OR costly:ti,ab OR costing:ti,ab	251,388
#28	economic*:ti,ab OR pharmacoeconomic*:ti,ab	117,900
#29	price*:ti,ab OR pricing:ti,ab	20,435
#30	expenditure*:ti NOT energy:ti	2,661
#31	expenditure*:ab NOT energy:ab	13,823
#32	'value *1 money':ti,ab	654
#33	budget*:ti,ab	15,798
#34	'technology assessment':ti,ab OR 'technology assessments':ti,ab	2,424
#35	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34	745,330
#36	#8 AND #35	3,485
#37	'quality of life'/exp	126,214
#38	'health status'/de	53,888
#39	'life style'/de	44,688
#40	'health survey'/de	100,801
#41	'socioeconomics'/de	88,609
#42	'quality of wellbeing':ti,ab	5
#43	#37 OR #38 OR #39 OR #40 OR #41 OR #42	374,167
#44	#8 AND #43	3,027
#45	'decision support system'/de	6,911
#46	'hidden markov model'/de	211
#47	'probability'/de	39,278
#48	markov:de,ti,ab	6,525
#49	'statistical model'/de	58,892
#50	'decision analysis':de,ti,ab	3,013
#51	'cost benefit analysis'/de	49,189
#52	#45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51	152,335
#53	#8 AND #52	617
#54	#36 OR #44 OR #53	5,928

Table 9.3.1.T1b. – EMBASE.com Abatacept search

EMBASE.com Session Results

No.	Query	Results
#55	'abatacept'/de	877
#56	'cytotoxic t lymphocyte associated antigen 4 immunoglobulin':de	24
#57	'cytotoxic t lymphocyte-associated antigen 4-immunoglobulin':de	24
#58	abatacept:ti,ab,tn OR orencia:ti,ab,tn OR belatacept:ti,ab,tn	341
#59	'bms 188667':ti,ab,tn OR bms188667:ti,ab,tn	63
#60	'bms 224818':ti,ab,tn OR bms224818:ti,ab,tn	12
#61	'ctla4 immunoglobulin':ti,ab,tn OR lea29y:ti,ab,tn OR 'ctla4 fc':ti,ab,tn	150
#62	'ctla4 ig':ti,ab,tn OR 'ctla 4 ig':ti,ab,tn OR ctla4ig:ti,ab,tn	838
#63	'cytotoxic t lymphocyte associated antigen 4 immunoglobulin':ti,ab,tn	11
#64	'332348 12 6':rn	817
#65	#55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64	1,745
#66	#54 AND #65	181

Table 9.3.1.T1c. – EMBASE.com Adalimumab search

EMBASE.com Session Results

No.	Query	Results
#67	**'adalimumab'**/de	3,667
#68	**'monoclonal antibody d2e7'**:de	39
#69	**D2e7**:de	52
#70	**adalimumab**:ti,ab,tn OR **humira**:ti,ab,tn OR **trudexa**:ti,ab,tn OR **d2e7**:ti,ab,tn	1,753
#71	**'331731 18 1'**:rn	3,667
#72	**#67** OR **#68** OR **#69** OR **#70**	3,799
#73	**#54** AND **#72**	592
#74	**#73** AND [2005-2009]/py	417

Table 9.3.1.T1d. – EMBASE.com Etanercept search

EMBASE.com Session Results

No.	Query	Results
#75	'etanercept'/de	7,536
#76	'tnfr fc fusion protein':de	495
#77	'tnfr-fc fusion protein':de	495

#78	etanercept:ti,ab,tn OR enbrel:ti,ab,tn	3,686
#79	'tnr 001':ti,ab,tn OR tnr001:ti,ab,tn OR 'tntr fc':ti,ab,tn	5
#80	'tumor necrosis factor receptor fc fusion protein':ti,ab,tn	21
#81	'tumour necrosis factor receptor fc fusion protein':ti,ab,tn	1
#82	'tnfr fc fusion protein':ti,ab,tn OR 'tnf receptor':ti,ab,tn OR 'tnt receptor':ti,ab,tn	3,644
#83	'tnf *5 fusion protein':ti,ab,tn OR 'tnt *5 fusion protein':ti,ab,tn	152
#84	'185243 69 0':rn OR '200013 86 1':rn	7,536
#85	#75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84	11,679
#86	#54 AND #85	976
#87	#86 AND [2005-2009]/py	530

Table 9.3.1.T1e. – EMBASE.com Infliximab search

EMBASE.com Session Results

No.	Query	Results
#88	'infliximab'/de	11,692
#89	'monoclonal antibody ca2':de	134
#90	infliximab:ti,ab,tn OR remicade:ti,ab,tn OR avakine:ti,ab,tn	5,865
#91	'mab ca2':ti,ab,tn OR 'monoclonal antibody ca2':ti,ab,tn	21
#92	'170277 31 3':rn	11,692
#93	#88 OR #89 OR #90 OR #91 OR #92	12,065
#94	#54 AND #93	1,034
#95	#94 AND [2005-2009]/py	597

Table 9.3.1.T1f. – EMBASE.com Golimumab search

EMBASE.com Session Results

No.	Query	Results
#96	'golimumab'/de	62
#97	golimumab:ti,ab,tn OR 'cnto 148':ti,ab,tn OR cnto148:ti,ab,tn	37
#98	'476181 74 5':rn	59
#99	#96 OR #97 OR #98	69
#100	#54 AND #99	16

Table 9.3.1.T1g. – EMBASE.com Certolizumab pegol search

EMBASE.com Session Results

No.	Query	Results
#101	'certolizumab pegol'/de	485
#102	certolizumab:de	490
#103	certolizumab:ti,ab,tn OR cimzia:ti,ab,tn	164
#104	cdp870:ti,ab,tn OR 'cdp 870':ti,ab,tn OR pha738144:ti,ab,tn OR 'pha 738144':ti,ab,tn	253
#105	'pegylated tumor necrosis factor alpha antibody fab fragment':ti,ab,tn	0
#106	'pegylated *5 fab fragment':ti,ab,tn	10
#107	'428863 50 7':rn	485
#108	#101 OR #102 OR #103 OR #104 OR #105 OR #106 OR #107	559
#109	#54 AND #108	73

Table 9.3.1.T1h. – EMBASE.com Rituximab search

EMBASE.com Session Results

No.	Query	Results
#110	'rituximab'/de	11,899
#111	rutiximab:de	1
#112	rituximab:ti,ab,tn OR mabthera:ti,ab,tn	5,175
#113	'idec c2b8':ti,ab,tn OR rituxan:ti,ab,tn OR rituxin:ti,ab,tn	1,464
#114	'174722 31 7':rn	11,899
#115	#110 OR #111 OR #112 OR #113 OR #114	12,288
#116	#54 AND #115	260

Table 9.3.1.T1i. – EMBASE.com Tocilizumab search

EMBASE.com Session Results

No.	Query	Results
#117	'atlizumab'/de	334
#118	atlizumab:ti,ab,tn OR tocilizumab:ti,ab,tn	122
#119	actemra:ti,ab,tn OR 'r 1569':ti,ab,tn OR r1569:ti,ab,tn	49
#120	'375823 41 9':rn	329
#121	#117 OR #118 OR #119 OR #120	352
#122	#54 AND #121	47

Table 9.3.1.T1j. – EMBASE.com complete search

EMBASE.com Session Results

No.	Query	Results
#1	**'rheumatoid arthritis'**/exp AND [1995-2009]/py	**47,683**
#2	**'rheumatoid arthritis'**:ti,ab OR **'rheumatic arthritis'**:ti,ab	**67,234**
#3	**'arthritis deformans'**:ti,ab OR **'arthrosis deformans'**:ti,ab	**287**
#4	**'chronic *3 polyarthritis'**:ti,ab OR **'chronic *3 poly arthritis'**:ti,ab	**1,647**
#5	**'chronic *3 rheumatism'**:ti,ab OR **'inflammatory *3 rheumatism'**:ti,ab	**523**
#6	**'inflammatory *3 polyarthritis'**:ti,ab OR **'inflammatory *3 poly arthritis'**:ti,ab	**271**
#7	**'beauvais disease'**:ti,ab OR **rheumarthritis**:ti,ab	**2**
#8	**#1** OR **#2** OR **#3** OR **#4** OR **#5** OR **#6** OR **#7**	**87,556**
#9	**'cost benefit analysis'**/de	**49,189**
#10	**'cost effectiveness analysis'**/de	**57,693**
#11	**'cost minimization analysis'**/de	**1,454**
#12	**'cost utility analysis'**/de	**2,445**
#13	**'economic evaluation'**/de	**4,436**
#14	**'economics'**/de	**170,692**
#15	**'cost'**/de	**44,701**
#16	**'cost control '**	**34,067**
#17	**'cost of illness'**/de	**9,304**
#18	**'health care cost'**/exp	**135,194**
#19	**'socioeconomics'**/de	**88,609**
#20	**'health economics'**/de	**26,548**
#21	**'medical fee'**/de	**8,752**
#22	**'hospital charge'**/de	**1,902**
#23	**'hospital costs'**/de	**9,207**
#24	**'pharmacoeconomics'**/exp	**119,724**
#25	**'fee'**/de	**12,800**
#26	**'capitation fee'**/de	**3,544**
#27	**Cost**:ti,ab OR **costs**:ti,ab OR **costed**:ti,ab OR **costly**:ti,ab OR **costing**:ti,ab	**251,388**
#28	**economic***:ti,ab OR **pharmacoeconomic***:ti,ab	**117,900**
#29	**price***:ti,ab OR **pricing**:ti,ab	**20,435**
#30	**expenditure***:ti NOT **energy**:ti	**2,661**
#31	**expenditure***:ab NOT **energy**:ab	**13,823**
#32	**'value *1 money'**:ti,ab	**654**
#33	**budget***:ti,ab	**15,798**
#34	**'technology assessment'**:ti,ab OR **'technology assessments'**:ti,ab	**2,424**
#35	**#9** OR **#10** OR **#11** OR **#12** OR **#13** OR **#14** OR **#15** OR **#16** OR **#17** OR **#18** OR **#19** OR **#20** OR **#21** OR **#22** OR **#23** OR **#24** OR **#25** OR **#26** OR **#27** OR **#28** OR **#29** OR **#30** OR **#31** OR **#32** OR **#33** OR **#34**	**745,330**
#36	**#8** AND **#35**	**3,485**
#37	**'quality of life'**/exp	**126,214**
#38	**'health status'**/de	**53,888**

#39	'life style'/de	44,688
#40	'health survey'/de	100,801
#41	'socioeconomics'/de	88,609
#42	'quality of wellbeing':ti,ab	5
#43	#37 OR #38 OR #39 OR #40 OR #41 OR #42	374,167
#44	#8 AND #43	3,027
#45	'decision support system'/de	6,911
#46	'hidden markov model'/de	211
#47	'probability'/de	39,278
#48	markov:de,ti,ab	6,525
#49	'statistical model'/de	58,892
#50	'decision analysis':de,ti,ab	3,013
#51	'cost benefit analysis'/de	49,189
#52	#45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51	152,335
#53	#8 AND #52	617
#54	#36 OR #44 OR #53	5,928
#55	'abatacept'/de	877
#56	'cytotoxic t lymphocyte associated antigen 4 immunoglobulin':de	24
#57	'cytotoxic t lymphocyte-associated antigen 4-immunoglobulin':de	24
#58	abatacept:ti,ab,tn OR orencia:ti,ab,tn OR belatacept:ti,ab,tn	341
#59	'bms 188667':ti,ab,tn OR bms188667:ti,ab,tn	63
#60	'bms 224818':ti,ab,tn OR bms224818:ti,ab,tn	12
#61	'ctla4 immunoglobulin':ti,ab,tn OR lea29y:ti,ab,tn OR 'ctla4 fc':ti,ab,tn	150
#62	'ctla4 ig':ti,ab,tn OR 'ctla 4 ig':ti,ab,tn OR ctla4ig:ti,ab,tn	838
#63	'cytotoxic t lymphocyte associated antigen 4 immunoglobulin':ti,ab,tn	11
#64	'332348 12 6':rn	817
#65	#55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64	1,745
#66	#54 AND #65	181
#67	'adalimumab'/de	3,667
#68	'monoclonal antibody d2e7':de	39
#69	d2e7:de	52
#70	adalimumab:ti,ab,tn OR humira:ti,ab,tn OR trudexa:ti,ab,tn OR d2e7:ti,ab,tn	1,753
#71	'331731 18 1':rn	3,667
#72	#67 OR #68 OR #69 OR #70	3,799
#73	#54 AND #72	592
#74	#73 AND [2005-2009]/py	417
#75	'etanercept'/de	7,536
#76	'tnfr fc fusion protein':de	495
#77	'tnfr-fc fusion protein':de	495
#78	etanercept:ti,ab,tn OR enbrel:ti,ab,tn	3,686
#79	'tnr 001':ti,ab,tn OR tnr001:ti,ab,tn OR 'tntr fc':ti,ab,tn	5
#80	'tumor necrosis factor receptor fc fusion protein':ti,ab,tn	21
#81	'tumour necrosis factor receptor fc fusion protein':ti,ab,tn	1
#82	'tnfr fc fusion protein':ti,ab,tn OR 'tnf receptor':ti,ab,tn OR 'tnt receptor':ti,ab,tn	3,644

#83	**'tnf *5 fusion protein'**:ti,ab,tn OR **'tnt *5 fusion protein'**:ti,ab,tn	**152**
#84	**'185243 69 0'**:rn OR **'200013 86 1'**:rn	**7,536**
#85	**#75** OR **#76** OR **#77** OR **#78** OR **#79** OR **#80** OR **#81** OR **#82** OR **#83** OR **#84**	**11,679**
#86	**#54** AND **#85**	**976**
#87	**#86** AND [2005-2009]/py	**530**
#88	**'infliximab'**/de	**11,692**
#89	**'monoclonal antibody ca2'**:de	**134**
#90	**infliximab**:ti,ab,tn OR **remicade**:ti,ab,tn OR **avakine**:ti,ab,tn	**5,865**
#91	**'mab ca2'**:ti,ab,tn OR **'monoclonal antibody ca2'**:ti,ab,tn	**21**
#92	**'170277 31 3'**:rn	**11,692**
#93	**#88** OR **#89** OR **#90** OR **#91** OR **#92**	**12,065**
#94	**#54** AND **#93**	**1,034**
#95	**#94** AND [2005-2009]/py	**597**
#96	**'golimumab'**/de	**62**
#97	**golimumab**:ti,ab,tn OR **'cnto 148'**:ti,ab,tn OR **cnto148**:ti,ab,tn	**37**
#98	**'476181 74 5'**:rn	**59**
#99	**#96** OR **#97** OR **#98**	**69**
#100	**#54** AND **#99**	**16**
#101	**'certolizumab pegol'**/de	**485**
#102	**certolizumab**:de	**490**
#103	**certolizumab**:ti,ab,tn OR **cimzia**:ti,ab,tn	**164**
#104	**Cdp870**:ti,ab,tn OR **'cdp 870'**:ti,ab,tn OR **pha738144**:ti,ab,tn OR **'pha 738144'**:ti,ab,tn	**253**
#105	**'pegylated tumor necrosis factor alpha antibody fab fragment'**:ti,ab,tn	**0**
#106	**'pegylated *5 fab fragment'**:ti,ab,tn	**10**
#107	**'428863 50 7'**:rn	**485**
#108	**#101** OR **#102** OR **#103** OR **#104** OR **#105** OR **#106** OR **#107**	**559**
#109	**#54** AND **#108**	**73**
#110	**'rituximab'**/de	**11,899**
#111	**rutiximab**:de	**1**
#112	**rituximab**:ti,ab,tn OR **mabthera**:ti,ab,tn	**5,175**
#113	**'idec c2b8'**:ti,ab,tn OR **rituxan**:ti,ab,tn OR **rituxin**:ti,ab,tn	**1,464**
#114	**'174722 31 7'**:rn	**11,899**
#115	**#110** OR **#111** OR **#112** OR **#113** OR **#114**	**12,288**
#116	**#54** AND **#115**	**260**
#117	**'atlizumab'**/de	**334**
#118	**atlizumab**:ti,ab,tn OR **tocilizumab**:ti,ab,tn	**122**
#119	**actemra**:ti,ab,tn OR **'r 1569'**:ti,ab,tn OR **r1569**:ti,ab,tn	**49**
#120	**'375823 41 9'**:rn	**329**
#121	**#117** OR **#118** OR **#119** OR **#120**	**352**
#122	**#54** AND **#121**	**47**
#123	**#66** OR **#74** OR **#87** OR **#95** OR **#100** OR **#109** OR **#116** OR **#122**	**862**

Table 9.3.1.T2. – The Cochrane Library search

Cochrane Library Current Search History

ID	Search	Hits
#1	MeSH descriptor **Arthritis, Rheumatoid** explode all trees	3383
#2	(rheumatoid OR rheumatic) next arthritis	4449
#3	(arthritis OR arthrosis) next deformans	13
#4	(chronic OR inflammatory) near/3 (polyarthritis OR "poly arthritis" OR rheumatism)	131
#5	"beauvais disease" or rheumarthritis	1
#6	(#1 OR #2 OR #3 OR #4 OR #5)	5126
#7	MeSH descriptor **Immunoconjugates**, this term only	39
#8	abatacept OR orencia OR BELATACEPT	32
#9	"bms 188667" OR bms188667	1
#10	"BMS 224818" OR BMS224818	4
#11	"CTLA4 immunoglobulin" OR LEA29Y OR "CTLA4 Fc"	9
#12	"CTLA4 Ig" OR "CTLA 4 ig" OR CTLA4Ig	7
#13	"cytotoxic T lymphocyte associated antigen 4 immunoglobulin"	0
#14	(#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13)	58
#15	(#6 AND #14)	33
#16	MeSH descriptor **Antibodies, Monoclonal**, this term only	2130
#17	adalimumab or humira OR trudexa or d2e7	127
#18	(#16 OR #17)	2180
#19	(#6 AND #18)	241
#20	(#19), from 2005 to 2008	136
#21	MeSH descriptor **Immunoglobulin G**, this term only	1699
#22	MeSH descriptor **Receptors, Tumor Necrosis Factor**, this term only	362
#23	(#21 AND #22)	223
#24	etanercept or enbrel	339
#25	"tnr 001" or tnr001 or "tntr fc"	0
#26	"tumor necrosis factor receptor Fc fusion protein"	5
#27	"tumour necrosis factor receptor Fc fusion protein"	0
#28	"tnfr fc fusion protein" or "tnf receptor" or "tnt receptor"	82
#29	(tnf NEAR/5 "fusion protein") or (tnt NEAR/5 "fusion protein")	19
#30	(#23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29)	432
#31	(#6 AND #30)	174

#32	(#31), from 2005 to 2008	103
#33	MeSH descriptor **Antibodies, Monoclonal**, this term only	2130
#34	infliximab or remicade or avakine	398
#35	"MAb cA2" or "monoclonal antibody cA2"	12
#36	(#33 OR #34 OR #35)	2270
#37	(#6 AND #36)	266
#38	(#37), from 2005 to 2008	151
#39	MeSH descriptor **Antibodies, Monoclonal**, this term only	2130
#40	golimumab OR "cnto 148" OR cnto148	4
#41	(#39 OR #40)	2132
#42	(#6 AND #41)	224
#43	MeSH descriptor **Immunoglobulin Fab Fragments**, this term only	391
#44	MeSH descriptor **Polyethylene Glycols**, this term only	876
#45	(#43 AND #44)	10
#46	certolizumab OR cimzia	11
#47	Cdp870 or "cdp 870" or pha738144 or "pha 738144"	6
#48	"pegylated tumor necrosis factor alpha antibody Fab fragment"	0
#49	pegylated NEAR/5 "Fab fragment"	4
#50	(#45 OR #46 OR #47 OR #48 OR #49)	16
#51	(#6 AND #50)	4
#52	MeSH descriptor **Antibodies, Monoclonal**, this term only	2130
#53	rituximab or mabthera	373
#54	"idec c2b8" or rituxan or rituxin	20
#55	(#52 OR #53 OR #54)	2388
#56	(#6 AND #55)	229
#57	MeSH descriptor **Antibodies, Monoclonal**, this term only	2130
#58	atlizumab OR tocilizumab	8
#59	actemra OR "r 1569" OR r1569	2
#60	(#57 OR #58 OR #59)	2131
#61	(#6 AND #60)	223
#62	(#15 OR #20 OR #32 OR #38 OR #42 OR #51 OR #56 OR #61)	336(*)

* Only records retrieved from the Health Technology Assessment database (HTA) and NHS Economic Evaluation Database (NHS EED) were exported – refer to Table 9.3.1.T3 below for a breakdown of database retrieval.

Table 9.3.1.T3. – Breakdown of database retrieval from The Cochrane Library

Database	Results
Cochrane Database of Systematic Reviews	16
Database of Abstracts of Reviews of Effects (DARE)	11
Cochrane Central Register of Controlled Trials (CENTRAL)	227
Cochrane Methodology Register (CMR)	2
Health Technology Assessment Database (HTA)	27(*)
NHS EED Economic Evaluation Database (NHSEED)	52(*)
Cochrane Groups	1
Total	**1**

* Only records from these two databases were exported.

Table 9.3.1.T4. – MEDLINE In process and Other Non-indexed Citations (PubMed) search

Search	Most Recent Queries	Result
#78	Search **#46 OR #48 OR #57 OR #61 OR #63 OR #69 OR #73 OR #77**	32
#77	Search **#38 AND #76**	0
#76	Search **#74 OR #75**	127
#75	Search **actemra[tw] OR "r 1569"[tw] OR r1569[tw]**	4
#74	Search **atlizumab[tw] OR tocilizumab[tw]**	126
#73	Search **#38 AND #72**	6
#72	Search **#70 OR #71**	4811
#71	Search **"idec c2b8"[tw] or rituxan[tw] or rituxin[tw]**	218
#70	Search **rituximab[tw] or mabthera[tw]**	4782
#69	Search **#38 AND #68**	0
#68	Search **#64 OR #65 OR #66 OR #67**	118
#67	Search **pegylated[tw] AND "Fab fragment"[tw]**	2
#66	Search **"pegylated tumor necrosis factor alpha antibody Fab fragment"[tw]**	0
#65	Search **cdp870[tw] OR "cdp 870"[tw] OR pha738144[tw] OR "pha 738144"[tw]**	72
#64	Search **certolizumab[tw] OR cimzia[tw]**	75
#63	Search **#38 AND #62**	0
#62	Search **golimumab[tw] OR "cnto 148"[tw] OR cnto148[tw]**	14
#61	Search **#38 AND #60**	11
#60	Search **#58 OR #59**	4657

#59	Search **"MAb cA2"[tw] or "monoclonal antibody cA2"[tw]**	21
#58	Search **infliximab[tw] or remicade[tw] or avakine[tw]**	4645
#57	Search **#38 AND #56**	13
#56	Search **#49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55**	7383
#55	Search **tnt[tw] AND "fusion protein"[tw]**	9
#54	Search **tnf[tw] AND "fusion protein"[tw]**	1395
#53	Search **"tnfr fc fusion protein"[tw] or "tnf receptor"[tw] or "tnt receptor"[tw]**	6440
#52	Search **"tumour necrosis factor receptor Fc fusion protein"[tw]**	0
#51	Search **"tumor necrosis factor receptor Fc fusion protein"[tw]**	0
#50	Search **"tnr 001"[tw] or tnr001[tw] or "tntr fc"[tw]**	2
#49	Search **etanercept[tw] or enbrel[tw]**	2078
#48	Search **#38 AND #47**	9
#47	Search **adalimumab[tw] or humira[tw] OR trudexa[tw] or d2e7[tw]**	1093
#46	Search **#38 AND #45**	5
#45	Search **#39 OR #40 OR #41 OR #42 OR #43 OR #44**	2018
#44	Search **"cytotoxic T lymphocyte associated antigen 4 immunoglobulin"[tw]**	14
#43	Search **"CTLA4 Ig"[tw] OR "CTLA 4 ig"[tw] OR CTLA4Ig[tw]**	786
#42	Search **"CTLA4 immunoglobulin"[tw] OR LEA29Y[tw] OR "CTLA4 Fc"[tw]**	63
#41	Search **"BMS 224818"[tw] OR BMS224818[tw]**	1
#40	Search **"bms 188667"[tw] OR bms188667[tw]**	13
#39	Search **abatacept[tw] OR orencia[tw] OR BELATACEPT[tw]**	1746
#38	Search **#35 OR #36 OR #37**	377
#37	Search **#34 AND pubmednotmedline[sb]**	50
#36	Search **#34 AND in process[sb]**	224
#35	Search **#34 NOT (medline[SB] OR oldmedline[sb])**	377
#34	Search **#19 OR #26 OR #33**	9135
#33	Search **#9 AND #32**	6346
#32	Search **#27 OR #28 OR #29 OR #30 OR #31**	1580240

#31	Search **"cost benefit analysis"[tw]**	44541
#30	Search **"decision analysis"[tw]**	2586
#29	Search **model*[tw]**	1535187
#28	Search **markov[tw]**	8003
#27	Search **"decision support"[tw]**	12224
#26	Search **#9 AND #25**	2098
#25	Search **#20 OR #21 OR #22 OR #23 OR #24**	193827
#24	Search **"quality of wellbeing"[tw]**	0
#23	Search **"value of life"[tw]**	5065
#22	Search **"health status"[tw]**	64707
#21	Search **"life style"[tw]**	33357
#20	Search **"quality of life"[tw]**	108074
#19	Search **#9 AND #18**	1612
#18	Search **#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17**	523116
#17	Search **"technology assessment"[tw] OR "technology assessments"[tw]**	7522
#16	Search **budget*[tw]**	18216
#15	Search **value[tw] AND money[tw]**	1127
#14	Search **expenditure*[tw] NOT energy[tw]**	21351
#13	Search **price*[tw] OR pricing[tw]**	16990
#12	Search **economic*[tw] OR pharmacoeconomic*[tw]**	356798
#11	Search **costed[tw] OR costly[tw] OR costing[tw]**	14407
#10	Search **cost[tw] OR costs[tw]**	267037
#9	Search **#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8**	86146
#8	Search **inflammatory[tw] AND "poly arthritis"[tw]**	4
#7	Search **inflammatory[tw] AND polyarthritis[tw]**	1162
#6	Search **inflammatory[tw] AND rheumatism[tw]**	918
#5	Search **chronic[tw] AND rheumatism[tw]**	1124
#4	Search **chronic[tw] AND "poly arthritis"[tw]**	3
#3	Search **chronic[tw] AND polyarthritis[tw]**	2750
#2	Search **"arthritis deformans"[tw] OR "arthrosis deformans"[tw]**	356
#1	Search **"rheumatoid arthritis"[tw] OR "rheumatic arthritis"[tw]**	83664

Table 9.3.1.T5. – HEED

AB = rheumatoid OR rheumatic OR rheumarthritis
AB = arthritis OR arthrosis
AB = abatacept OR orencia OR BELATACEPT
AB = bms 188667 OR bms188667
AB = BMS 224818 OR BMS224818
AB = CTLA4 immunoglobulin OR LEA29Y OR CTLA4 Fc
AB = CTLA4 Ig OR CTLA 4 ig OR CTLA4Ig
AB = cytotoxic T lymphocyte associated antigen 4 immunoglobulin
AB = adalimumab or humira OR trudexa or d2e7
AB = etanercept or enbrel Or tnr 001 OR tnr001 OR tntr
AB =tumor necrosis factor receptor Fc fusion protein
AB = tumour necrosis factor receptor Fc fusion protein
AB = tnfr fc fusion protein or tnf receptor or tnt receptor
AB = infliximab or remicade or avakine
AB = MAb cA2 or monoclonal antibody cA2
AB = golimumab OR cnto 148 OR cnto148
AB = certolizumab OR cimzia
AB = cdp870 or cdp 870 or pha738144 or pha 738144
AB = pegylated tumor necrosis factor alpha antibody Fab fragment
AB = rituximab or mabthera
AB = idec c2b8 or rituxan or rituxin
AB = atlizumab OR tocilizumab
AB = actemra OR r 1569 OR r1569

9.3.2 The date on which the search was conducted.

Please see response to 10.3.1

9.3.3 The date span of the search.

No time limits were applied, except for the agents covered by the review in Chet et al. 2006 (TA 130). In the latter case, searches for Adalimumab, Etanercept and Infliximab were limited to articles published from 2005. Table 10.3.3.T1 presents the applied time limits to the updated search.

Table 10.3.3.T1 Time limits on the updated search

Intervention	Date span	Notes
Abatacept	No limit	Not considered in TA130
Adalimumab	2005 – present	
Etanercept	2005 – present	
Infliximab	2005 – present	
Golimumab	No limit	Not considered in TA130
Certolizumab pegol	No limit	Not considered in TA130
Rituximab	No limit	Not considered in TA130
Tocilizumab	No limit	Not considered in TA130

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(2) Bansback NJ, Brennan A, Ghatnekar O. Cost effectiveness of adalimumab in the treatment of patients with moderate to severe rheumatoid arthritis in Sweden. *Ann Rheum Dis* 2005; 64(7):995-1002.

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APPENDIX 4: Comparison of Results in Subpopulations

The following sections explores the potential influence of subpopulations and possible confounding factors when reviewing the data for each of the patient groups (DMARD IR and TNF IR)

POOLED DMARD IR POPULATION (WA17822, 17823 AND WA18063)

The impact of demographic and baseline characteristics on the primary endpoint (ACR20 response) was explored using data from the pooled DMARD inadequate responder population.

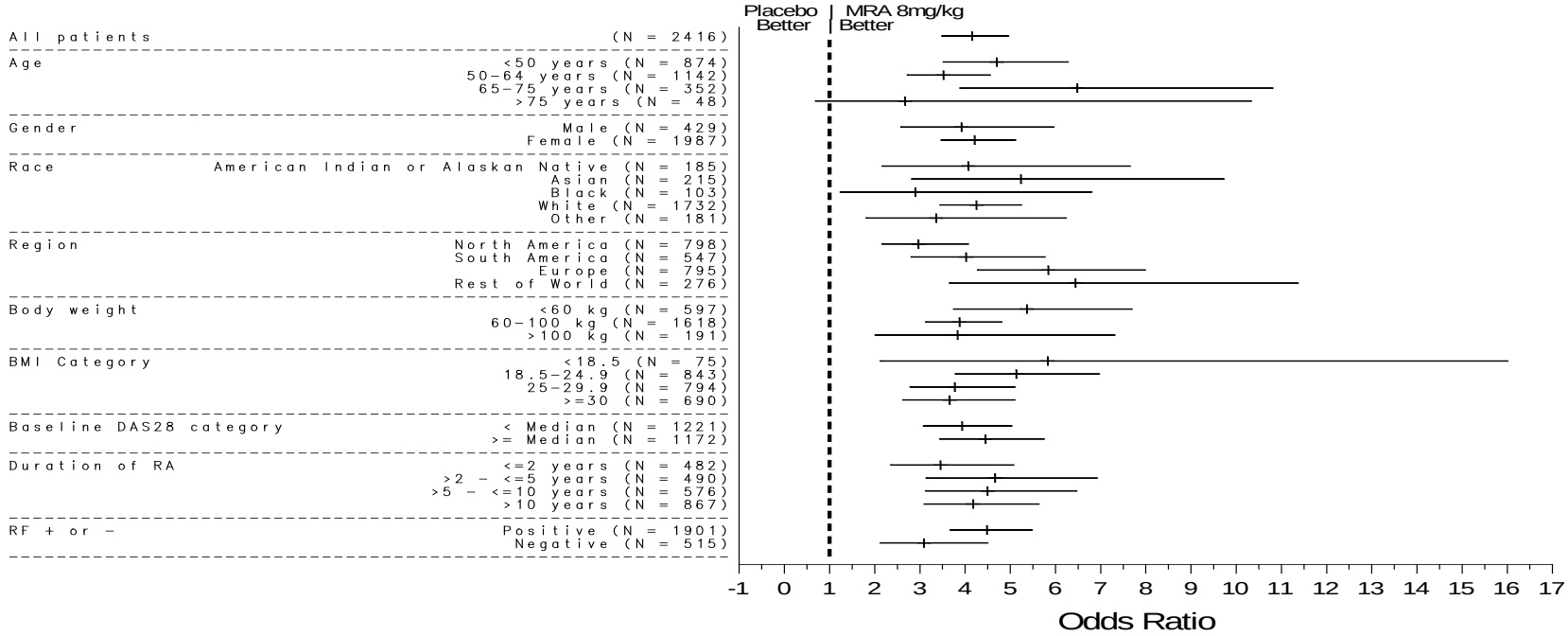
Key findings:

- The proportion of patients achieving an ACR20 response in the TCZ 8 mg/kg + DMARD-treated patients was consistently higher compared with placebo + DMARD patients across all the subgroups examined.
- Differences within subgroups were small. Lower ACR20 response rates were observed in a small subgroup of patients aged > 75 years, in black patients, patients > 100 kg, RF-negative patients and in North American patients.
- No obvious reason was identified to explain these small differences; however, it is likely that a number of confounding factors exist, e.g. North American and black patients were shown to be heavier.

A summary of ACR20 response at week 24 by intrinsic factors is shown in Figure 1 below. A summary of ACR20 response at week 24 by extrinsic factors is below in Figure 2.

Figure 1: Summary of ACR20 Response at Week 24 by Intrinsic Factors – Pooled DMARD Inadequate Responders (ITT Population)

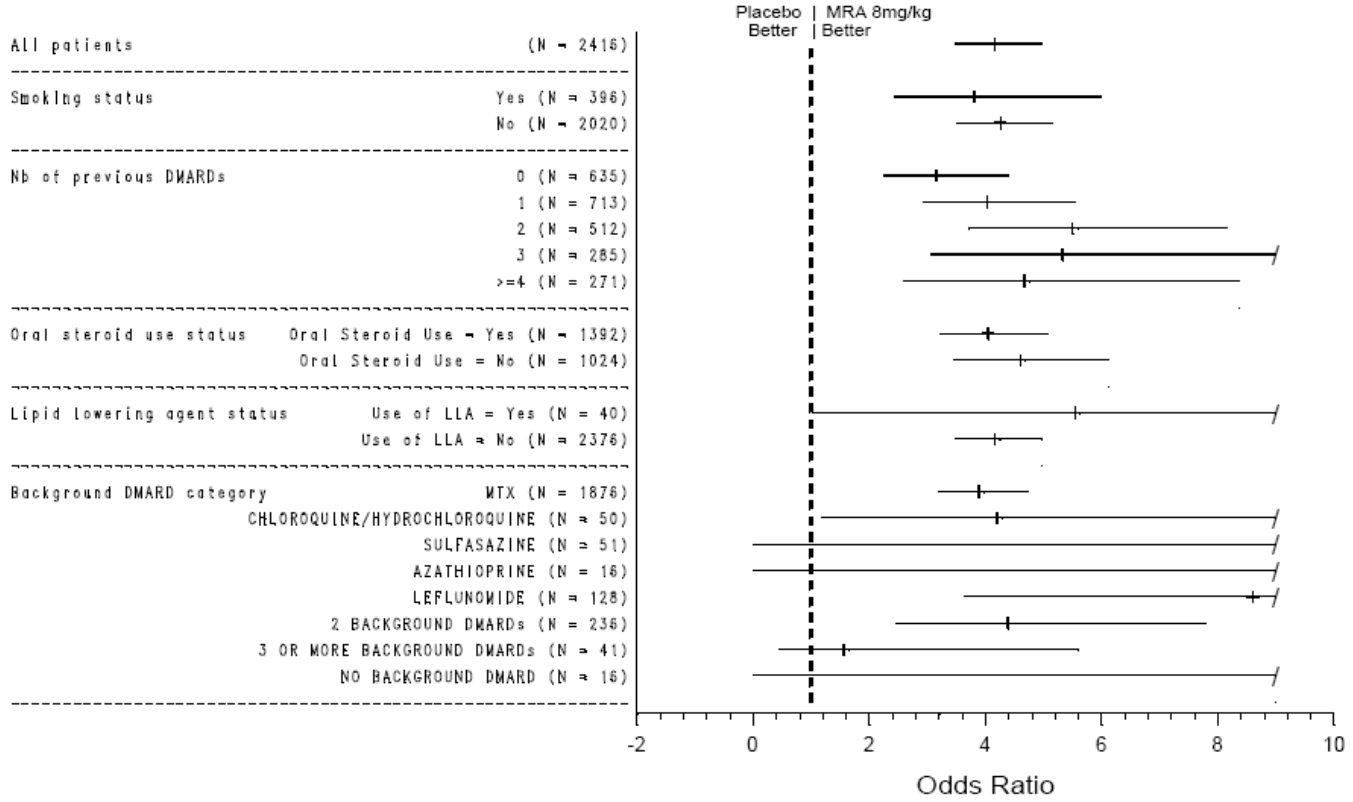
EGforestintpooli Summary of ACR20 Response at Week 24 by Intrinsic Factors - 6 Month Pooled Data (ITT Population)



LOCF used for joint counts, no imputation used for missing HAQ Score, CRP, ESR and VAS assessments. CRP is used primarily for the calculation of the ACR response, if missing, ESR will be substituted. Patients who receive escape therapy, withdraw prematurely or where an ACR can not be calculated, will be set to 'Non Responder'.
/ = Confidence Interval is too wide to display on the plot

Program : $PROD/cd11935h/EGforest.sas / Output : $PROD/cd11935h/reports/EGforestintpooli.cgm
12SEP2007 17:03

Figure 2; Summary of ACR20 Response at Week 24 by Extrinsic Factors – Pooled DMARD Inadequate Responders (ITT Population)



LOCF used for joint counts, no imputation used for missing HAQ Score, CRP, ESR and VAS assessments. CRP is used primarily for the calculation of the ACR response, if missing, ESR will be substituted. Patients who receive escape therapy, withdraw prematurely or where an ACR can not be calculated, will be set to 'Non Responder'.
/ = Confidence Interval is too wide to display on the plot

Demographic Subgroups

Age

The ACR20 response with TCZ 8 mg/kg + DMARD was similar in males and females (58% and 59%, respectively) and across age subgroups (ACR20 response rates were 65%, 56% and 59%, respectively, in the following subgroups < 50 years, 50-64 years, 65-75 years). In patients > 75 years of age, the ACR20 response rate was less pronounced at 36% (Table 1 below); however, the number of patients in this subgroup was small (~25 per treatment group), leading to wider confidence intervals around the estimate of treatment effect. Importantly, the treatment effect versus the placebo + DMARD group was maintained (36% vs 17.4% TCZ 8 mg/kg + DMARD and placebo + DMARD, respectively). Demographic differences between patients aged > 75 years in the TCZ group and the other age categories included duration of disease (longer in > 75 years) and proportion of patients who were RF positive (lower in > 75 year age group). Age had no impact on the pharmacokinetics of TCZ.

Table 1:: Percentage of Patients with an ACR20 Response at Week 24 by Age Category – Pooled DMARD Inadequate Responders (ITT Population)

	Placebo + DMARD N=1010	TCZ 8 mg/kg + DMARD N=1406
< 50 years		
N	390	484
Responders	110 (28.2%)	314 (64.9%)
50-64 years		
N	457	685
Responders	122 (26.7%)	385 (56.2%)
65-75 years		
N	140	212
Responders	25 (17.9%)	124 (58.5%)
> 75 years		
N	23	25
Responders	4 (17.4%)	9 (36.0%)

Race

The majority of patients in the DMARD inadequate responder population were white. The ACR20 response with TCZ 8 mg/kg + DMARD was similar across the subgroups of white, Asian and other patients (

Table 2 below). In American Indian/Alaskan Native patients, the ACR20 response was more pronounced in both the TCZ 8 mg/kg + DMARD and placebo+DMARD group. In black patients the ACR20 response was less pronounced in the TCZ group; however a treatment effect versus the placebo + DMARD group was maintained. No demographic differences between American Indian/Alaskan Native patients and the other race categories were observed, however, a difference in weight was observed in black patients (heavier) than patients in other categories). Race had no impact on the pharmacokinetics of TCZ.

Table 2: Percentage of Patients with an ACR20 Response at Week 24 by Race – Pooled DMARD Inadequate Responders (ITT Population)

	Placebo + DMARD N=1010	TCZ 8 mg/kg + DMARD N=1406
American Indian or Alaskan Native		
N	69	116
Responders	25 (36.2%)	81 (69.8%)
Asian		
N	88	127
Responders	19 (21.6%)	75 (59.1%)
Black		
N	44	59
Responders	11 (25.0%)	29 (49.2%)
White		
N	724	1008
Responders	181 (25.0%)	591 (58.6%)
Other		
N	85	96
Responders	25 (29.4%)	56 (58.3%)

Weight/BMI

Although it appeared that response to TCZ 8 mg/kg + DMARD decreased slightly with increasing body weight (ACR20 response rates were 65%, 58% and 50%, respectively, in the < 60 kg, 60-100 kg, > 100 kg subgroups [Table 3 below] and BMI (ACR20 response rates were 71%, 63%, 59% and 55%, respectively, in the < 18.5, 18.5-24.9, 25-29.9, > 30 subgroups), a treatment effect versus the placebo + DMARD group was maintained. The majority of patients in the pooled DMARD inadequate responder population were between 60 and 100 kg and in comparison the number of patients in the weight category > 100 kg was relatively small. There were no clinically important differences observed in the baseline demographics across the weight categories. Conversely, using the same weight categories exposure of TCZ is slightly higher in heavier patients (> 100 kg) compared with lower body weights.

A similar effect was observed in the TCZ 4 mg/kg + DMARD group in an analysis by weight. The number of ACR20 responders was lower in patients > 100 kg (26% vs 51%-55% in the lower weight categories). Conversely the ACR20 response rate by BMI categories was similar (50%, 56%, 46% and 48%, respectively, in the < 18.5, 18.5-24.9, 25-29.9, > 30 subgroups).

Table 3: Percentage of Patients with an ACR20 Response at Week 24 by Weight – Pooled DMARD Inadequate Responders (ITT Population)

	Placebo + DMARD N=1010	TCZ 8 mg/kg + DMARD N=1406
Weight < 60 kg		
N	252	345
Responders	64 (25.4%)	223 (64.6%)
Weight 60-100 kg		
N	667	951
Responders	117 (26.5%)	55 (58.4%)
Weight > 100 kg		
N	87	104
Responders	18 (20.7%)	52 (50.0%)

In a logistic regression model of the ACR20 response, there were no significant interactions with treatment group at the 10% level for age, gender, race, body weight and BMI, indicating that the treatment effect is similar in each subgroup.

Geographic Region

The subgroups by region included North America (including Canada), South America (including Central America and Mexico), Europe (including Turkey and Israel) and Rest of World (including eg, Australia, Asia and South Africa).
The proportion of patients achieving an ACR20 response in the TCZ group was higher in South America, Europe and Rest of World compared with North America (Table 4 below). Although the proportion of ACR20 responders was lower in North America, the treatment effect vs. the placebo + DMARD group was maintained. Demographic differences between patients enrolled in North America and the other regions included duration of disease (longer in North America) and weight (heavier in North America).

In a logistic regression model of the ACR20 response, a treatment by region interaction was found to be significant at the 5% level ($p = 0.0488$). Although the treatment comparison was found to be highly significant in all regions ($p < 0.0001$), it appears that the magnitude of treatment effect is higher in the Rest of the World (odds ratio=6.3; 95% CI [3.6; 11.1]) and in Europe (odd ratio=5.7; 95% CI [4.2; 7.8]) than in North America (odds ratio=2.9; 95% CI [2.1; 3.9]), Table 5 below.

Table 4: Percentage of Patients with an ACR20 Response at Week 24 by Region – Pooled DMARD Inadequate Responders (ITT Population)

	Placebo + DMARD N=1010	TCZ 8 mg/kg + DMARD N=1406
North America (including Canada)		
N	309	489
Responders	73 (23.6%)	234 (47.9%)
Odd ratio (95% CI)		2.9 [2.1; 3.9]
p-value		<0.0001
South America (including Central America)		
N	229	318
Responders	82 (35.8%)	220 (69.2%)
Odd ratio (95% CI)		3.9 [2.7; 5.6]
p-value		<0.0001
Europe (including Turkey and Israel)		
N	357	438
Responders	85 (23.8%)	283 (64.6%)
Odd ratio (95% CI)		5.7 [4.2; 7.8]
p-value		<0.0001
Rest of World (Australia, Asia and South Africa)		
N	115	161
Responders	21 (18.3%)	95 (59.0%)
Odd ratio (95% CI)		6.3 [3.6; 11.1]
p-value		<0.0001

Baseline Disease Characteristics

Duration of RA and DAS28

There were no clear differences in ACR20 response in the TCZ 8 mg/kg + DMARD group between subgroups defined by disease duration of RA (≤ 2 years, > 2 to ≤ 5 years, > 5 to ≤ 10 years, > 10 years, 58-62%), or by baseline disease activity (DAS28 < median at baseline, ≥ median at baseline, 58% vs. 61%, respectively). The median DAS28 value at baseline was 6.7 in both treatment groups.

Rheumatoid Factor (RF)

The proportion of patients achieving an ACR20 response in the 8 mg/kg TCZ + DMARD group was slightly lower in RF-negative patients compared with RF-positive patients (52% vs 61%, respectively); however, a treatment effect versus placebo + DMARD was maintained (Table 5 below).

Table 5: Percentage of Patients with an ACR20 Response at Week 24 by Rheumatoid Factor Status – DMARD Inadequate Responders (ITT Population)

	Placebo + DMARD N=1010	TCZ 8 mg/kg + DMARD N=1406
Rheumatoid Factor Positive		
N	776	1125
Responders	201 (25.9%)	687 (61.1%)
Rheumatoid Factor Negative		
N	234	281
Responders	60 (25.9%)	145 (51.6%)

In a logistic regression model of the ACR20 response, there were no significant interactions with treatment group at the 10% level for baseline DAS28, duration of RA or RF.

CRP and ESR

In a logistic regression model of the ACR20 response, there was a significant treatment by baseline CRP interaction at the 5% level ($p = 0.0389$). In order to assess the treatment effects within different baseline CRP categories, the baseline CRP values were categorized as follows: < 0.3, ≥ 0.3 to < 1, ≥ 1 to <3, ≥ 3 to < 10 and ≥ 10 mg/dL.

The proportion of ACR20 responders in the TCZ 8 mg/kg + DMARD group increased with increasing baseline CRP levels. The treatment comparison with placebo + DMARD was found to be significant in all CRP categories (Table 6 below).

Table 6: Proportion of ACR20 Responders at Week 24 by Treatment Group and CRP Category – Pooled DMARD Inadequate Responders (ITT population)

	Placebo + DMARD N=1010	TCZ 8 mg/kg + DMARD N=1406
CRP < 0.3 mg/dL		
N	101	152
Responders	27 (27%)	72 (47%)
Odd ratio (95% CI)		2.4 [1.4; 4.4]
p-value		0.0014
CRP ≥ 0.3 to < 1 mg/dL		
N	323	385
Responders	79 (24%)	217 (56%)
Odd ratio (95% CI)		4.0 [2.9; 5.5]
p-value		< 0.0001
CRP ≥ 1 to < 3 mg/dL		
N	328	471
Responders	84 (26%)	271 (58%)
Odd ratio (95% CI)		3.9 [2.9; 5.3]
p-value		< 0.0001
CRP ≥ 3 to < 10 mg/dL		
N	229	352
Responders	64 (28%)	240 (68%)
Odd ratio (95% CI)		5.5 [3.8; 7.9]
p-value		< 0.0001
CRP ≥ 10 mg/dL		
N	29	46
Responders	7 (24%)	32 (70%)
Odd ratio (95% CI)		7.1 [2.5; 20.5]
p-value		0.0003

There was no significant interaction with treatment group at the 10% level for baseline ESR levels.

HAQ and Joint Counts

In a logistic regression model of the ACR20 response, there were no significant interactions with treatment group at the 10% level for baseline HAQ, tender or swollen joint counts.

Baseline Medications

There were no clear differences in ACR20 response between patients taking or not taking oral corticosteroids at baseline.

There were no clear differences in ACR20 response by number of previous DMARDs used (ACR20 response rates ranged from 56% to 64% in patients who had received 0, 1, 2 or 3 prior DMARDs). In patients who had previously taken ≥ 4 DMARDs, the ACR20 response rate was less pronounced at 48%; however, the number of patients in this subgroup was smaller (approximately 11% of ITT). In this subgroup a treatment effect versus the placebo + DMARD group was maintained (48% in the TCZ 8 mg/kg + DMARD group vs. 16% in the placebo + DMARD group).

In a logistic regression model of the ACR20 response, there were no significant interactions with treatment group at the 10% level for oral corticosteroid use and number of previous DMARDs.

PRIOR ANTI-TNF THERAPY (WA18062)

Irrespective of the number of previously failed anti-TNF medications, there were no discernible differences between the proportions of ACR20 responders in patients who had failed one anti-TNF compared with those who had failed two or three anti-TNFs for the TCZ 8 mg/kg + MTX group (Table 7)

Table 7: ACR20, 50 and 70 Responses at Week 24 by Number of Failed Anti-TNF Medications (ITT Population)

		Placebo+MTX	TCZ4mg+MTX	TCZ8mg+MTX
1 prior TNF	ACR**20** *n= responders (%)*	76 **8** ***(10.5)***	81 **28** ***(34.6)***	92 **45** ***(48.9)***
	ACR**50** *n= responders (%)*	76 **5** ***(6.6)***	81 **15** ***(18.5)***	92 **28** ***(30.4)***
	ACR**70** *n= responders (%)*	76 **2** ***(2.6)***	81 **6** ***(7.4)***	92 **11** ***(12.0)***
2 prior TNF	ACR**20** *n= responders (%)*	64 **7** ***(10.9)***	60 **17** ***(28.3)***	52 **26** ***(50.0)***
	ACR**50** *n= responders (%)*	64 **1** ***(1.6)***	60 **8** ***(13.3)***	52 **16** ***(30.8)***
	ACR**70** *n= responders (%)*	64 **0** ***(0.0)***	60 **2** ***(3.3)***	52 **8** ***(15.4)***
3 prior TNF	ACR**20** *n= responders (%)*	18 **1** ***(5.6)***	18 **4** ***(22.2)***	26 **14** ***(53.8)***
	ACR**50** *n= responders (%)*	18 **0** ***(0.0)***	18 **4** ***(22.2)***	26 **5** ***(19.2)***
	ACR**70** *n= responders (%)*	18 **0** ***(0.0)***	18 **0** ***(0.0)***	26 **2** ***(7.7)***

In general, ACR20 responses to TCZ 8 mg/kg + MTX treatment were similar between subgroups defined by most recently failed (for reasons of safety/efficacy) anti-TNF medications (ACR20 response rates were 52%, 53% and 44%, respectively, in

patients who had most recently failed treatment with etanercept, adalimumab or infliximab).

BACKGROUND DMARD (WA18063)

Clinically relevant improvements in ACR response were evident when TCZ 8 mg/kg was added to a broad variety of background DMARD regimens allowed in study WA18063

In a logistic regression model of the ACR20 response, there were no significant interactions with treatment group at the 10% level for background DMARD. For that reason the use of the full ITT population when considered the decision problem despite the fact the indication is TCZ in combination with MTX only is justified.

Appendix 5: Review of previous NICE HAQ change assumptions

A key parameter in the ACE cost-effectiveness model for rheumatoid arthritis is an estimate of whether and how quickly patients' functional status may change while on treatment. This parameter is important because the patients' functional status during each model cycle determines the utility for the patient and thus effectiveness of the treatment. The faster patients deteriorate the lower the lifetime utility gain.

Previous assessments by NICE have used differing assumptions about on treatment clinical change.

- STA 130 (anti-TNFs) accepted that HAQ change while on treatment with anti-TNF agents was zero (Section 4.3.11). HAQ changes for DMARDs and palliation were 0.045 and 0.0600 per six month cycle respectively.

- STA 126 (Rituximab) used the following assumptions as reported in section 3.17.1 and 4.10)
    - Biologic -- .030 HAQ points per year
    - DMARD -- .045 HAQ points per year
    - Palliation -- .060 HAQ points per year

- STA 141 (Abatacept) used the following assumptions as reported in sections (3.10 and 4.20)
    - Biologic
        - 0.030 HAQ points per year
    - MTX
        - 0.045 HAQ points per year
        - 0.060 HAQ points per year

The basis for non-zero on treatment HAQ change in the rituximab and abatacept assessments was explained by NICE in TA126 (Rituximab) in section 3.17.1

For biologics:

> *"Patients receiving rituximab were assumed to have underlying HAQ progression commensurate with the general population (a constant increase of HAQ score indicating worsening functional disability of 0.03 a year).*

For patients on DMARDs and palliation the rate was justified as multiples of the biologic progression:

> *"Patients receiving palliative care were assumed to have HAQ progression twice that of the general population, while those on other DMARDs had underlying HAQ progression of 0.045 a year."*

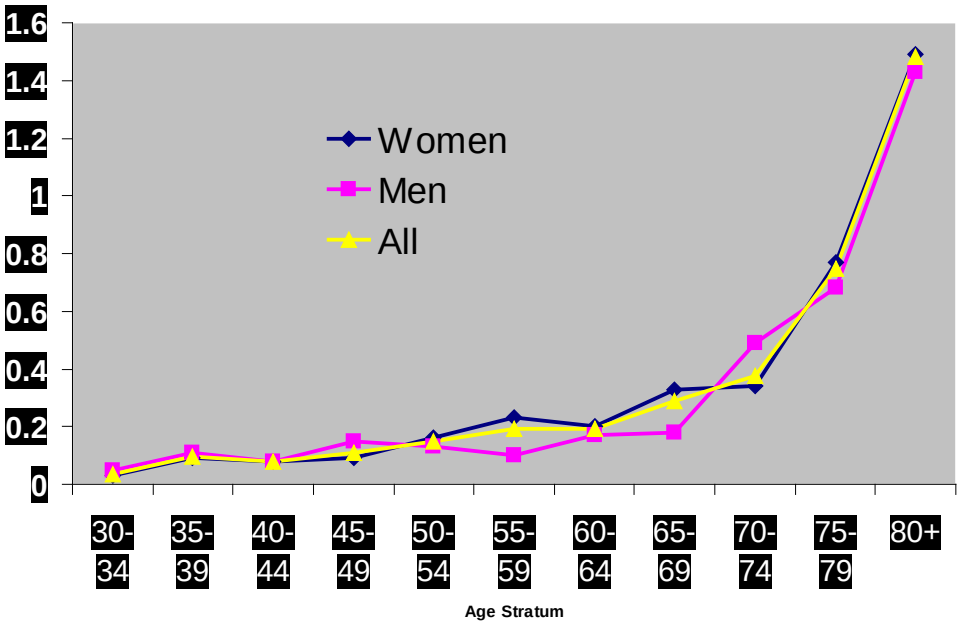
Discussion

Neither the HTA report, the FAD nor the ERG report cite the source of the 0.03/year (0.15 per cycle) progression rate. However, a literature search identified a study by

Krishnan et al. [Normative values for the health assessment questionnaire disability index. Arthritis and Rheumatism. Vol 50 No. 3 pp953-960] from which this progression rate for the normal population seems to have been derived.

The Krishnan study consisted of a random sample of 1,530 Finnish adults, who completed a mailed questionnaire in June, 2000. Table 2 in the analysis reports HAQ score mean and standard deviation stratified by age in five year increments. The estimate of a progression rate of 0.03 per year was derived by comparing HAQ scores for youngest and oldest age groups (0.03 and 1.49 respectively) and finding the slope per year. (The progression rate per year is then estimated as 1.46/50 = .0292.)

Figure 1 below shows the Krishnan data.



Several issues should be highlighted about Krishnan's findings from the perspective of their application in RA cost effectiveness models. These facts suggest that 0.03 HAQ change per year may be a substantial overestimate of change in the 'normal' population (and thus the biologic treated population – as per NICE technical assessments for rituximab and abatacept).

- Baseline age in RA models is 50-60 years.
- Biologic agents are the first agent in model treatment sequences.
- The mean change per year reported by Krishnan for this age group is 0.01 per year – far less than the rate suggested in the NICE HTA reports (0.03).
- Current regimens contain three or fewer biologic agents.
- Average time on biologic treatment in ACE model is 5.0 years (assuming 10% withdrawal rate and exponential decay).

- Thus 15 years is average on-treatment time for all biologic agents combined.
- Based on Krishnan's data a patient starting biologic treatment at age fifty and completing biologic treatment at age 65 would experience an estimated HAQ change of .011 per year.

- This is one-third the rate ascribed in the previous NICE HTAs.

Table 1: HAQ Scores by Age Group Reported by Krishnan et al.

Age Group	*Actual HAQ*	*Actual Rate of Change per year*
30	0.03	
35	0.09	0.012
40	0.08	-0.002
45	0.09	0.002
50	0.16	0.014
55	0.23	0.014
60	0.2	-0.006
65	0.33	0.026
70	0.34	0.002
75	0.77	0.086
80+	1.49	0.144
mean rate of change for patients 50-65	0.011	

Finally, it may be worth noting in our argument that over 15 years the estimated change in HAQ is 0.165, which is substantially less than a minimally important clinical change in HAQ score (usually estimated to be 0.22 – 0.27). Thus, with the use of this estimate the change in HAQ while on treatment with biologics would be well below the level that either a patient or physician would recognize.

Appendix 6: ACR response rates

Unadjusted ACR response rates				
DMARD-IR	**ACR 20**	**ACR 50**	**ACR 70**	**Source**
Tocilizumab LITHE	0.563	0.322	0.126	CSR
Tocilizumab OPTION	0.585	0.439	0.22	CSR
Tocilizumab Pooled DMARD-IR population (OPTION, TOWARD & LITHE)	0.592	0.37	0.185	CSR, EMEA submission
Tocilizumab TOWARD	0.608	0.376	0.205	CSR
Adalimumab	0.633	0.391	0.208	Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, et al. Radiographic, Clinical, and Functional Outcomes of Treatment With Adalimumab (a Human Anti-Tumor Necrosis Factor Monoclonal Antibody) in Patients With Active Rheumatoid Arthritis Receiving Concomitant Methotrexate Therapy. Arth & Rheum 2004; 50 (5): 1400-1411.
Ciclosporin	0.25	0.1	0.02	Assume same as placebo
Etanercept	0.71	0.39	0.15	Weinblatt ME, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med 1999; 340 (4): 253-259.
Gold	0.25	0.1	0.02	Assume same as placebo
Infliximab	0.52	0.27	0.1	Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, et al. Infliximab (chimeric anti-tumour necrosis factor α monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. Lancet 1999; 354: 1932-39.; weighted average of the two 3mg arms.
Leflunomide	0.52	0.34	0.2	Strand V, Cohen S, Schiff M, et al. Treatment of active rheumatoid arthritis with Leflunomide compared with placebo and methotrexate. Arch Intern med 1999; 159: 2542-2550.

Unadjusted ACR response rates – cont…				
DMARD-IR	**ACR 20**	**ACR 50**	**ACR 70**	**Source**
Rituximab (TNF-IR)	0.51	0.27	0.12	Cohen et al. 2006
Palliative care	0.25	0.1	0.02	CSR
TNF-IR	**ACR 20**	**ACR 50**	**ACR 70**	**Source**
Tocilizumab RADIATE	0.50	0.29	0.12	CSR
Ciclosporin	0.10	0.04	0.01	Assume same as palliative care
Gold	0.10	0.04	0.01	Assume same as palliative care
Leflunomide	0.10	0.04	0.01	Assume same as palliative care
Rituximab (TNF-IR)	0.51	0.27	0.12	Cohen et al. 2006
Palliative care	0.10	0.04	0.01	Radiate CSR

Appendix 7: Monitoring assumptions and frequency

Treatment	Pre-treatment	First six months	Subsequent time	Average Time on treatment	Reference
Etanercept	At least one OPV, FBC, ESR, CRP, LFT, CXR, U&E	One OPV per month, 4 GPV and 13 FBC, ESR, CRP, LFT, U&E for the 6 month period	One OPV, one GPV and one of FBC, ESR, CRP, LFT, U&E bimonthly	3.76	NICE TA126; D. Porter, personal communication
Adalimumab	At least one OPV, FBC, ESR, CRP, LFT, CXR, U&E	One OPV per month, 4 GPV and 13 FBC, ESR, CRP, LFT, U&E for the 6 month period	One OPV, one GPV and one of FBC, ESR, CRP, LFT, U&E bimonthly	3.76	NICE TA126; D. Porter, personal communication
Leflunomide	At least one OPV, FBC, ESR, CRP, LFT, CXR	13 OPV, 4 GPV and 13 FBC, ESR, CRP, LFT, U&E for the 6 month period.	One OPV, one GPV and one of FBC, ESR, CRP, LFT, U&E bimonthly	0.72	NICE TA126; D. Porter, personal communication
Gold	At least one OPV, FBC, ESR, CRP, LFT, CXR	26 OPV, 18 GPV, and 26 FBC, ESR, CRP, LFT, U&E for the 6 month period	One OPV, one GPV and one of FBC, ESR, CRP, LFT, U&E monthly	0.71	NICE TA126; D. Porter, personal communication
Ciclosporin	At least one OPV, FBC, ESR, CRP, LFT, CXR	13 OPV, 4 GPV and 13 FBC, ESR, CRP, LFT, U&E for the 6 month period.	One OPV, one GPV and one of FBC, ESR, CRP, LFT, U&E monthly	0.70	NICE TA126; D. Porter, personal communication
Palliative care	At least one OPV, FBC, ESR, CRP, LFT, CXR	13 OPV, 4 GPV and 13 FBC, ESR, CRP, LFT, U&E for the 6 month period	One OPV, one GPV and one of FBC, ESR, CRP, LFT, U&E monthly	15.95 years	NICE TA126; D. Porter, personal communication

*OPV outpatient visit, GPV general practitioner visit, FBC full blood count, ESR erythrocyte sedimentation, CRP C-reactive protein, LFT liver function test, CXR chest X-ray, U&E urea, electrolytes and creatinine

Table 2: Costs of monitoring elements

Outpatient visit (OPV) first attendance	£183 per visit	Reference Costs 2006/07
Outpatient visit (OPV) follow-up	£109 per visit	
GP visit (GPV)	£46 per visit	PSSRU 2008
Full blood count (FBC)	£14.58 per test	Barton et al. (2004); inflated to 2008 costs
Erythrocyte sedimentation (ESR) and C-reactive protein (CRP)	£14.58 per test	Barton et al. (2004); inflated to 2008 costs
Liver function test (LFT)	£8.09 per test	Barton et al. (2004); inflated to 2008 costs
Urea, electrolytes and creatinine (U&E)	£8.09 per test	Barton et al. (2004); inflated to 2008 costs
Chest X-ray (CXR)	£21.26 per test	Barton et al. (2004); inflated to 2008 costs

Appendix 8: MTC

Search strategy used for the MTC:

rheumatoid arthritis (in title or abstract) OR rheumatoid arthritis (mesh heading) AND randomised controlled trial (publication type) OR clinical trial (publication type) AND etanercept OR etanercept OR infliximab OR infliximab OR adalimumab OR adalimumab OR certolizumab OR cimzia OR (biologic AND disease modifying) OR (biologic AND DMARD) OR tumor necrosis factor-alpha (mesh heading) OF TNF (in title or abstract) AND ACR-20 OR ACR-20 OR ACR-20 OR ACR-50 OR ACR-50 OR ACR-50 OR ACR-70 OR ACR-70 OR ACR-70 OR ACR core parameters OR ACR-N OR Disease Activity Score OR DAS OR EULAR response OR fatigue; publication year > 1989

Table A1:. Overview of Study Design of Included Trials in the MTC

Source	Trial design	Number of patients	Patient treatment history	Compared interventions (See Note 1)	Background treatment
OPTION trial(46;47)	Phase III Randomised, double-blind, placebo-controlled trial	623	Patients with moderate to severe active RA with an inadequate response to MTX therapy	Tocilizumab 8 mg/kg i.v. every 4 weeks vs. [Tocilizumab 4 mg/kg i.v. every 4 weeks] vs. placebo	MTX
TOWARD trial(48)	Phase III Randomised, double-blind, placebo-controlled trial	1216	Patients with active RA who had an inadequate response to DMARD therapy	Tocilizumab 8 mg/kg i.v. every 4 weeks vs. placebo	DMARDs

Source	Trial design	Number of patients	Patient treatment history	Compared interventions (See Note 1)	Background treatment
LITHE trial	Phase III, randomised, double-blind, placebo-controlled trial	1196	Patients with moderate to severe active RA with inadequate response to MTX	Tocilizumab 8 mg/kg i.v. every 4 weeks [Tocilizumab 4 mg/kg i.v. every 4 weeks] placebo	MTX
Weinblatt et al, 2003 (ARMADA)(49)	Randomised, double-blind, placebo-controlled trial	271	Patients with active RA despite treatment with MTX	[adalimumab 80 mg s.c. injection every other week] vs. adalimumab 40 mg s.c. injection every other week vs. [adalimumab 20 mg s.c. injection every other week] vs. placebo	MTX
Furst et al, 2003 (STAR)(50)	Randomised, double-blind, placebo-controlled trial	636	Patients with active RA despite treatment with DMARDs	adalimumab 40 mg every other week s.c. injection vs. placebo	standard anti rheumatic therapy
Van der Putte et al, 2004(51)	Randomised, double-blind, placebo-controlled trial	544	Patients with active RA despite treatment with DMARDs	adalimumab 40 mg every other week s.c. injection vs.	usual concomitant therapy

Source	Trial design	Number of patients	Patient treatment history	Compared interventions (See Note 1)	Background treatment
				[adalimumab 40 mg weekly s.c. injection] vs. [adalimumab 20 mg every other week s.c. injection] vs. adalimumab 20 mg weekly s.c. injection vs. placebo	
Keystone et al, 2004(52)	Randomised, double-blind, placebo-controlled trial	619	Patients with active RA despite treatment with MTX	adalimumab 40 mg every other week s.c. injection vs. [adalimumab 20 mg every other week s.c. injection] vs. placebo	MTX
Weinblatt et al, 1999(53)	Randomised, double-blind, placebo-controlled trial	89	Patients with persistent RA despite receiving MTX	etanercept 25 mg 2/w s.c. injection vs. placebo	MTX
Klareskog et al, 2004 (TEMPO-	Randomised, double-blind, active controlled study	686	Patients with active RA despite previous treatment with DMARDs	etanercept 25 mg 2/w s.c. injection plus MTX vs. [etanercept 25 mg 2/w s.c injection] vs.	none

Source	Trial design	Number of patients	Patient treatment history	Compared interventions (See Note 1)	Background treatment
I)(54)				MTX	
Combe et al, 2006(55)	Randomised, double-blind, active controlled study	254	Patients with active RA despite treatment with sulfasalazine	etanercept 25mg s.c. 2/w injection + sulfasalazine 2-3 mg/day vs. [etanercept 25mg s.c. 2/w injection] vs. sulfasalazine 2-3 mg/day	none
Moreland et al, 1999(56)	Randomised, double-blind, placebo-controlled trial	234	Patients with active RA despite treatment with DMARDs	etanercept 25 mg 2/w s.c. injection vs. [etanercept 10 mg 2/w s.c. injection] vs. placebo	none
Maini et al, 1999 (ATTRACT-I)(57)	Randomised, double-blind, placebo-controlled trial	428	Patients with active RA despite treatment with MTX	[infliximab 10 mg/kg infusion every 4 weeks] vs. [infliximab 10 mg/kg infusion every 8 weeks] vs. infliximab 3 mg/kg infusion every 4 weeks vs. infliximab 3 mg/kg infusion every 8 weeks vs. placebo	MTX
Westhovens et al, 2006	Randomised, placebo controlled, double-blind	1084	Patients with active RA despite receiving	[infliximab 10 mg/kg infusion at weeks 0, 2, 6, and 14] vs.	MTX

Source	Trial design	Number of patients	Patient treatment history	Compared interventions (See Note 1)	Background treatment
(START)	trial		MTX	infliximab 3 mg/kg infusion at weeks 0, 2, 6, and 14 vs placebo	
Schiff et al, 2008	Randomised, double blind, placebo controlledl	431	Patients with active RA despite receiving MTX treatment.	Infliximab 3 mg/kg i.v. infusion once every 8 weeks. Abatacept 10 mg/kg i.v. infusion vs. placebo.	MTX
Kremer et al, 2003(58)	Randomised, double-blind, placebo-controlled	339	Patient with active RA with inadequate response to MTX	abatacept i.v. infusion 10 mg/kg vs. [abatacept i.v. infusion 2 mg/kg] vs. placebo	MTX
Kremer et al, 2006(59)	Randomised, double-blind, placebo-controlled trial	652	Patients with active RA despite MTX treatment	abatacept 10 mg/kg i.v. infusion once-monthly vs. placebo	MTX stable dosage NSAIDs/ glucorticoids
Emery et al, 2006 (DANCER)(6	Phase IIb Randomised, double-blind, placebo-controlled	465	Patients with active RA that is resistant to DMARDs, including biologic agents	rituximab 2x1,000-mg i.v. infusion doses at day 1 and 15 vs. [rituximab 2x500-mg i.v. infusion doses at day 1	MTX

Source	Trial design	Number of patients	Patient treatment history	Compared interventions (See Note 1)	Background treatment
0)	multi-factorial Trial			and 15] vs. placebo	
Edwards et al, 2004(61)	Randomised, double-blind, placebo-controlled trial	652	Patients who had active RA despite treatment with MTX	rituximab (1000 mg on days 1 and 15) plus MTX (≥10 mg per week) vs. [rituximab (1000 mg on days 1 and 15) plus cyclophosphamide (750 mg on days 3 and 17)] vs. [rituximab (1000 mg on days 1 and 15)] vs. MTX (≥10 mg per week) (control)	corticosteriods

Compared interventions in square brackets [ ] indicate dosages that are not included on the label.

Table 2: Overview of Characteristics of Patients Included in the MTC

Source	Compared interventions	Gender (%F)	Age (years)	Years since diagnosis	Mean no. of prior DMARDs	%pts on NSAIDs	%pts on corticoidsteriods	Tender joint count	Swollen joint count	Patients assessment of pain	Patients global assessment of disease activity	Physician global assessment of disease activity	HAQ	C-reactive protein level
OPTION trial	Tocilizumab 8 mg/kg i.v. every 4 weeks	85	50.8	7.47	1.5	65.5	54.9	31.9 (15.47).	19.5 (11.33)	59.9 (22.44)	64.8 (22.15)	64 (15.3)	1.6 (0.62)	2.6 (2.6)
	Tocilizumab 4 mg/kg i.v. every 4 weeks	82	51.4	7.43	1.5	68.4	54.7	33.2 (15.62)	20 (10.91)	60.7 (20.96)	65.6 (20.86)	63.6 (15.79)	1.6 (0.64)	2.8 (3.4)
	Placebo	78	50.6	7.78	1.7	68.1	54.4	32.8 (16.05)	20.7 (11.71)	57.3 (22.15)	63.6 (21.82)	63.7 (14.8)	1.5 (0.63)	2.4 (2.8)
TOWARD trial	Tocilizumab 8 mg/kg i.v. every 4 weeks	81	53.0	9.8	1.6	nr	nr	30.1 (16)	19.7 (11.6)	58.4 (22.5)	66.2 (22.7)	63.6 (16.5)	1.5 (0.62)	2.6 (3.2)

	placebo	84	53.5	9.8	1.6			29.1 (14.8)	18.7 (10.8)	58.5 (23.4)	65.5 (23.7)	63.4 (16.9)	1.5 (0.62)	2.6 (4.7)
LITHE trial	Tocilizumab 8 mg/kg i.v. every 4 weeks	82	53.4	9.29	1.6	nr	39	29.3 (15.2)	17.3 (9.5)	55.7 (22.3)	62.7 (22.5)	62.7 (16.9)	1.5 (0.60)	2.3 (2.6)
	Tocilizumab 4 mg/kg i.v. every 4 weeks	84	51.4	9.43	1.7		34	27.9 (14.2)	17.0 (9.8)	53.3 (22.0)	61.0 (23.3)	62.3 (16.7)	1.5 (0.64)	2.1 (2.4)
	Placebo	83	51.3	8.94	1.6		33	27.9 (14.8)	16.6 (9.2)	53.3 (22.1)	63.1 (23.4)	63.1 (17.3)	1.5 (0.62)	2.2 (2.5)
Weinblatt et al, 2003 (ARMADA)	adalimumab 80 mg s.c injection every other week .	75.3	55.5	12.8	3.1	nr	46 (total of adalimumab) 58	30.2 (15.7)	17 (8.2)	55 (23.7)	58.8 (24.9)	62.6 (14.7)	1.55 (0.66)	2.8 (2.7)
	adalimumab 40 mg s.c injection every other week .	74.6	57.2	12.2	2.9			28 (12.7)	17.3 (8.6)	53 (22.0)	56.9 (21.1)	58.7 (15.8)	1.55 (0.61)	2.1 (1.8)
	adalimumab 20 mg s.c injection every	75.4	53.5	13.1	3.0			28.5 (14.4)	17.6 (8.7)	55.1 (20.6)	57.6 (21.6)	60.5 (17.3)	1.52 (0.62	2.8 (3.1)

	other week .												)	
	placebo	82.3	56	11.1	3			28.7 (15.2)	16.9 (9.5)	57.2 (21)	58 (23.2)	58.9 (15.3)	1.64 (0.63)	3.1 (3.9)
Furst et al, 2003 (STAR)	adalimumab 40 mg every other week s.c injection .	79.2	55.6	11.5	1.2	63.8	54.4	nr	nr	nr	nr	nr	nr	nr
	placebo	79.6	55	9.3	1.1	62.3	50.9							
Van de Putte et al, 2004	adalimumab 40 mg every other week s.c. injection .	79.6	52.7	10.6	3.8	82.3	68.1	33.9 (15.8)	20.5 (10.6)	70.3 (19.9)	72.6 (19.3)	67.3 (16.6)	1.83 (0.59)	4.62
	adalimumab 40 mg weekly s.c. injection .	78.6	51.8	11.9	3.8	76.7	81.6	33.8 (14.0)	19.4 (8.8)	71.4 (19.1)	74.4 (18.6)	68.0 (16.8)	1.83 (0.57)	4.19
	adalimumab 20 mg every other week s.c. injection	79.2	53.1	9.3	3.7	81.1	69.8	33.7 (14.3)	19.4 (8.6)	73.8 (18.2)	75.1 (18.2)	69.6 (17.6)	1.88 (0.60)	3.76
	adalimumab 20 mg weekly s.c. injection .	72.3	54.4	11.3	3.6	75.0	67.8	35.3 (14.9)	19.8 (9.7)	71.1 (21.0)	74.0 (20.1)	68.1 (17.5)	1.88 (0.63	3.76

													)	
	placebo	77.3	53.5	11.6	3.6	83.6	67.3	35.5 (14.2)	19.8 (9.3)	70.2 (18.1)	71.8 (19.9)	68.5 (18.2)	1.88 (0.64)	3.92
Keystone et al, 2004	adalimumab 40 mg every other week s.c injection .	76.3	56.1	11.0	2.4	nr	nr	27.3 (12.7)	19.3 (9.8)	55.9 (20.4)	52.7 (21.0)	62.0 (16.7)	1.45 (0.63)	1.8 (2.3)
	adalimumab 20 mg every other week s.c injection .	73	56.1	10.9	2.4			27.9 (13.6)	19.6 (9.9)	55.2 (23.0)	51.9 (23.1)	61.6 (16.8)	1.44 (0.64)	1.4 (1.4)
	placebo							56.1 (12.0)	19.0 (9.5)	56.3 (22.9)	54.3 (22.9)	61.3 (17.3)	1.48 (0.59)	1.8 (2.1)
Maini et al, 1999 (ATTRACT-I)	infliximab 10 mg/kg infusion every 4 weeks .	73	52	8.7	2.5	68	65	35	23	6.6	6.0	6.0	1.5	2.4
	infliximab 10 mg/kg infusion every 8 weeks .	77	55	9.0	2.5	77	57	30	20	6.7	6.4	6.4	1.8	2.5

	infliximab 3 mg/kg infusion every 4 weeks .	77	51	7.2	2.6	76	53	31	20	6.9	5.7	6.2	1.8	2.0
	infliximab 3 mg/kg infusion every 8 weeks .	81	56	8.4	2.8	79	63	32	19	7.0	6.6	6.1	1.8	3.1
	placebo	80	51	6.9	2.5	72	64	24	19	6.7	6.2	6.5	1.8	3
Westhovens et al, 2006 (START)	infliximab 10 mg/kg infusionat weeks 0, 2, 6, and 14 .	78	52	6.3	nr	41.3	59	22	15	5.9	5.7	6.2	1.5	1.6
	infliximab 3 mg/kg infusion at weeks 0, 2, 6, and 14 .	80	53	7.8		43.3	59	22	15	6.1	5.6	6.2	1.5	1.6
	placebo	83	52	8.4		39.4	59	22	15	5.9	5.7	6.3	1.5	1.2
Schiff et al, 2008	Vs. Infliximab 3 mg/kg i.v. infusion once every eight weeks	82.4	49.1	7.3	nr	86.1	71.5	31.7	20.3	nr	nr	nr	1.7	3.3
	Vs. abatacept 10	83.3	49.0	7.9	nr	85.3	75.6	31.6	21.3	nr	nr	nr	1.8	3.1

	mg/kg i.v. infusion once monthly													
	Placebo	87.3	49.4	8.4	nr	84.5	70.0	30.3	20.1	nr	nr	nr	1.8	2.7
Weinblatt et al, 1999	etanercept 25 mg 2/w s.c. injection .	73	53	13	2.8	80	70	only median values presented						
	placebo	90	48	13	2.7	75	53							
Klareskog et al, 2004 (TEMPO-I)	etanercept 25 mg 2/w s.c injection plus MTX .	74	52.5	6.8	2.3	88	62	nr	nr	nr	nr	nr	nr	nr
	etanercept 25 mg 2/w s.c injection .	77	53.2.	6.3	2.3	88	57							
	MTX	79	53	6.8	2.3	86	64							
Combe et	etanercept 25mg s.c.	80.2	50.6	6.5	nr	nr	nr	31.3	19.4	58.5	nr	nr	1.6	only

al, 2006	2/w injection + sulfasalazine 2-3 mg/day .							(14.1)	(10.4)	(20.7)			(0.6)	median values presented
	etanercept 25mg s.c. 2/w injection .	78.6	51.3	7.1				29.7 (14.7)	19.1 (10.1)	62.6 (21.7)			1.7 (0.6)	
	sulfasalazine 2-3 mg/day	82	53.3	5.6				31.3 (14)	18.65 (11.1)	58.8 (20)			1.6 (0.5)	
Moreland et al, 1999	etanercept 25 mg 2/w s.c injection .	74	53	11	3.3	67	81	33	25	6.7	7.0	6.9	1.6	4.7
	etanercept 10 mg 2/w s.c injection .	84	53	13	3.4	67	66	34	25	6.6	6.9	6.9	1.7	5.3
	placebo	76	51	12	3	84	58	35	25	6.5	6.9	6.9	1.7	4.1
Kremer et al, 2003	Abatacept i.v infusion 10 mg/kg	75	55.8	9.7	2.6	nr	nr	30.8 (12.2)	21.3 (8.4)	62.1 (21.4)	60.1 (20.7)	62.1 (14.8)	1 (0.5)	2.9 (2.8)
	Abatacept i.v infusion 2 mg/kg	63	54.4	9.7	5.7			28.2 (12)	20.2 (8.9)	64.5 (22.3)	59.4 (23.7)	61.0 (16.7)	1 (0.5)	3.2 (2.6)
	placebo	66	54.7	8.9	2.6			29.2 (13)	21.8 (8.8)	65.2 (22.1)	62.8 (21.6)	63.3 (15.5)	1 (0.6)	3.2 (3.2)

Kremer et al, 2006	Abatacept 10 mg/kg i.v infusion once-monthly	81.7	50.4	8.9	nr	82.6	68.5	nr	nr	nr	nr	nr	nr	nr
	placebo	77.8	51.5	8.5		85.5	72.1							
Emery et al, 2006 (DANCER)	Rituximab 2 1,000-mg i.v. infusion doses at day 1 and 15	80	51.1	10.8	2.5	nr	nr	32	22	nr	nr	nr	1.7	3.0
	Rituximab 2 500-mg i.v. infusion doses at day 1 and 15	83	51.4	11.1	2.5			33	22				1.8	3.2
	placebo	80	51.1	9.3	2.2 (excl. MTX)			35	21				1.7	3.3
Edwards et al, 2004	Rituximab (1000 mg on days 1 and 15) plus MTX ≥ 10 mg per week)	75	54	12	2.5	nr	nr	nr	nr	nr	nr	nr	nr	nr
	Rituximab (1000 mg on days 1 and 15)	83	53	10	2.6									

plus cyclophosphamide (750 mg on days 3 and 17)				
Rituximab (1000 mg on days 1 and 15)	73	54	9	2.5
MTX ≥10 mg per week) (control)	80	54	11	2.6

Compared interventions presented in grey font indicate dosages not included in the label.

Table A3: Reported Data for ACR 20/50/70 Responders in Conventional DMARD-IR Patients (All Studies)

Reference	placebo				Tocilizumab				TNFα inhibitors				Abatacept				Rituximab			
	ACR 20	ACR 50	ACR 70	*n*	ACR 20	ACR 50	ACR 70	*n*	ACR 20	ACR 50	ACR 70	*n*	ACR 20	ACR 50	ACR 70	*n*	ACR 20	ACR 50	ACR 70	*n*
OPTION	54	22	4	*204*	120	90	45	*205*												
TOWARD	101	37	12	*413*	488	302	165	*803*												
LITHE	106	38	8	393	224	128	50	398												
Weinblatt et al, 2003	9	5	3	*62*					45	37	18	*67*								
Furst et al, 2003	111	36	11	*318*					168	92	47	*318*								
van der Putte et al, 2004	21	9	2	*110*					52	25	14	*113*								
Keystone et al, 2004	59	19	5	*200*					131	81	43	*207*								
Weinblatt et al, 1999	8	1	1	*30*					42	23	10	*59*								
Klareskog et al, 2004	164	91	34	*228*					189	134	81	*231*								
Combe et al, 2006	14	7	1	*50*					75	53	25	*101*								
Moreland et al, 1999	9	4	1	*80*					46	31	12	*78*								
Maini et al, 1999	18	4	1	*88*					92	47	17	*172*								
Westhovens et al, 2007	87	33	16	*363*					199	110	48	360								
Schiff et al, 2008	46	22	10	*110*					98	61	40	165	104	63	32	*156*				
Kremer et al, 2003	42	14	2	*119*									69	42	19	*115*				
Kremer et al, 2006	87	37	14	*219*									294	173	86	*433*				
Edwards et al, 2004	15	5	2	*40*													29	17	9	*40*
Emery et al, 2006	28	13	5	*122*													54	34	20	*122*

Table A4: Relative Treatment Effect for ACR 20/50/70 Responses vs. Placebo in DMARD-IR Patients (Base Case Analysis)

Treatment vs. placebo	Relative risk	2.5%CrL	97.5%CrL	Odds ratio	2.5%CrL	97.5%CrL	Ranking	Probability of being the best treatment
ACR 20								
tocilizumab	2.06	1.64	2.45	4.06	2.32	7.03	2	46%
TNF-a group	1.99	1.72	2.32	3.67	2.64	5.43	2	21%
abatacept	1.85	1.39	2.29	3.06	1.69	5.41	3	10%
rituximab	1.90	1.28	2.50	3.26	1.46	7.53	3	23%
ACR 50								
tocilizumab	3.60	2.49	4.98	5.61	3.12	10.25	1	59%
TNF-a group	3.19	2.51	4.26	4.56	3.23	7.18	2	17%
abatacept	2.72	1.71	4.01	3.57	1.90	6.58	3	6%
rituximab	2.90	1.52	4.93	3.93	1.63	9.97	3	19%
ACR 70								
tocilizumab	6.75	4.90	9.44	9.08	6.03	14.35	1	87%

TNF-a group	3.81	3.05	4.80	4.36	3.40	5.63	3	0%
abatacept	3.42	2.47	4.76	3.83	2.65	5.62	4	0%
rituximab	4.33	2.15	8.91	5.08	2.27	13.09	2	13%

A random effects model was used for ACR 20 and ACR 50 and a fixed effects model was used for ACR 70 analyses.

Table A5: Relative Treatment Effect for ACR 20/50/70 Responses of Tocilizumab vs. Other Biologic Agents in the Management of DMARD-IR patients (Base Case Analysis)

Tocilizumab vs. alternatives	Relative risk	2.5%CrL	97.5%CrL	Odds ratio	2.5%CrL	97.5%CrL	Probability of Tocilizumab being the better treatment
ACR 20							
TNF-a group	1.04	0.79	1.27	1.11	0.55	2.06	64%
abatacept	1.11	0.82	1.55	1.33	0.60	2.99	78%
rituximab	1.08	0.76	1.66	1.25	0.46	3.29	68%
ACR 50							
TNF-a group	1.13	0.70	1.61	1.24	0.57	2.39	74%
abatacept	1.32	0.78	2.31	1.58	0.68	3.78	88%
rituximab	1.24	0.66	2.52	1.43	0.48	4.13	75%
ACR 70							
TNF-a group	1.77	1.22	2.58	2.09	1.28	3.50	>99%
abatacept	1.98	1.28	3.07	2.37	1.36	4.24	>99%

rituximab	1.56	0.73	3.30	1.79	0.64	4.48	87%

A random effects mode used for ACR 20 and ACR 50 and a fixed effects model for ACR 70 analyses.

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