NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Abatacept for the treatment of rheumatoid arthritis after the failure of conventional disease-modifying anti-rheumatic drugs

Manufacturer submission of evidence

November 2010

Bristol-Myers Squibb Pharmaceuticals Ltd

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Instructions for manufacturers and sponsors

This is the specification for submission of evidence to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. It shows manufacturers and sponsors what information NICE requires and the format in which it should be presented. NICE acknowledges that for medical devices manufacturers particular sections might not be as relevant as they are for pharmaceuticals manufacturers. When possible the specification will refer to requirements for medical devices, but if it hasn't done so, manufacturers or sponsors of medical devices should respond to the best of their ability in the context of the question being addressed.

Use of the specification and completion of appendices 1 to 13 (sections 9.1 to 9.13) are mandatory (when applicable), and the format should be followed whenever possible. Reasons for not following this format must be clearly stated. Sections that are not considered relevant should be marked 'N/A' and a reason given for this response. The specification should be completed with reference to the NICE document 'Guide to the methods of technology appraisal' (www.nice.org.uk), particularly with regard to the 'reference case'. Users should see NICE's 'Guide to the single technology appraisal (STA) process' (www.nice.org.uk) for further details on some of the procedural topics referred to only briefly here.

If a submission is based on preliminary regulatory recommendations, the manufacturer or sponsor must advise NICE immediately of any variation between the preliminary and final approval.

A submission should be as brief and informative as possible. It is expected that the main body of the submission will not usually exceed **100 pages excluding the pages covered by the template**. The submission should be sent to NICE electronically in Word or a compatible format, and not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level

of detail requested, but that is considered to be relevant to the submission. Appendices are not normally presented to the Appraisal Committee. Any additional appendices should be clearly referenced in the body of the submission and should not be used for core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the clinical-effectiveness section with ‘see appendix X’. Clinical trial reports and protocols should not be submitted, but must be made available on request.

Trials should be identified by the first author or trial ID, rather than by relying on numerical referencing alone (for example, ‘Trial 123/Jones et al[126]’ rather than ‘One trial[126]’).

For information on submitting cost-effectiveness analysis models, disclosure of information and equality and diversity, users should see ‘Related procedures for evidence submission’, appendix 10.

If a patient access scheme is to be included in the submission, please refer to the patient access scheme submission template available on request. Please submit both documents and ensure consistency between them.

Executive summary

The UK approved name, brand name, marketing status and principal mechanism of action of the proposed technology.

The first official approval for abatacept (Orencia®) was granted to Bristol Myers Squibb (BMS) on 23 December 2005 in the United States of America.

Orencia® is approved and marketed in the following countries: Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Columbia, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, India, Ireland, Italy, Luxembourg, Netherlands, Norway, Peru, Poland, Portugal, Romania, Russia, Slovak Republic, Spain, Sweden, Switzerland, Lichtenstein, United Kingdom, United States of America and Venezuela.

Abatacept is a human fusion protein that consists of an 'active' extracellular CTLA-4 domain linked to an 'inert' Fc portion of human immunoglobulin. Abatacept binds to CD80 and CD86 on T-cells preventing co-stimulatory signals required for full T-cell activation. This subsequently downregulates the downstream inflammatory events which lead to joint damage and bone erosion associated with Rheumatoid Arthritis (RA), including the activation of rheumatoid factor (RF) producing B cells, macrophage activation and the production of inflammatory cytokines such as TNFα, IL-1 and IL-6. Abatacept modulates T-cell co-stimulation without inducing depletion of T-cells or other leukocytes. This mechanism of action is unique in comparison to other biologics licensed for the same indication.

This unique mechanism of action allows abatacept to exert its effect on the immune system which in turn offers another pharmacological tool to manage rheumatoid arthritis (RA).

The formulation(s), strength(s), pack size(s), maximum quantity(ies), anticipated frequency of any repeat courses of treatment and acquisition cost.

Abatacept is available as a powder for concentrate for solution for infusion. Each vial contains 250 mg powder. Pack sizes are 1, 2, or 3 vials.

Abatacept is available at a list price of £302.40 for a 250mg vial. However, based on an agreement with the Department of Health, the net cost to the NHS is £242.17 per vial (excluding VAT).

The indication(s) and any restriction(s).

Abatacept in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who responded inadequately to previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) including methotrexate (MTX) or a TNF-alpha inhibitor.

A reduction in the progression of joint damage and improvement of physical function have been demonstrated during combination treatment with abatacept and methotrexate.

Abatacept in combination with methotrexate is indicated for the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis (JIA) in paediatric patients 6 years of age and older who have had an insufficient response to other DMARDs including at least one TNF inhibitor. Abatacept has not been studied in children under 6 years old.

The recommended course of treatment.

Abatacept is administered as a 30-minute intravenous infusion at the dose specified below. Following the initial administration, abatacept should be given 2 and 4 weeks after the first infusion, then every 4 weeks thereafter.

Table 1 Dosage per body weight

Body Weight	Dose	Number of Vials
< 60 kg	500 mg	2
≥60 kg to ≤100 kg	750 mg	3
> 100 kg	1,000 mg	4

The main comparator(s).

When a patient is initially diagnosed with RA, the aim is to initiate treatment as quickly as possible.

The current treatment pathway is to initiate conventional DMARDs (eg MTX) as first line therapy (either alone or in combination with other DMARDs), using non –steroidal anti-inflammatory drugs (NSAIDs) to relieve symptoms.

Patients failing to respond to at least two conventional DMARDs (one of which should be MTX), and have active disease, can progress to treatment with anti-Tumour Necrosis Factor alpha (anti-TNFα) agents.

The scope of this appraisal lists two groups of comparators:

1. Conventional DMARDs (cDMARDs): as this submission is for 1st line biologic use, it is appropriate to compare abatacept against cDMARDs based on the current treatment pathway in the UK. The use of cDMARDs as a base case comparator is a well recognised approach that has been used in previous appraisals (TA130, TA195).

2. Alternative biologic agents: adalimumab, certolizumab, etanercept, golimumab and infliximab. All of the biologic agents are administered subcutaneously (sc), except for infliximab which is an intravenous infusion, as is abatacept.

Whilst for most patients a sc administered agent will provide a satisfactory route of administration, some patients benefit more from an IV administered drug. These patients include those:

- who cannot self inject
- who have a strong likelihood to be non-compliant
- for whom a monthly review at the infusion centre would be desirable because of co-morbidities or other reasons related to the primary pathology of RA

This submission will therefore focus on the comparison of abatacept to both cDMARDs and infliximab.

Whether the key clinical evidence in the submission comes from head-to-head randomised controlled trials (RCTs), from an indirect and/or mixed treatment comparison, or from non-randomised studies.

The key clinical evidence in the submission comes from RCTs, and is complemented by non-randomised studies, on all the comparators listed in the scope.

In the absence of head-to-head RCTs, a mixed treatment comparison (MTC) of the RCT evidence using placebo as the common comparator was undertaken to analyse the relative effectiveness of these medicines.

The main results of the RCTs and any relevant non-RCT evidence.

Abatacept clinical effectiveness compared with cDMARDs

The clinical evidence from the three RCTs and non-RCT data presented for abatacept in this submission demonstrates a better efficacy profile of abatacept compared with placebo for the treatment of moderate to severe RA in patients with an inadequate response to MTX.

Abatacept has demonstrated a consistent improvement in the primary and secondary outcome measures for patients with active, moderate to severe RA, with an inadequate response to MTX.

The AIM (Abatacept in Inadequate responders to Methotrexate) study was designed to obtain relative efficacy and safety data on the treatment effect of abatacept versus placebo. The study utilised a double-blind, randomised, placebo controlled design for 12 months.

- Abatacept showed significant clinical improvements compared with placebo for the outcome measures of disease activity of ACR20, 50 and 70; DAS28, HAQ-DI; SF-36; HRQol and radiographic progression.

- Clinical improvements seen in the original abatacept group were maintained over a 4 year open label extension period. ACR20, ACR50 and ACR70 benefits were maintained at 5 years, as well as DAS28, HAQ-DI, SF36 and radiographic assessments.

The results from AIM are further supported by the Kremer Phase 2b study which showed clinically meaningful, durable and sustained efficacy results through to Year 7. In addition, there is robust RCT evidence from the ATTEST study for the target population which also further supports these results.

These findings are supported by a mixed treatment comparison, (MTC) which shows abatacept to be more efficacious than placebo.

Abatacept clinical effectiveness compared with infliximab

The data from the ATTEST (Abatacept or infliximab versus placebo, a Trial for Tolerability, Efficacy and Safety in Treating RA) study demonstrated a better efficacy profile of abatacept compared with infliximab.

This study was designed to obtain data on the magnitude of the treatment effect in RA of abatacept or infliximab versus placebo, and to obtain relative efficacy and safety data for these two biologic treatments in a single study. The study utilised a double-blind,

randomised, placebo controlled design for the first 6 months to validate efficacy responses, while the study duration allowed for the opportunity to directly compare the safety profile of the active biologic treatment groups through 1 year (Schiff et al 2008).

- Abatacept had a greater reduction in mean DAS28 change from baseline at 1 year compared with infliximab;
- At 52 weeks the percentages of ACR50 and ACR70 responders were numerically higher for abatacept compared with infliximab.
- At 1 year, 35.3% of patients receiving abatacept achieved a Low Disease Activity Score (LDAS) (DAS28<3.2) compared with 22.4% of patients who had received infliximab.
- In addition, 18.7% of patients received abatacept achieved remission (DAS28<2.6) compared with 12.2% of infliximab patients.
- The infliximab group had a lower reduction in HAQ-DI change from baseline, and a lower percentage of responders, than the abatacept group at both 6 months and 1 year.

Abatacept clinical safety

Abatacept was generally well tolerated in the RA patient population, with no unexpected or unusual adverse events reported. Most adverse events were mild to moderate.

The favourable long-term safety of abatacept has been shown over a period exceeding 7 years and encompassing more than 12,132 patient years experience.

Results from the ATTEST study showed that abatacept demonstrated fewer SAEs, lower discontinuation rates due to SAES/AEs, and lower serious infusion and acute infusion events compared with infliximab.

Additional considerations

BMS feel it would be useful to put the abatacept clinical efficacy and safety data into the broader context of the UK therapeutic landscape for RA. It will also allow a more detailed discussion of the reasons why it is important for there to be a choice of IV agents available to physicians and patients, especially as abatacept offers clear benefits over the currenty approved first line biologic – infliximab.

Immunology of infliximab

The immunogenicity of biologic agents raises potential safety and efficacy concerns. Infliximab is a chimeric monoclonal antibody to TNF containing both human and murine regions. Because infliximab contains murine sequences (i.e. mouse), its administration is associated with formation of human anti-chimeric antibodies (HACA), or neutralising antibodies. (Haraoui et al 2004).

Studies have shown that the efficacy of some biological therapies diminishes over a period of time, leading to the need for the dose escalation to maintain therapeutic effect, substantially increasing the cost of treatment (Wolbink et al 2005, Bartelds et al 2007, van der Laken et al 2007). In addition, the development of antibodies is associated with an increased risk of infusion reactions and a reduced duration of response to treatment.

Such phenomena may be, at least partially, due to the development of neutralising antibodies against infliximab.

Immunology of abatacept

Abatacept, does not appear to be highly immunogenic because it is a human fusion protein.

Several studies have evaluated the impact of abatacept on the immune response. These report that an important and distinguishing characteristic of abatacept is its low immunogenicity, as assessed in patients across multiple phase 2 and phase 3 RA clinical trials (Sibilia and Westhovens 2007, Haggerty et al 2007).

This is important because, as the clinical data from both the RCT and non-RCT long term extensions (LTEs) in this submission show, abatacept maintains its clinical effect over several years, without the need for dose escalation. In contrast, infliximab treatment is associated with loss of response, requiring dose increases in 31% of patients within the first year of treatment (Blom et al 2010).

TB reactivation

Treatment of RA and other autoimmune disorders with anti-TNFα agents is associated with an increased risk of reactivation of latent Mycobacterium tuberculosis. This is because TNF is a proinflammatory cytokine that plays a central role in both the host inflammatory response to mycobacterial infection and in the immunopathology of tuberculosis (TB) itself. Consequently, progression of a recently acquired tuberculosis infection, or reactivation of a remotely acquired infection, can be expected with anti-TNF agents such as infliximab (Gardam et al 2003).

Whilst the clinical data for abatacept are not as mature as those for infliximab, there are indications that abatacept seems to have a lower propensity to reactivate latent TB. It has been suggested by Khraishi et al that abatacept's differential mechanism of action could explain the lower rates of TB reactivation observed in abatacept clinical trials (Khraishi 2009).

Conclusion

Whilst there is a broad armamentarium available to treat RA, the biologic DMARDs are mostly delivered via sc administration. However, certain patient groups are not suitable for sc delivery of pharmacotherapies, therefore there is a need to have IV agents available.

The two available IV agents (infliximab and abatacept) can be clearly differentiated from each other, with abatacept offering a more favourable treatment option than infliximab in terms of dose effectiveness, clinical efficacy and safety, and immunological profile.

In relation to the economic evaluation, details of:

the type of economic evaluation and justification for the approach used

the pivotal assumptions underlying the model/analysis

the mean costs, outcomes and incremental cost-effectiveness ratios (ICERs) from the evaluation.

A patient level simulation model was developed to assess the cost utility in patients with RA who are MTX-IR. The basis for this model was the BRAM (Birmingham RA Model) and a review of RA models used in previous NICE technology appraisals.

Barton et al (2004) describe the intention behind this type of model as the creation of "a realistic set of virtual patient histories". In contrast to a cohort-model, a patient-level simulation presents the variability in outcomes across individuals, rather than a single average outcome. Therefore, this model structure was considered most appropriate as it allowed for a realistic representation of the complex nature of RA as a disease and the heterogeneity of causal factors without relying on over simplistic assumptions or jeopardising transparency.

The pivotal assumptions within the model are as follows:

- Changes in HAQ occur over a 3-month period. HAQ scores do not change quickly, but change gradually over time with a maximum HAQ value of 3.
- Response to therapy is defined as a 0.3 improvement in HAQ score in all comparisons, since this is in accordance with the endpoint in the different clinical trials.
- After discontinuation, patient HAQ score will rebound back to their baseline HAQ plus the progression rate of treatment.
- Dose increase was taken into account for infliximab, etanercept and adalimumab.

Abatacept is compared to both cDMARDs and infliximab (Section 2).

Tabulation of the base-case results (Tables 1 and 2):

Table 2 Base-case cost-effectiveness results of abatacept and the biologic agents vs. cDMARDs

	Total QALY	Total LY	Total cost	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus cDMARD (QALYs)
cDMARD	4.88	27.39	£76,276				
Certolizumab pegol	6.16	27.61	£103,976	£27,700	0.22	1.28	£21,592
Etanercept	6.12	27.60	£107,653	£31,377	0.22	1.24	£25,361
Infliximab	5.96	27.57	£109,419	£33,143	0.19	1.08	£30,693
Adalimumab	6.29	27.64	£111,922	£35,645	0.25	1.41	£25,359
Abatacept	6.16	27.60	£114,548	£38,272	0.21	1.28	£29,916
Golimumab	6.25	27.63	£115,372	£39,096	0.24	1.37	£28,592

QALY=Quality-adjusted life year LY=Life year LYG=Life year gained ICER=Incremental cost effectiveness ratio

Table 3 Base-case cost-effectiveness results of abatacept vs. infliximab

	Total QALY	Total LY	Total cost	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus infliximab (QALYs)
Infliximab	5.959	27.572	£109,419	£5,129	0.02	0.20	£25,711

QALY=Quality-adjusted life year LY=Life year LYG=Life year gained ICER=Incremental cost effectiveness ratio

This analysis demonstrates that the effectiveness and costs of abatacept when compared to cDMARDs is in line with other biologic agents recommended by NICE.

In addition it is demonstrated that abatacept is a cost-effective treatment option in comparison to infliximab.

When appropriate, please present the results for the intervention and comparator(s) incrementally to indicate when options are dominated or when there is extended dominance. For example:

The analysis in Tables 4 and 5 show that abatacept is a cost-effective treatment option in comparison to cDMARDS or to infliximab, for patients with RA who have had an inadequate response to MTX. Abatacept is expected to accrue more benefits with slightly higher costs. The probabilistic sensitivity analylses (PSA) below confirm these findings.

Table 4 Incremental cost-effectiveness results (ICERs) (each biological DMARD vs.cDMARD)

	Total QALY			Total cost			Incremental costs (£)			Incremental QALYs			ICER (£) versus cDMARD (QALYs)		
	Mean	**2.5%**	**97.5%**	**Mean**	**2.5%**	**97.5%**	**Mean**	**2.5%**	**97.5%**	**Mean**	**2.5%**	**97.5%**	**Mean**	**2.5%**	**97.5%**
cDMARD	4.75	4.65	4.86	75,095	73,754	76,472									
Certolizumab pegol	6.05	5.88	6.22	103,385	100,721	106,119	28,290	25,388	30,794	1.30	1.12	1.49	21,833	17,056	27,531
Etanercept	6.02	5.84	6.20	107,067	104,267	109,844	31,973	29,615	34,380	1.27	1.14	1.39	25,232	21,339	30,043
Infliximab	5.84	5.68	6.02	108,456	105,453	111,643	33,362	30,282	36,364	1.09	0.92	1.26	30,565	24,084	39,535
Adalimumab	6.15	5.98	6.34	111,436	108,594	114,601	36,342	33,483	39,392	1.40	1.22	1.58	25,963	21,256	32,207
Abatacept	6.07	5.91	6.24	114,596	111,278	117,673	39,502	36,738	42,422	1.32	1.20	1.44	29,888	25,538	35,341
Golimumab	6.13	5.97	6.30	114,105	110,812	117,436	39,010	36,044	42,014	1.38	1.21	1.57	28,332	22,915	34,855

cDMARD: conventional DMARD, QALY: Quality Adjusted Life Year, ICER: Incremental Cost Effectiveness Ratio

Table 5 Incremental cost-effectiveness results (ICERs) (abatacept vs. cDMARD and vs. infliximab)

	Incremental costs (£) Mean and 95% CI			Incremental QALYs Mean and 95% CI			ICER (£) versus cDMARD (QALYs) Mean and 95% CI			% of abatacept being CE at WTP £30,000
	Mean	**2.5%**	**97.5%**	**Mean**	**2.5%**	**97.5%**	**Mean**	**2.5%**	**97.5%**	
cDMARD	39,502	36,738	42,422	1.32	1.20	1.44	29,888	25,538	35,341	55%
Infliximab	6,140	3,568	8,889	0.23	0.05	0.42	26,680	8,547	163,810	61%

cDMARD: conventional DMARD, QALY: Quality Adjusted Life Year, ICER: Incremental Cost Effectiveness Ratio, CE: cost effectiveness

Subgroup analyses considered and clinical- and cost-effectiveness results.

Although subgroups were identified in the scope, a paucity of data made it not possible to conduct a de novo analysis; therefore no subgroup analyses were performed.

Conclusions

The evidence presented in this submission supports the proposition that abatacept should be made available to patients with an insufficient response or intolerance to cDMARDs, and specifically for patients who require an IV infusion for their first line biologic treatment choice.

- The long-term efficacy and safety data (up to 7 years) in the target population shows that abatacept demonstrates sustained/improved clinical efficacy over time, with a favourable safety profile.
- Abatacept demonstrates a unique mode of action offering immunological advantages over infliximab.
- There is no evidence of any loss of efficacy over time, or requirement for dose escalation, with abatacept.
- There is a need for drugs administered by IV in the treatment paradigm for RA.
- Compared to infliximab, abatacept shows improved efficacy and safety when studied in the same population of patients.
- An economic model used in previous NICE technology appraisals was adopted. This analysis demonstrates that abatacept is cost-effective when compared to cDMARDs and infliximab.

Therefore, the Appraisal Committee should recommend abatacept as a treatment option for RA for patients with an insufficient response or intolerance to cDMARDs.

List of Abbreviations

ACR	American College of Rheumatology
ADL	Activities of Daily Living
AE(s)	Adverse event(s)
AIM	Abatacept in Inadequate Methotrexate Responders
ANCOVA	Analysis of covariance
APC	Antigen presenting cell
ARRIVE	Abatacept Researched in RA patients with an Inadequate anti-TNF response to Validate Effectiveness
ASSURE	Abatacept Study of Safety in Use with other RA therapies
ATTAIN	Abatacept in Anti-TNFα Inadequate responders
ATTEST	Abatacept or infliximab vs placebo, a Trial for Tolerability, Efficacy and Safety in Treating rheumatoid arthritis
BHPR	British Health Professionals in Rheumatology
BRAM	Birmingham Rheumatoid Arthritis Model
BMS	Bristol-Myers Squibb
BSR	British Society of Rheumatology
BSRBR	British Society of Rheumatology Biologics Registry
CCP	Cyclic citrullinated peptide
CFB	Change from baseline
CHF	Congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CRP	C-reactive protein
CSR	Clinical study report
CT	Clinical trial
CTLA-4	Cytotoxic T-lymphocyte-associated antigen 4
DAS28	Disease activity score 28 joint count
DMARD(s)	Disease modifying anti-rheumatic drug(s)
cDMARDs	Conventional Disease modifying anti-rheumatic drug(s)
EC	European Commission
EMA	European Medicines Agency
ES	Erosion score
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FAD	Final Appraisal Determination
FDA	Food and Drug Administration
GMS	Genant-modified Sharp Score
GO-AFTER	Golimumab After Former anti-tumour necrosis factor α Therapy Evaluated in Rheumatoid arthritis
GPRD	General Practice Research Database
HACA	Human anti-chimeric antibody
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire Disability Index

HCQ	Hydroxychloroquine
HLA	Human leukocyte antigen
HRQoL/HRQL	Health-related quality of life
ICER	Incremental cost effectiveness ratio
IgG	Human immunoglobulin G
IL	Interleukin
ITT	Intention to treat
IV	Intravenous
JIA	Juvenile idiopathic arthritis
JSN	Joint space narrowing
LDAS	Low disease activity state
LTE	Long-term extension
LY	Life year
LYG	Life year gained
m-HAQ	Modified Health Assessment Questionnaire
MCS	Mental Component Summary
MHC	Major histocompatibility complex
MOS-SPI	Medical Outcomes Study Sleep Problem Index
MTC	Mixed Treatment Comparison
MTX	Methotrexate
MTX-IR	Methotrexate inadequate response
NICE	National Institute for Health and Clinical Excellence
NOAR	Norfolk Arthritis Register
NSAIDs	Nonsteroidal anti-inflammatory drugs
PCS	Physical Component Summary
PCT	Primary Care Trust
PSA	Probabalistic Sensitivity Analysis
PSS	Personal Social Service
QALY	Quality-adjusted life year
QoL	Quality of life
RA	Rheumatoid arthritis
RADIATE	Research on Actemra Determining efficacy after Anti-TNF failures
RANK	Receptor activator of NK-κB ligand
RCT	Randomised controlled/clinical trial
RF	Rheumatoid factor
SAE	Serious adverse event
sc	subcutaneous
SD	Standard deviation
SE	Standard error
SF-36	Short-Form 36 questionnaire
SJC	Swollen joint count
SMC	Scottish Medicines Consortium

SmPC	Summary of Product Characteristics
SSZ	Sulfasalazine
STA	Single technology appraisal
STPR	Stratégies Thérapeutiques de la Polyarthrite Rhumatoıde
STURE	Stockholm tumour necrosis factor follow up registry
SUNRISE	Study UNderstanding RItuximab's Safety and Efficacy in RA
TB	Tuberculosis
TEMPO	Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes
TJC	Tender joint count
TNF	Tumour necrosis factor
TNFα	Tumour necrosis factor alpha
VAS	Visual analogue scale

Section A – Decision problem

1 Description of technology under assessment

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

Approved name: abatacept

Brand name: Orencia®

Therapeutic class: Selective immunosuppressants

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

Abatacept is a biological agent that leads to immunosupression. It was specifically developed for the treatment of autoimmune diseases which, although diverse in organ target and disease manifestation, have the same general T-cell-mediated aetiopathology (Choy and Panayi 2001).

In rheumatoid arthritis (RA) it is thought that T cells are driving the autoimmune responses that lead to synovitis and the other inflammatory features of RA. The mode of action of abatacept is focused on preventing T-cell activation, thus down regulating the immune response of the inflammatory disease.

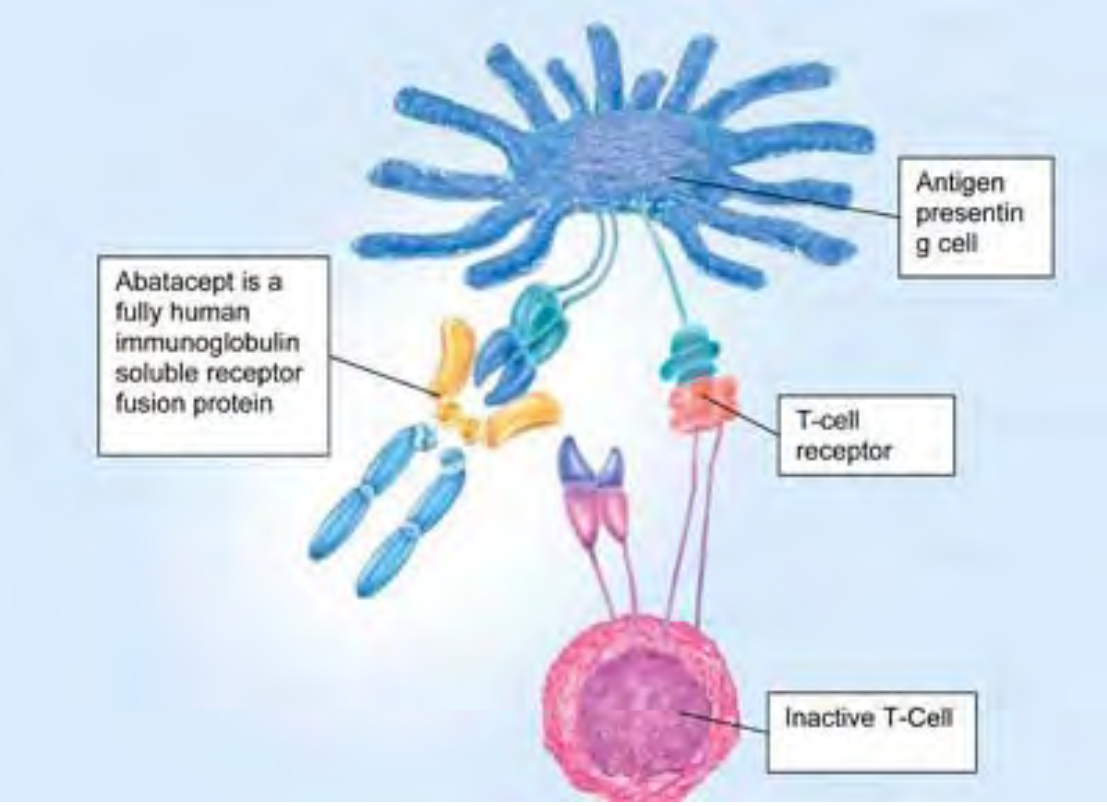
Full T-cell activation requires the interaction of T-cells with antigen-presenting cells (APCs) and two signals which result from receptor interactions (Figure A1).

- Signal 1 results from the interaction of major histocompatability complex (MHC)–peptide on APCs with the T-cell receptor.
- Signal 2, a co-stimulatory signal, results from the engagement of CD80/CD86 on APCs with CD28 on T cells.

Under normal conditions, a pathogen-derived peptide would lead to full T-cell activation. Over time, a regulatory protein, CTLA-4, is subsequently upregulated on T cells and binds to CD80/86 with a much higher affinity than CD28. Unlike CD28, CTLA-4 downregulates T-cell activation. This homeostatic mechanism serves to keep the immune system ‘in check’.

Abatacept is a fusion protein that consists of an 'active' extracellular CTLA-4 domain linked to an 'inert' Fc portion of human immunoglobulin. Abatacept therefore binds to CD80/86 and prevents the co-stimulatory signal 2 required for full T-cell activation. This subsequently prevents the downstream events which lead to the joint damage and bone erosion associated with RA, including the activation of rheumatoid factor (RF) producing B cells, macrophage activation and the production of inflammatory cytokines such as TNFα, and interleukins, IL-1 and IL-6.

Figure A 1 Mechanism of action of abatacept



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

Abatacept was approved in the EU in May 2007 for the treatment of adult RA. Abatacept in combination with methotrexate (MTX) is indicated for the treatment of moderate to severe active RA in adult patients who have had an insufficient response or intolerance to other DMARDs including at least one TNF inhibitor. A reduction in the progression of joint damage and improvement of physical

function has been demonstrated during combination treatment with abatacept and methotrexate.

A type II variation to the Marketing Authorisation was obtained in January 2010. The following indication was added: Abatacept in combination with methotrexate is indicated for the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis (JIA) in paediatric patients 6 years of age and older who have had an insufficient response to other DMARDs including at least one TNF inhibitor. Abatacept has not been studied in children under 6 years old.

In May 2010, the European Medicines Agency (EMA) issued a positive Committee for Medicinal Products for Human Use (CHMP) opinion and on 1st July 2010 the European Commission (EC) granted a licence to change the adult RA indication as follows:

Abatacept in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who responded inadequately to previous therapy with one or more disease-modifying anti-rheumatic drugs including methotrexate or a TNF-alpha inhibitor. A reduction in the progression of joint damage and improvement of physical function has been demonstrated during combination treatment with abatacept and methotrexate.

There was no change to the JIA indication.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the licence).

No special conditions are attached to the current Marketing Authorisation.

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

As in Section 1.3 above, on 1st July 2010 the EC granted an update to the licensed indication.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

IM101-119 A Phase 3b multicentre, randomised, double-blind, placebo-controlled study to assess short-term changes in synovitis and structural damage outcomes in subjects with active RA and inadequate response to methotrexate, treated with abatacept versus placebo on a background therapy with MTX.

This study completed in May 2010 (www.clinicaltrials.gov). Fifty patients were enrolled. It is anticipated that the Primary outcome and 4 month results will be available towards the end of 2010, with publications planned Q2/Q3 2011. The 1 year results are anticipated Q1 2011, with publication following.

IM101-179 A multicentre, open-label study to assess early response to abatacept with background methotrexate using power doppler ultrasonography in patients with active RA and inadequate response to MTX. This study is still recruiting with an estimated completion date of October 2011 (www.clinicaltrials.gov).

AIM The AIM study 4 year long term extension (LTE) data was presented as a poster at the Amercian College of Rheumatology 2009 and at the European Society of Rheumatology meeting in 2010. A publication is in progress to be submitted to a peer reviewed journal before end of 2010.

ATTAIN The ATTAIN 4.5 year data (4 year LTE) is due to be submitted for publication in a peer reviewed journal before end of 2010.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

The technology is already available.

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

Abatacept is approved and marketed in the following countries: Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Columbia, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, India, Ireland, Italy, Luxembourg, Netherlands, Norway, Peru, Poland, Portugal, Romania, Russia, Slovak Republic, Spain, Sweden, Switzerland, Lichtenstein, United Kingdom, United States of America and Venezuela.

Abatacept is approved but not marketed in the following countries: Hong Kong, Macau, Mexico, New Zealand, Singapore and Turkey, and other EU countries not listed above.

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

Scottish Medicines Consortium (SMC) issued guidance No. 400/07 – Abatacept, 250mg powder for concentrate for solution (September 2007, updated following publication of NICE TA195).

National Institute for Health and Clinical Excellence (NICE) issued clinical guideline 79. Management of RA in adults (TA141).

Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor. Guidance was published on the NICE website on August 25th, 2010 (TA195).

BMS will also be submitting to the SMC for our latest indication in Q1 2011, with guidance anticipated to be published at the end of 2011.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table A 1 Unit costs of technology being appraised

Pharmaceutical formulation	Powder for concentrate for solution for infusion
Acquisition cost (excluding VAT)	250 mg powder for solution for infusion: 1 vial=£242.17 1.2µm filter: 1=£3.00
Method of administration	parenteral
Doses	<60kg 500mg, 60-100kg 750mg, >100kg 1000mg
Dosing frequency	It should be given 2 and 4 weeks after the first infusion, then every 4 weeks thereafter.
Average length of a course of treatment	If a response to abatacept is not present within 6 months of treatment, the continuation of the treatment should be reconsidered.
Average cost of a course of treatment	People require a total of 14 infusions in the first year and 13 infusions in subsequent years. Abatacept is available in 250-mg vials at a list price of £302.40. However, based on an agreement between BMS and the Department of Health, the net cost to the NHS will be £242.17 per vial (excluding VAT). The dose of abatacept depends on body weight: people weighing less than 60 kg, 60–100 kg and over 100 kg require 500 mg, 750 mg and 1000 mg respectively. The annual drug costs associated with abatacept vary according to body weight and the number of infusions required. For a person weighing between 60 and 100 kg, the annual drug cost will be £10,171.14 in the first year and £9,444.63 in subsequent years. (reference: NICE TA195 and BMS/DoH confidential correspondence)
Anticipated average interval between courses of treatments	As above, every 4 weeks
Anticipated number of repeat courses of treatments	See above
Dose adjustments	Dosed according to patient body weight-as above.

Reference: Orencia SPC July 2010

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

No

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

No, there are no special requirements; guidance is the same as for the other biological agents. Patients should be screened for latent infections such as tuberculosis (TB) and viral hepatitis, in accordance with published guidelines, before starting abatacept therapy. Abatacept should not be initiated in patients with active infections until they are controlled.

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

Methotrexate (MTX) is prescribed in combination with abatacept over the course of treatment. MTX is usually prescribed with a folic acid supplement.

2 Context

Rheumatoid arthritis (RA) is a chronic and progressive autoimmune disorder, characterised by joint inflammation and swelling leading to deformity, functional impairment, pain, fatigue and disability. There is a combination of genetic, hormonal, environmental and nutritional factors involved in the aetiology of the condition. As RA is a heterogeneous disease, the armamentarium of biological agents available to rheumatology clinicians needs to offer as wide a choice as possible.

T-cells play a central role in orchestrating the inflammatory cascade in RA, which contributes to cartilage degradation, re-absorption of bony tissue and progressive and cumulative joint damage. This inevitably has quality-of-life, social and economic consequences. Abatacept works by preventing the activation of T cells during the inflammatory immune response, a unique mode of action, which offers different characteristics to the currently available biologic agents.

As certain patient groups are not suitable for subcutaneous delivery of pharmacotherapies, there is a real need to have intravenous infusion (IV) agents available.

The two available IV agents (infliximab and abatacept) can be clearly differentiated from each other, with abatacept offering a more favourable treatment option than infliximab in terms of dose effectiveness, clinical efficacy and safety, and immunological profile.

Therefore we ask the Appraisal Committee to recommend abatacept as a treatment alternative for patients with RA who experience an inadequate response to traditional DMARDs and for whom a subcutaneous administered agent is not suitable.

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

RA is a chronic and progressive systemic autoimmune disorder characterised by inflammation and swelling of synovial joints leading to joint deformity, functional impairment, pain, fatigue, and ultimately, disability. It typically affects the small joints of the hands and feet, and usually both sides of the body equally in a symmetrical distribution, though any synovial joint can be affected. In patients with established and aggressive disease most joints will be affected over time.

Influencers of rheumatoid arthritis

What triggers RA is unknown; what is known is that the disease is associated with a combination of influencers, including genetic, hormonal, environmental and nutritional factors.

- Genetic

As a proportion of the disease incidence, about 60% can be explained by genetic factors (Felson 2005; Fox 2005). Fifty percent of the genetic predisposition to RA is attributable to alterations in the MHC; specific sites on the MHC are associated with susceptibility to RA. The human leukocyte antigen (HLA) gene HLA-DR4 appears in about two-thirds of RA patients, compared with about 30% of people without RA. A function of HLA-DR is the presentation of peptides to T-cells for mounting an immune response to particular antigens. Studies have also focused on the genes that code for cytokines. The most intriguing evidence relates to TNFα, the genes for which are located on the MHC site (Fox 2005).

- Hormonal

Indirect evidence suggests that hormonal factors affect the occurrence and/or severity of RA; for instance, the disease often goes into remission during pregnancy. The anti-inflammatory effects of high cortisol and oestrogen levels – such as occur during pregnancy – may help to moderate RA, while increased prolactin in breast-feeding women may increase the disease risk (Felson 2005). Men with RA typically have low circulating testosterone levels.

- Environmental

Certain environmental factors (viruses, bacteria and smoking) increase the risk of RA, while certain nutritional factors (omega 3

and 9 fatty acids, cryptoxanthin and selenium) decrease the risk (Felson 2005; Firestein 2005).

Immunology

Many cytokines and inflammatory markers are elevated in RA and these mediators have a variety of roles in RA pathology. T-cells play a central role in orchestrating the inflammatory cascade by stimulating monocytes, macrophages and synovial fibroblasts to produce inflammatory cytokines such as IL-1, IL-6 and TNFα. These inflammatory mediators promote the further recruitment and activation of inflammatory cells (such as neutrophils and lymphocytes) and trigger the release of cartilage-degrading proteases from synovial fibroblasts, osteoclasts and chondrocytes. This process not only contributes to cartilage degradation, but also leads to reabsorption of bony tissue and, ultimately, to joint damage – which is progressive and cumulative. This inevitably has quality-of-life, social and economic consequences.

RA can also manifest as a systemic autoimmune disease, affecting many systems – musculoskeletal, nervous, respiratory, cardiovascular, renal and haematological, amongst others (Kosinski et al 2002).

Morbidities

Comorbid conditions are common in patients with RA, the most frequent co morbidities being; hypertension, depression, gastroenterological diseases and respiratory disease (Brouwer et al 2004). Morbidity in RA is high; pain, fatigue and loss of motion in joints make it harder for a patient with RA to remain in employment or live normally. Patients have problems with activities of daily living (ADL), such as dressing, bathing, and walking, and usually need help from family, friends or carers. Successful treatment of severe RA may enable these individuals to return to work or care for themselves.

Quality-of-Life

People with RA report a decreased Health-Related Quality of Life (HRQoL). When measured using the physical and mental component scores of validated HRQoL questionnaires such as the SF-36, HRQoL was as poor in patients with RA as in those with congestive heart failure (CHF) and advanced diabetes (Kosinski et al 2002). RA may cause patients to feel depressed or anxious. The onset of RA often interferes with social roles and may be associated with feelings of helplessness, loss of self-esteem and other psychological difficulties, affecting sleep patterns and causing fatigue. In addition to the significant impact of RA on patients' HRQoL, caregivers and family members are also subject to the

burden associated with caring for a chronically ill person (Brouwer et al 2004; Cooper 2000).

Disability and mortality

While the course of the disease varies across the RA population, in general patients usually experience moderate disability within 2 years of diagnosis, and after 10 years 30% are severely disabled. Patients with more severe RA also have higher mortality rates than those without RA. Patients with severe RA die 3-18 years earlier than those without RA, with a death rate 1.3-2 times higher in a given 10-year period. Death rates are highest in patients with early loss of physical function and co morbidities such as cardiovascular disease (Felson 2005).

The economic burden of RA for society is substantial since the onset of the disease often occurs during the most productive years of the sufferer's life.

2.2 How many patients are assumed to be eligible? How is this figure derived?

It has been estimated that the prevalence of RA in the adult UK population is 0.86% (Symmons et al 2002). Using recent UK population estimates, this prevalence results in 346,357 RA patients (TA195).

The NICE Clinical Guideline for RA (CG79) recommends that patients achieve a DAS28 of 5.1 before receiving a first biologic agent based on The British Society of Rheumatology (BSR) guidelines published in 2005 (Ledingham et al 2005).

Patients with a DAS28 of ≥ 5.1 are estimated to be 10% of the total rheumatoid population (TA195), resulting in 34,656 patients in the UK.

However, the latest BSR guidelines published in March (Deighton et al 2010) this year recommend that the criteria for being eligible to receive a biologic agent in the UK be lowered from a (Disease Activity Score) DAS28 of 5.1 to a DAS28 of >3.2 (i.e. from severe disease to moderate disease).

Patients with a DAS28 of ≥3.2 are estimated to be 30% of the total rheumatoid population, resulting in 103,907 patients in the UK.

Out of the estimated eligible population currently 10% receive an IV administered biologic agent.

2.3 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

The clinical effectiveness and cost effectiveness of anakinra for rheumatoid arthritis. *November 2003 TA72*

Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis. *October 2007 TA130*

Rheumatoid arthritis. National clinical guideline for management and treatment in adults. *February 2009 CG79*

Certolizumab pegol for the treatment of rheumatoid arthritis. *February 2010. TA186*

Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor. *August 2010. TA195*

2.4 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

Treatment pathway for rheumatoid arthritis

There is currently no cure for RA; however various treatments are available. Non-pharmacological treatments include physical therapy, orthoses, occupational therapy and nutritional therapy, but none of these prevent the progression of joint destruction.

Painkillers and anti-inflammatory drugs (including steroids), are used to alleviate the symptoms, while disease-modifying anti-rheumatic drugs (DMARDs) inhibit the underlying immune process and prevent long-term damage. Traditional DMARDs do not inhibit the underlying progression of the disease completely (de Vries-Bouwstra et al 2005) and are associated with adverse events and multiple organ toxicities (Fleischmann et al 2004). However, biologic DMARDs have been shown to halt disease progression, with over 50% of patients achieving remission.

Current clinical guidelines recommend the use of a combination of two traditional DMARDs, including MTX, before a patient becomes

eligible for the use of biologics (Deighton et al 2010, NICE RA Clinical Guideline Feb 2009). Whilst the recently updated BSR guidelines recommend the use of biologics in patients with a DAS ≥ 3.2, the NICE guidelines still base its eligibility on older guidelines recommending biologics only for patients with a DAS ≥ 5.1 (Deighton et al 2010, NICE RA Clinical Guideline Feb 2009).

Biologic DMARDs

The biologic DMARDs can be differentiated by their molecular class as well as their mode of administration. One group of biologic agents are classified as monoclonal antibodies (adalimumab, certolizumab, golimumab, infliximab, and rituximab) the other group are human fusion proteins (abatacept and etanercept). While some of the biologic agents are administered by sc injection (adalimumab, certolizumab, etanercept, and golimumab), two are administered by IV infusion (abatacept and infliximab). The infusion time for infliximab is 2 hours; for abatacept IV is 30 minutes.

Because of the variety of biologic agents available for treating RA it is important that the physician understands the differences between the different agents. By putting the needs and requirements of the individual patient at the centre of their decision making, and by considering every parameter that may influence the efficacy, safety and appropriateness of their chosen biologic intervention, they will be able to choose the best biologic for their patient.

Administration of anti-rheumatic drugs

While subcutaneous administration of biologic agents may be suitable for some patients, there are patients for whom IV infusion is the preferred route.

Subcutaneous delivery of pharmacotherapy is common with well recognised advantages. However, for some RA patients, especially in those in whom manual dexterity has been compromised through disease effects, age or infirmity, self-administration may present insurmountable problems. Another group of patients for whom a sc administration is less favourable, are patients with difficulties to adhere to/comply with their drug therapy. The advantages of sc are therefore somewhat negated when the delivery of medication has to be managed through nursing care at home.

There may also be certain patients, or groups of patients, for whom the clinical team do not feel self-administration of a complex medication regimen is appropriate. It may be too difficult for some patients with special needs, or domestic difficulties, to receive and store biologic agents in the home. There may be others with small children who therefore would not want such medication stored in their house. In addition, there may be some patients whom the Rheumatology Unit feel require closer supervision, e.g. medically

complex cases. Finally, patients with needle phobia will find self-injection impossible.

In these circumstances, IV infusion is a viable alternative to sc (Scarpato et al 2010).

2.5 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

Infliximab vs. abatacept

Infliximab and abatacept have distinct differences in terms of their type of molecule which have major implications with regard their respective benefit/risk ratios, and clinical effectiveness and safety profiles.

As discussed above, the two biologic agents delivered by IV infusion are infliximab and abatacept.

With two IV infusion agents available this submission will focus on infliximab [recommended by NICE in TA130] and abatacept. Infliximab is a monoclonal antibody, abatacept a human fusion protein. The differences in their immunology, and their mode of action, lead to important issues with regard to their relative clinical efficacy and safety profiles. These are described in more detail below.

Immunology of infliximab

Infliximab is associated with the formation of neutralising antibodies which leads to a loss of effectiveness over time and therefore the need for dose escalation in a significant proportion of patients in order to maintain clinical efficacy. This dose escalation results in increased drug costs.

The immunogenicity of biologic agents raises potential safety and efficacy concerns. Infliximab is a chimeric monoclonal antibody to TNF that contains human constant and murine variable regions of IgG1. Because infliximab contains murine sequences (i.e. non-human sections), its administration is associated with formation of (neutralising) human anti-chimeric antibodies (HACA). (Haraoui et al 2004).

In the Biologic Observational Switchover Survey (BOSS) – which monitored efficacy and serious adverse events in patients with RA who switched from infliximab to etanercept – Haraoui et al (2004) found that 48% of patients tested positive for antibodies against

infliximab. In contrast, etanercept (which does not contain murine sequences) did not appear to be highly immunogenic.

Why is this phenomenon important? Recent studies have shown that the efficacy of some biological therapies diminishes over a period of time, leading to the need for dose escalation (to maintain therapeutic effect). This leads to increased costs of treatment (Wolbink et al 2005, Bartelds et al 2007, van der Laken et al 2007). In addition, the development of antibodies is associated with an increased risk of infusion reactions and reduced duration of response to treatment. Such phenomena may be, at least partially, due to the development of neutralising antibodies against infliximab.

Further studies conducted in RA patients (Ariza-Ariza et al 2007, Kievit et al 2006, Blom et al 2010) support the findings of Haraoui et al (2004), while evidence from other disease areas also suggest a therapeutic issue with HACA formation. (Baert et al 2003).

Finally, Anderson (2005) suggested that a decline in drug effectiveness due to a mounting antibody response can lead to the need for dose escalation, which has been reported for anti-TNFα agents after long-term treatment.

Infliximab: loss of clinical effectiveness leading to dose escalation

As the clinical data from the RCT and non-RCT LTEs in this submission show, abatacept maintains its clinical effect over several years, without the need for dose escalation. In contrast, infliximab treatment is associated with a loss of response, requiring dose increases in 31% of patients within the first year of treatment (Blom et al 2010). Such a dose escalation is also presented in published data from the ATTRACT clinical trial (Maini et al 1999, Lipsky et al 2000, van Vollenhoven et al 2004).

It is important to remember that this use of higher infliximab doses is associated with significantly increased costs.

Infliximab dose escalation in clinical practice

In communications with national and international rheumatologists it is clear that infliximab dose escalation is frequently used in clinical practice (van Vollenhoven 2004). The two main reasons given for this are:

(1) inadequate results with the original dose

(2) treatment effects last for less than the planned interval between infusions.

The DART study (Blom et al 2010) assessed current clinical practice in the treatment of RA patients by comparing dose escalation with adalimumab, etanercept and infliximab and the

associated costs of treatment. The results from a 44 European centre study showed that, in the first year of treatment, dose escalation to maintain a clinical response was performed in <1% of cases with with etanercept, 8% of cases with adalimumab and 29% of cases with infliximab. Thus, the results of the DART study showed that infliximab is associated with a high proportion of dose escalation, and therefore increased costs to the health service.

Unlike infliximab, abatacept is not associated with the 'hidden costs' of potential dose escalations.

Immunology of abatacept

Abatacept does not appear to be highly immunogenic because it is a humanised fusion protein, and so is not associated with the formation of HACA. Thus, unlike infliximab, abatacept does not require dose escalation, and the related increases in costs.

Abatacept does not appear to be highly immunogenic because of its biologic structure (i.e. a fusion protein composed of a human immunoglobulin-g Fc portion fused to the extracellular domain of CTLA-4).

Several studies have evaluated the impact of abatacept – or selective co-stimulation modulation – on the immune response. These conclude that an important and distinguishing characteristic of abatacept is its low immunogenicity, as assessed in patients across multiple Phase 2 and Phase 3 RA clinical trials (Sibilia and Westhovens 2007, Haggerty et al 2007).

Haggerty et al (2007) showed abatacept to be associated with a low incidence of immunogenicity in patients with RA. Of 2,237 patients with both pre- and post base-line samples available, only 62 (2.8%) were classified as having an immune response to abatacept or CTLA-4. No apparent relationship was found between immunogenicity and safety and efficacy; indeed, no consistent pattern was observed between antibody response and loss of efficacy and it was not associated with any adverse sequelae. However, because the number of patients that sero-converted (and who therefore had anti-abatacept antibodies) was so small, it was difficult to make any firm conclusions (Sibilia and Westhovens 2007).

Thus, the available data highlight clear differences between abatacept and infliximab in terms of their immunology, differences which may have significant consequences with regard their relative clinical effectiveness and safety in different patient populations.

TB reactivation by infliximab

Due to its mode-of-action, infliximab may be expected to be associated with reactivation of *Mycobacterium tuberculosis* (TB) infections.

It has been estimated that *Mycobacterium tuberculosis* infects about a third of the world's population (i.e. close to 2 billion people) (Dye et al 1999). Treatment of RA and other autoimmune disorders with anti-tumor necrosis factor (anti-TNF) agents is associated with an increased risk of reactivation of latent *M. tuberculosis*. This is because TNF is a proinflammatory cytokine that plays a central role in both the host inflammatory response to mycobacterial infection and in the immunopathology of tuberculosis (TB) itself. Consequently, progression of recently acquired tuberculosis infection, or reactivation of remotely acquired infection, should be expected with anti-TNF agents (Gardam et al 2003).

Figure A 2 Role of TNF agents in the cellular immune response to M tuberculosis infection

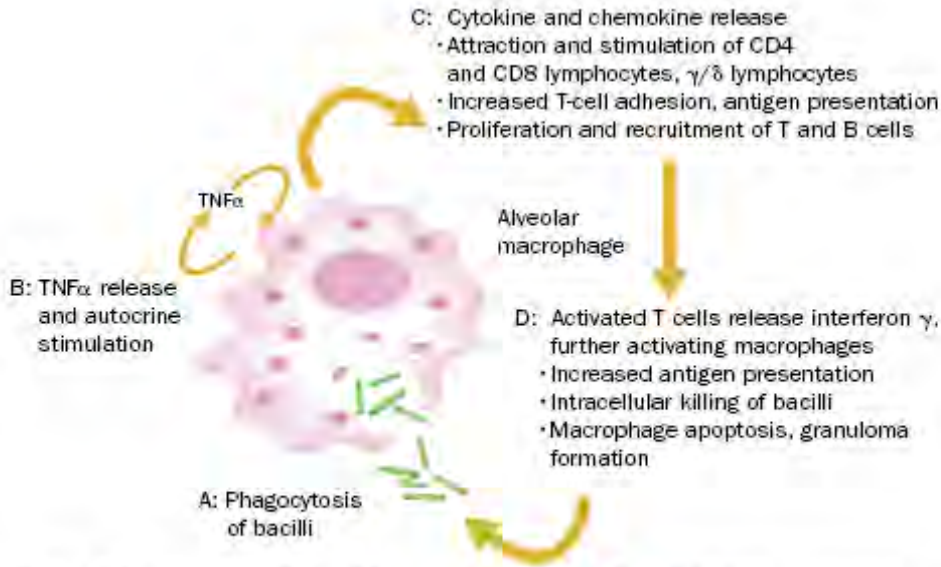


Figure 1. Schematic representation of the central role of TNFα in the cellular immune response to M tuberculosis infection.

Data suggest that the risk of development of active tuberculosis is greater with infliximab than with etanercept (Gardam et al 2003).

Khraishi (2009) reported that although all anti-TNF agents neutralise TNF-α activity *in vitro*, the monoclonal antibodies (including infliximab) are also able to fix complement, and therefore lyse cells that express surface-bound TNF-α (Santora et al 2001). Whilst the full significance of this is not clear, important immune system cells, (including T cells and neutrophils), express membrane-bound TNF-α, the disruption of which may result in additional immunosuppression. This may explain the higher rates of

TB reactivation observed with the monoclonal antibodies (Khraishi 2009).

The different mode of action of abatacept and its potential impact on TB reactivation

Because of its different mode-of-action to infliximab, abatacept may be expected to have a low propensity to reactivate TB.

While the clinical data for abatacept are not as mature as those for infliximab, there are indications that because of its different mode-of-action, abatacept could have a lower propensity to reactivate latent *M. tuberculosis*.

Abatacept has a different mode-of-action to the anti-TNF biologics (Ndejembi et al 2005, Tay et al 2007, Khraishi 2009). Abatacept is therefore thought to primarily affect adaptive immunity or antigen-specific immunity, with less effect on innate immunity (the primary defense against pathogens) (Khraishi 2009).

In a pre-clinical study Bigbee et al (2007) studied a chronic model of latent *M. tuberculosis* reactivation in mice. There was 100% mortality seen in the mouse population receiving murine TNF inhibitor antibody, which was attributed to disseminated TB infection. The anti-TNFα treated mice had a group mean survival time of 44 days, a significant difference ($p<0.0001$) compared to control group. Abatacept did not impair the ability of mice to control a chronic *M. tuberculosis* infection while, in contrast, mice treated with anti-TNF therapy showed increased pathology and bacterial load, with 100% mortality by week 9. One must be cautious, however, in extrapolating these data to the clinical situation.

Smitten et al (2008) assessed the risk of infection in the cumulative abatacept trial experience by examining the incidence of hospitalised infections over time, and comparing the number observed to that expected (based on external cohorts of RA patient treated with non-biologic DMARDs). Overall, Smitten et al looked at data from 4,150 patients from 8 clinical trials, which included a total of 10,365 patient-years. The median exposure to abatacept was 26.2 months.

Six cases of *M. tuberculosis* were reported, equating to 0.06 events per 100 patient-years. In these studies patients were tested for TB prior to study entry. Most of the cases of TB occurred in regions where TB is endemic (Mexico [3], Thailand [1], Portugal [1], Brazil [1].

The ARRIVE trial (Schiff et al 2009) was a 6 month study assessing the safety, tolerability and efficacy of abatacept in patients with RA who had failed one anti-TNF and who were switched to abatacept

directly or after completing a washout period. The relevance of this study is that patients were included in the study even if they tested positive for purified protein derivative (PPD, the tuberculosis skin text). Despite the inclusion of these patients, there were no cases of TB during this 6 month study.

Finally, the Orencia Summary of Product Characteristics (2010) for abatacept reports that there was no increase of tuberculosis observed in the pivotal abatacept placebo-controlled trials. Nevertheless, the SPC recommends that patients should be screened for latent tuberculosis prior to initiating abatacept.

Thus, overall, the clinical data suggest that abatacept has a low propensity to reactivate TB infections. It has been suggested by Khraishi et al that abatacept's differential mechanism of action could explain the lower rates of TB reactivation observed in the abatacept clinical trials (Khraishi 2009). Thus, abatacept could be a suitable agent of choice for the physician in those patients who may be at risk of TB.

Choosing the appropriate biologic agent: onset of action

Infliximab and abatacept can be clearly differentiated clinically by their different profiles with regard onset of action and maintenance of clinical effect.

As will be shown in more detail in the Clinical Evidence section of this submission, there are differences between infliximab and abatacept with regard to onset of action and maintenance of effect. Such differences in clinical properties should allow physicians to choose the most appropriate first line biologic for their patients

There may be some patients whom the clinician feels would benefit from a biologic therapy with a slightly slower onset of action than the anti-TNFα therapies, but with incremental benefits over a longer period. Thus, patients with moderate to severe disease, but without the prognostic features suggestive of rapid progression (for example, patients with very high baseline acute phase markers, very high swollen joint counts, or evidence of erosive disease) could benefit most in these circumstances.

2.6 Please identify the main comparator(s) and justify their selection.

The main comparators for consideration within this appraisal are as advised within the final scope:

1) Conventional DMARDs (cDMARDs)

It is appropriate to compare abatacept against cDMARDs based on the current treatment pathway in the UK. The use of cDMARDs as a

base case comparator is a well recognised approach that has been used in previous appraisals

2) Biologics: infliximab

The reasons behind this selection are explained above.

2.7 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

Adverse reactions are not included in the cost-effectiveness evaluation based on the assumption that there are no clear differences in adverse reactions between treatments, meaning that adverse events are not expected to be a cost-driver.

2.8 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

For the current economic evaluation, costs were obtained from Kobelt et al (2002) publication. These costs are based on a UK NHS perspective. This analysis also shows direct costs in relation to HAQ score which is applicable as the economic model is driven by a change in HAQ score.

2.9 Does the technology require additional infrastructure to be put in place?

Abatacept is administered as an IV infusion over 30 minutes.

3 Equity and equality

In certain situations an anti-TNF agent may not be the optimal first line biologic treatment choice for eligible patients with RA. For a small percentage of patients alternative therapeutic options, with a different mode-of-action and different mode of administration, may be more suitable.

When treating this highly heterogenous chronic disease, the armamentarium of biological agents available to rheumatology specialists needs to offer the clinician as wide a choice of therapeutic options as possible, so that the most suitable pharmacotherapy can be matched to the needs of the individual patients

3.1 Identification of equity and equalities issues

3.1.1 Please specify any issues relating to equity or equalities in NICE guidance, or protocols for the condition for which the technology is being used.

Abatacept is most suitable for those patients who require or reasonably request intravenous infusion.

In terms of Equity and Equality, the principal sub groups of patients who are dealt with in an inequitable and disadvantaged way compared to the overall group of RA patients are those small but significant numbers of patients who require or request intravenous infusion with abatacept.

The protocols which explain how a patient is placed in the category of requiring or reasonably requesting intravenous infusion are:-

i. Those who cannot or will not in practice self administer subcutaneously. These include those who are mentally ill and who cannot be expected to self administer. These include those who have genuine provable clinically diagnosed needle phobias. These include those who are in dysfunctional families who cannot reasonably be expected to have medications at home or in the vicinity at home of young and vulnerable children.

ii. Those who require close regular monitoring, including those who have co morbidities, for example: advanced heart disease; cancer; malignancies; or active infection.

Those who would particularly benefit from regular attendance at a site which has available staff during administration of the treatment. These include the aged and infirm and those with special needs. Those with disabilities including clinical depression which prevent or discourage them from active pursuit of their best options for treatment and who need help and care in monitoring and treating their condition.

In terms of Equality legislation, the issues are of how to prevent the inequalities that arise out of Age, Disability and Race.

Age carries with it a number of co morbidities, traits and physical and mental weaknesses that in practice prevent optimal treatment options and choice.

Disability both physical and mental prevents proper take up of the right treatment.

Race is relevant in regard principally to the preponderance of TB among ethnic, racial and national sub groups which affects the actual likelihood of a person being at risk of being placed in a position that they cannot take advantage of current treatments.

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

There are several issues of equity and equality.

Equity issues.

The current situation is one of inequity to those identified at 3.1.1 This inequity is altered and ameliorated by abatacept rectifying the current disadvantaged population groups who suffer from the lack of coverage by current treatment options in those stated criteria.

Equity allows consideration by the Institute of wider parameter than Equality legislation. Socio-economic disadvantage, lack of language skills, lack of social and intellectual skills play a part. Equity allows consideration of matters with a number of different and disparate factors at the same time. Equity allows consideration of an issue “in the round”. Here, there are likely to be patients with not just one but a multiple of the identified factors at 3.1.1. which would put them at risk of falling outside or through the current net of treatments.

Equality issues.

Equality issues arise out of the provisions of the Equality Act 2010 ("the Act") which received Royal Assent 8 April 2010.

There is nothing known as authorising outside the Act (in the NHS Act 2006 or the Regulations empowering the Institute for example) that allows the Institute to consider any recommendation as an exception to the provisions of the Act.

The technology is compliant with the provisions of the Act. (see Addendum)

Application.

The population groups that may presently be dealt with in an unequal way by the current treatment options are those who have the protected characteristics of Age, Disability and Race.

The fact that some of the population may benefit from current treatment and who have the protected characteristics of Age, Disability and Race does not exempt consideration of sub groups of the population who also share the characteristics of Age, Disability and Race who cannot or will not benefit from current treatment.

The principal group which would benefit from abatacept is that of the disabled on the issue of intravenous infusion compared to subcutaneous self injection.

When that group is further defined by reasons of inability or unwillingness to pursue treatment with infliximab, then it is discriminated against by reason of the protected characteristic.

Protected characteristics particularly in Age and Disability may overlap but this is not a reason not to consider those factors which do overlap.

The main risk is from indirect discrimination.

Age

Rheumatoid arthritis can start at a relatively early age, but is more prevalent over the age of 55.

It is accepted that most patients even in this age group will prefer subcutaneous self injection.

It is submitted that when further defined by reason of having some or all the characteristics at 3.1.1., the age groups do not enjoy the full range of benefits of the current treatment when they are unable or unwilling to self administer, unable to receive benefit from other treatments and unable to maintain their treatment without regular

referral to infusion. In a significant proportion of patients infliximab has a requirement for increasing dosage to sustain efficacy, which in turn requires increased health resource utilisation. This age group, has greater impedance to the pursuit of their optimal treatment. The patient in this group is required to make the conscious effort to attend and complain about their treatment. Abatacept requires once a month attendance for a ½ hour infusion in a low stress monitoring environment. Abatacept shows no evidence that once successful it will require increased dosage.

This age group is at risk of indirect discrimination by reason of disproportionately participating in optimal treatment.

Disability

See Addendum for the definition as far as this Act (except Part 12 and section 190) applies in relation to a person who has had a disability.

Disablement can be physical or mental and need only be such as have a substantial and long term effect on their ability to carry out day to day functions. Here, a function can include a requirement that the person has to self inject. Disablement takes many forms. It can include manual dexterity, phobias, impairment both physical and mental. The fact that some otherwise disabled people can take advantage of current treatments does not exclude consideration by the Institute of those that cannot so benefit. The Institute must take into account the abilities of the otherwise well and compare these to the disabled for the purposes of considering whether discrimination (direct or indirect) does or could occur. It is submitted that there are degrees of disablement. In this context otherwise well would mean that they may be in some ways disabled but not so disabled as to not be able to receive Infliximab. A person here who is discriminated against is a person who cannot self inject. The Act recognises to do otherwise would make the exercise nonsensical. In this case, those who for reason of disablement cannot act as sensibly or as pro actively in terms of their treatment are at a disadvantage to those who are well enough otherwise to be able to look after themselves. NOTE. It must not be assumed here that because a person has an appointed carer they take themselves out of the protected characteristic of disablement.

Race

See Addendum for definition and defined direct and indirect discrimination.

Race here includes those of an ethnic or national origin. Race under the Act is not simply a matter of genetics. Here, those who are of Asian ethnicity or Pakistani nationality or Northern Indian or Bangladeshi or Northern African background would be included.

These sub groups have an increased susceptibility to active TB, dormant TB and risk of contracting TB. In addition, in the inner cities whose diet may be poor may be more likely to contract TB. TB rules out a number of current treatments. Here, the person would be discriminated against where they were also unable to receive the full benefit of the current treatment options and be placed in one or more of the protocols through 3.1.1.

3.1.3 How have the clinical and cost-effectiveness analyses addressed

The studies of the technology indicate that following the initial period of assessment and adjustment to the correct dose level, there is no evidence of any significant required increase in dose level of abatacept over the period of treatment.

By comparison, following DART and the report Moots et al (2008), Kievit et al (2006), there is a significant body of evidence of a significant required increase in dose levels in infliximab. Implicit in that (and a hidden cost) is the cost-time element of further input of clinical and medical consultation, investigation and alteration of dose or treatment. Consequently, the patient will also suffer repeated periods of ever reducing effectiveness over time such that until rectified by altered dose level or increased frequency of given dose level, they will suffer a reduction in quality of life and potential increase in damage progressing (for example, as measured by radiographic assessments) exposing them to a heightened level of disability.

The absence of evidence of this syndrome in abatacept is in itself significant. Searches were made for any such evidence. The lack of evidence is relied upon to indicate the case for reliable, known, quantifiable and predictable levels of treatment (and cost) for the effect desired.

Addendum

3.1.2 Equality

The relevant provisions of the Act in force from 1 October 2010 are Ss. 4, 5, 6, 9, 13, 15, 19, 23, 158 and Schedule 19. These are set out in full at the end of this submission.

The relevant sections not yet in force but which may well shortly be brought into force are Ss. 1, 14, 149.

Submissions on the Act are divided into two parts. Firstly those relating to the parts currently force (Ss. 4, 13, 15, 19, 23, 158 and Schedule 19). Secondly those relating to the parts not yet in force but likely to come into force during the period f the currency of the Institutes guidance (Ss. 1, 14, 149).

The benefit of consideration being given by the Institute to the second set of submissions is the same as was recognised by the Institute when making and adopting their guidance "Institute Revised Equality Scheme 2010 – 2013" (as at 17 March 2010). The Institute recognised that although the Act had not at that time yet received Royal Assent, it was very likely to do so and that whilst it was not known exactly which sections would come into operation or effect at which time, the legislation was likely to be something which would operate on any guidance subsequently issued by the Institute. Moreover the Act introduced new pieces of legislation and brought together a number of disparate pieces of existing legislation which already affected the duties of the Institute. Different dates for the coming into effect of sections of the Act have occurred as a normal course of events. These have included the 8 April 2010, 6 July 2010 and 1 October 2010 so far. This is in part explained by certain sections imposing new duties upon which full consultation and risk assessment has had to take place. There is no known indication from the government that any part of the Act will not be brought into effect in due course.

The approach of making two sets of submissions allows the Institute a choice as to whether to take account of only the current sections of the Act in force or to take account of both either severally or together.

It is submitted that compliance with the Act requires consideration of at least the first set of submissions.

It is submitted that consideration of the second set of submissions is not precluded, is not unlawful and makes a good deal of sense.

The recommendations made by the Institute are likely to be in effect for a good time once made and usually for up to 3 years without review. Within that time, these sections not yet in force could well be brought into law by Order of the Minister. If the second set of submissions are not considered now any recommendations would not have taken the sense and meaning of these provisions into account. Confusion might then arise in the lawfulness of application of NICE guidance to clinical situations.

First set of submissions (Ss. 4, 5, 6, 9, 13, 15, 19, 23, 158 and Schedule 19 – all in force).

Preamble

The Act provides that the Institute has a duty (whether as a public authority under Schedule 19 of the Act or merely exercising public functions) to have due regard to the provisions of the Act when making decisions and recommendations.

There are three main issues arising out of the duties of the Institute under the Act in regard to the protected characteristics of Age, Disability and Race (Ss. 4 and 15 of the Act).

The issues currently relate to the risk of infringing - or continuing to infringe - the provisions of the Act in terms of direct and indirect discrimination (ss. 13 and 19 of the Act).

The Institute is empowered under Section 23 to make a comparison by reference to circumstances (in which there is no material difference in cases) when considering whether there has been direct discrimination between abilities and disabilities.

The Act provides under s.158 that the Institute may make recommendations which are or amount to positive action.

KEY POINT A person may be disabled in more than one way. A person who can not receive for example infliximab may be considered disabled under the Act.

Equality Issues

Ss 4 The protected characteristics

The following characteristics are protected characteristics—

age;

disability;

gender reassignment;

marriage and civil partnership;

pregnancy and maternity;

race;

religion or belief;

sex;

sexual orientation.

Ss 5 Age

1. In relation to the protected characteristic of age—

    a. a reference to a person who has a particular protected characteristic is a reference to a person of a particular age group;

b. a reference to persons who share a protected characteristic is a reference to persons of the same age group.

2. A reference to an age group is a reference to a group of persons defined by reference to age, whether by reference to a particular age or to a range of ages.

Ss 6 Disability

1. A person (P) has a disability if—

   a. P has a physical or mental impairment, and

   b. the impairment has a substantial and long-term adverse effect on P's ability to carry out normal day-to-day activities.

2. A reference to a disabled person is a reference to a person who has a disability.

3. In relation to the protected characteristic of disability—

   a. a reference to a person who has a particular protected characteristic is a reference to a person who has a particular disability;

   b. a reference to persons who share a protected characteristic is a reference to persons who have the same disability.

4. This Act (except Part 12 and section 190) applies in relation to a person who has had a disability as it applies in relation to a person who has the disability; accordingly (except in that Part and that section)—

   a. a reference (however expressed) to a person who has a disability includes a reference to a person who has had the disability, and

   b. a reference (however expressed) to a person who does not have a disability includes a reference to a person who has not had the disability.

5. A Minister of the Crown may issue guidance about matters to be taken into account in deciding any question for the purposes of subsection (1).

6. Schedule 1 (disability: supplementary provision) has effect.

Ss 9 Race

1. Race includes—

    a. colour;

    b. nationality;

    c. ethnic or national origins.

2. In relation to the protected characteristic of race—

    a. a reference to a person who has a particular protected characteristic is a reference to a person of a particular racial group;

    b. a reference to persons who share a protected characteristic is a reference to persons of the same racial group.

3. A racial group is a group of persons defined by reference to race; and a reference to a person's racial group is a reference to a racial group into which the person falls.

4. The fact that a racial group comprises two or more distinct racial groups does not prevent it from constituting a particular racial group.

5. A Minister of the Crown may by order—

    a. amend this section so as to provide for caste to be an aspect of race;

    b. amend this Act so as to provide for an exception to a provision of this Act to apply, or not to apply, to caste or to apply, or not to apply, to caste in specified circumstances.

6. The power under section 207(4)(b), in its application to subsection (5), includes power to amend this Act.

Ss 13 Direct discrimination

1. A person (A) discriminates against another (B) if, because of a protected characteristic, A treats B less favourably than A treats or would treat others.

2. If the protected characteristic is age, A does not discriminate against B if A can show A's treatment of B to be a proportionate means of achieving a legitimate aim.

3. If the protected characteristic is disability, and B is not a disabled person, A does not discriminate against B only

because A treats or would treat disabled persons more favourably than A treats B.

4. If the protected characteristic is marriage and civil partnership, this section applies to a contravention of Part 5 (work) only if the treatment is because it is B who is married or a civil partner.

5. If the protected characteristic is race, less favourable treatment includes segregating B from others.

6. If the protected characteristic is sex—

    a. less favourable treatment of a woman includes less favourable treatment of her because she is breast-feeding;

    b. in a case where B is a man, no account is to be taken of special treatment afforded to a woman in connection with pregnancy or childbirth.

7. Subsection (6)(a) does not apply for the purposes of Part 5 (work).

8. This section is subject to sections 17(6) and 18(7).

15 Discrimination arising from disability

1. A person (A) discriminates against a disabled person (B) if—

    a. A treats B unfavourably because of something arising in consequence of B's disability, and

    b. A cannot show that the treatment is a proportionate means of achieving a legitimate aim.

2. Subsection (1) does not apply if A shows that A did not know, and could not reasonably have been expected to know, that B had the disability.

Ss 19 Indirect discrimination

1. A person (A) discriminates against another (B) if A applies to B a provision, criterion or practice which is discriminatory in relation to a relevant protected characteristic of B's.

2. For the purposes of subsection (1), a provision, criterion or practice is discriminatory in relation to a relevant protected characteristic of B's if—

    a. A applies, or would apply, it to persons with whom B does not share the characteristic,

b. it puts, or would put, persons with whom B shares the characteristic at a particular disadvantage when compared with persons with whom B does not share it,

c. puts, or would put, B at that disadvantage, and

d. A cannot show it to be a proportionate means of achieving a legitimate aim.

3. The relevant protected characteristics are—

age;

disability;

gender reassignment;

marriage and civil partnership;

race;

religion or belief;

sex;

sexual orientation.

Ss 158 Positive action: general

1. This section applies if a person (P) reasonably thinks that—

a. persons who share a protected characteristic suffer a disadvantage connected to the characteristic,

b. persons who share a protected characteristic have needs that are different from the needs of persons who do not share it, or

c. participation in an activity by persons who share a protected characteristic is disproportionately low.

2. This Act does not prohibit P from taking any action which is a proportionate means of achieving the aim of—

a. enabling or encouraging persons who share the protected characteristic to overcome or minimise that disadvantage,

b. meeting those needs, or

c. enabling or encouraging persons who share the protected characteristic to participate in that activity.

3. Regulations may specify action, or descriptions of action, to which subsection (2) does not apply.

4. This section does not apply to—

    a. within section 159(3), or

    b. anything that is permitted by virtue of section 104.

5. If section 104(7) is repealed by virtue of section 105, this section will not apply to anything that would have been so permitted but for the repeal.

6. This section does not enable P to do anything that is prohibited by or under an enactment other than this Act.

Second set of submissions (ss. 1, 14, 149 – not yet in force).

Section 1 allows consideration of socio economic factors which would be relevant to those parts of the UK such as impoverished inner cities and areas where large numbers of population are susceptible to TB.

Section 14 allows discrimination to occur when combinations of characteristics occur for example Race and Age, Age and Disablement and Disablement and Age.

Section 149 makes explicit the duty to promote equality in a number of different ways.

Ss 1 Public sector duty regarding socio-economic inequalities

1. An authority to which this section applies must, when making decisions of a strategic nature about how to exercise its functions, have due regard to the desirability of exercising them in a way that is designed to reduce the inequalities of outcome which result from socio-economic disadvantage.

2. In deciding how to fulfil a duty to which it is subject under subsection (1), an authority must take into account any guidance issued by a Minister of the Crown.

3. The authorities to which this section applies are—

    a. a Minister of the Crown;

    b. a government department other than the Security Service, the Secret Intelligence Service or the Government Communications Head-quarters;

    c. a county council or district council in England;

d. the Greater London Authority;

e. a London borough council;

f. the Common Council of the City of London in its capacity as a local authority;

g. the Council of the Isles of Scilly;

h. a Strategic Health Authority established under section 13 of the National Health Service Act 2006, or continued in existence by virtue of that section;

i. a Primary Care Trust established under section 18 of that Act, or continued in existence by virtue of that section;

j. a regional development agency established by the Regional Development Agencies Act 1998;

k. a police authority established for an area in England.

4. This section also applies to an authority that—

a. is a partner authority in relation to a responsible local authority, and

b. not fall within subsection (3),

but only in relation to its participation in the preparation or modification of a sustainable community strategy.

5. In subsection (4)—

"partner authority" has the meaning given by section 104 of the Local Government and Public Involvement in Health Act 2007;

"responsible local authority" has the meaning given by section 103 of that Act;

"sustainable community strategy" means a strategy prepared under section 4 of the Local Government Act 2000.

6. The reference to inequalities in subsection (1) does not include any inequalities experienced by a person as a result of being a person subject to immigration control within the meaning given by section 115(9) of the Immigration and Asylum Act 1999.

Ss 14 Combined discrimination: dual characteristics

1. A person (A) discriminates against another (B) if, because of a combination of two relevant protected characteristics, A treats B less favourably than A treats or would treat a person who does not share either of those characteristics.

2. The relevant protected characteristics are—

    a. age;

    b. disability;

    c. gender reassignment;

    d. race

    e. religion or belief;

    f. sex;

    g. sexual orientation.

3. For the purposes of establishing a contravention of this Act by virtue of subsection (1), B need not show that A's treatment of B is direct discrimination because of each of the characteristics in the combination (taken separately).

4. But B cannot establish a contravention of this Act by virtue of subsection (1) if, in reliance on another provision of this Act or any other enactment, A shows that A's treatment of B is not direct discrimination because of either or both of the characteristics in the combination.

5. Subsection (1) does not apply to a combination of characteristics that includes disability in circumstances where, if a claim of direct discrimination because of disability were to be brought, it would come within section 116 (special educational needs).

6. A Minister of the Crown may by order amend this section so as to—

    a. make further provision about circumstances in which B can, or in which B cannot, establish a contravention of this Act by virtue of subsection (1);

    b. specify other circumstances in which subsection (1) does not apply.

7. The references to direct discrimination are to a contravention of this Act by virtue of section 13.

Ss 149 Public sector equality duty

1. A public authority must, in the exercise of its functions, have due regard to the need to—

    a. eliminate discrimination, harassment, victimisation and any other conduct that is prohibited by or under this Act;

    b. advance equality of opportunity between persons who share a relevant protected characteristic and persons who do not share it;

    c. foster good relations between persons who share a relevant protected characteristic and persons who do not share it.

2. A person who is not a public authority but who exercises public functions must, in the exercise of those functions, have due regard to the matters mentioned in subsection (1).

3. Having due regard to the need to advance equality of opportunity between persons who share a relevant protected characteristic and persons who do not share it involves having due regard, in particular, to the need to—

    a. remove or minimise disadvantages suffered by persons who share a relevant protected characteristic that are connected to that characteristic;

    b. take steps to meet the needs of persons who share a relevant protected characteristic that are different from the needs of persons who do not share it;

    c. encourage persons who share a relevant protected characteristic to participate in public life or in any other activity in which participation by such persons is disproportionately low.

4. The steps involved in meeting the needs of disabled persons that are different from the needs of persons who are not disabled include, in particular, steps to take account of disabled persons' disabilities.

5. Having due regard to the need to foster good relations between persons who share a relevant protected characteristic and persons who do not share it involves having due regard, in particular, to the need to—

    a. tackle prejudice, and

    b. promote understanding.

6. Compliance with the duties in this section may involve treating some persons more favourably than others; but that is not to be taken as permitting conduct that would otherwise be prohibited by or under this Act.

7. The relevant protected characteristics are—

   age;

   disability;

   gender reassignment;

   pregnancy and maternity;

   race;

   religion or belief;

   sex;

   sexual orientation.

8. A reference to conduct that is prohibited by or under this Act includes a reference to—

   a. a breach of an equality clause or rule;

   b. a breach of a non-discrimination rule.

   c. Schedule 18 (exceptions) has effect.

4 Statement of the decision problem

Is abatacept a clinically and cost-effective treatment alternative for patients with moderate to severe rheumatoid arthritis after the failure of conventional DMARDs, including methotrexate.

Table A 2 Summary NICE scope

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	Adults with rheumatoid arthritis who have an inadequate response to one or more conventional DMARDs including methotrexate	As per scope	
Intervention	Abatacept	As per scope	
Comparator(s)	▪ Conventional DMARDs ▪ Biologics (adalimumab, etanercept, infliximab, certolizumab pegol, golimumab	Conventional DMARDs and infliximab	Conventional DMARDs were used as a comparator based on the current treatment pathway in the UK and is an approach used in previous NICE appraisals. Infliximab was used as a comparator as this is the only biologic agent administered intravenously.
Outcomes	▪ Disease activity ▪ Physical Function ▪ Joint damage ▪ Pain ▪ Mortality ▪ Fatigue ▪ Extra-articular manifestations of disease ▪ Adverse effects of treatment ▪ Health-related quality-of-life.	As per scope	
Economic analysis	The reference case stipulates	As per scope	

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
	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 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.		
Subgroups to be considered	If the evidence allows, the appraisal will consider subgroups based on: ▪ Severity of disease activity: moderate to severe disease and severe disease ▪ Auto antibody status including rheumatoid factor and anti-CCP	None	A paucity of data did not make it possible to conduct these subgroup analyses

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Special considerations, including issues related to equity or equality	Consultees at the scoping workshop highlighted that abatacept had a unique mechanism of action to the other available biologic therapies. This appraisal will consider the use of abatacept only after the failure of conventional DMARDs alone. It will not include a review of the guidance in technology appraisal 195 relating to the use of abatacept after the failure of a TNF inhibitor.	As per scope	

Section B – Clinical and cost effectiveness

Table B 1 Overview of sections

Element of health technology assessment	Reference case	Section in 'Guide to the methods of technology appraisal'
Defining the decision problem	The scope developed by NICE	5.2.5 and 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 and 5.2.6
Perspective costs	NHS and PSS	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 and 5.2.12
Synthesis of evidence on outcomes	Based on 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; PSS, Personal Social Services; QALY(s), quality-adjusted life year(s)

5 Clinical evidence

5.1 Identification of studies

5.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 9.2, appendix 2.

Evidence was collected on the efficacy and safety of abatacept in the management of RA patients following inadequate response to, or intolerance to, MTX. The search strategy closely followed the methods outlined and used by the Health Technology Assessment Groups at the University of Birmingham, in the reviews conducted by NICE in 2004 and 2006 (Barton et al 2004, Chen et al 2006).

The following electronic databases were searched to identify relevant studies:

- Medline via Dialog Datastar. Medline 1980 to date (MEYY) and Medline-In-Process (MEIP) were searched on January 21, 2010. The search was updated on October 13, 2010.
- Embase via Dialog Datastar. Embase 1980 to date was searched on January 21, 2010. The search was updated on October 13, 2010.
- The Cochrane Library, accessed via Wiley Interscience, http://www.mrw.interscience.wiley.com/, was searched on January 21, 2010. Library was searched with unrestricted dates up to January 21, 2010. The search was updated on October 13, 2010.

All Phase II and Phase III studies undertaken as part of the drug development plan for abatacept by BMS were considered and clinical study reports (CSRs) obtained for review.

The search was restricted to studies relating to humans and clinical trials. Only English language articles/abstracts and studies that were published between January 1980 and October 2010 were considered. The search was further restricted manually according to inclusion/exclusion criteria listed in Section 5.2.1.

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

Additionally, the two conference websites below were searched for relevant abstracts:

- European League Against Rheumatism (EULAR), 2008-2010, via the EULAR website http://www.eular.org was searched on October 13, 2010.
- American College of Rheumatology (ACR), 2008-2010, via the ACR website http://www.rheumatology.org/ was searched on October 13, 2010.

Poster presentations and unpublished manuscripts relating to the use of abatacept in MTX inadequate responders were also provided by BMS.

5.2 Study selection

5.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

All citations were downloaded into Reference Manager (version 10) and any duplicates removed. The relevance of each identified citation was assessed using the title and abstract according to the pre-defined selection criteria presented in Table B2. Full text articles (i.e. publications) were obtained, if available, for the abstracts which met these criteria. Each study was then re-evaluated as to whether it met the inclusion and exclusion criteria. Those meeting the inclusion selection criteria were included in this submission.

In total, 10 publications reporting on 3 clinical trials and 2 long-term extension (LTE) studies were selected for review.

All publications were English language papers.

Meta-analyses were identified and reviewed for the purpose of checking bibliographies but were excluded from the list of included studies.

An additional 6 conference abstracts, 3 poster presentations, and 1 unpublished manuscript were also selected by a hand-search of conferences.

Table B 2 Eligibility criteria used in search strategy

	Clinical effectiveness
Inclusion criteria	Population: adult patients with moderate to severe RA who inadequately responded to MTX. Interventions: abatacept in the proposed indication. Comparators: another biological DMARD, a conventional DMARD, or placebo (including 'do nothing' option). Outcomes: outcomes reported at interim time points, if necessary to enable comparisons across trials over equal time periods, and studies that include the following endpoints: • *Efficacy parameters:* Change From Baseline (CFB) in HAQ score at 24/28 and 48/54 weeks, ACR20, ACR50, ACR70 response rates at 24/28 weeks and 48/54 weeks • *Safety parameters:* Withdrawals due to adverse events at 24/28 weeks. Study design: human studies; published RCTs at any phase beyond Phase I that involve de novo use of the biologic therapies of interest. Open label extensions with parallel design or comparing different doses or schedules of the drug were also considered. RCTs may be blinded or unblinded. Language restrictions: English
Exclusion criteria	Population: disease other than RA; patients with early RA; paediatric patients. Interventions: other biologic therapies; conventional DMARDs. Outcomes: laboratory measures aimed at investigating disease or treatment mechanisms; no reported relevant clinical outcome. Study design: non-randomised and uncontrolled trials (unless an extension of an included RCT); conversion/ crossover or switch studies; pharmacokinetic studies; observational studies; reviews; update or commentaries on data published elsewhere; case reports; letters to the editor; animal or *in vitro* studies. Language restrictions: non-English

ACR: American College of Rheumatology; DMARD: disease-modifying antirheumatic drugs; MTX: methrotrexate; RA: rheumatoid arthritis; RCT: randomised controlled trial

5.2.2 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 5.2.4.

The QUOROM flow diagram describing the RCT selection process is illustrated in Figure B1.

Three RCTs, from 5 publications, meeting the selection criteria for the indicated patient population and comparing abatacept with other therapies (or placebo) were included in this submission.

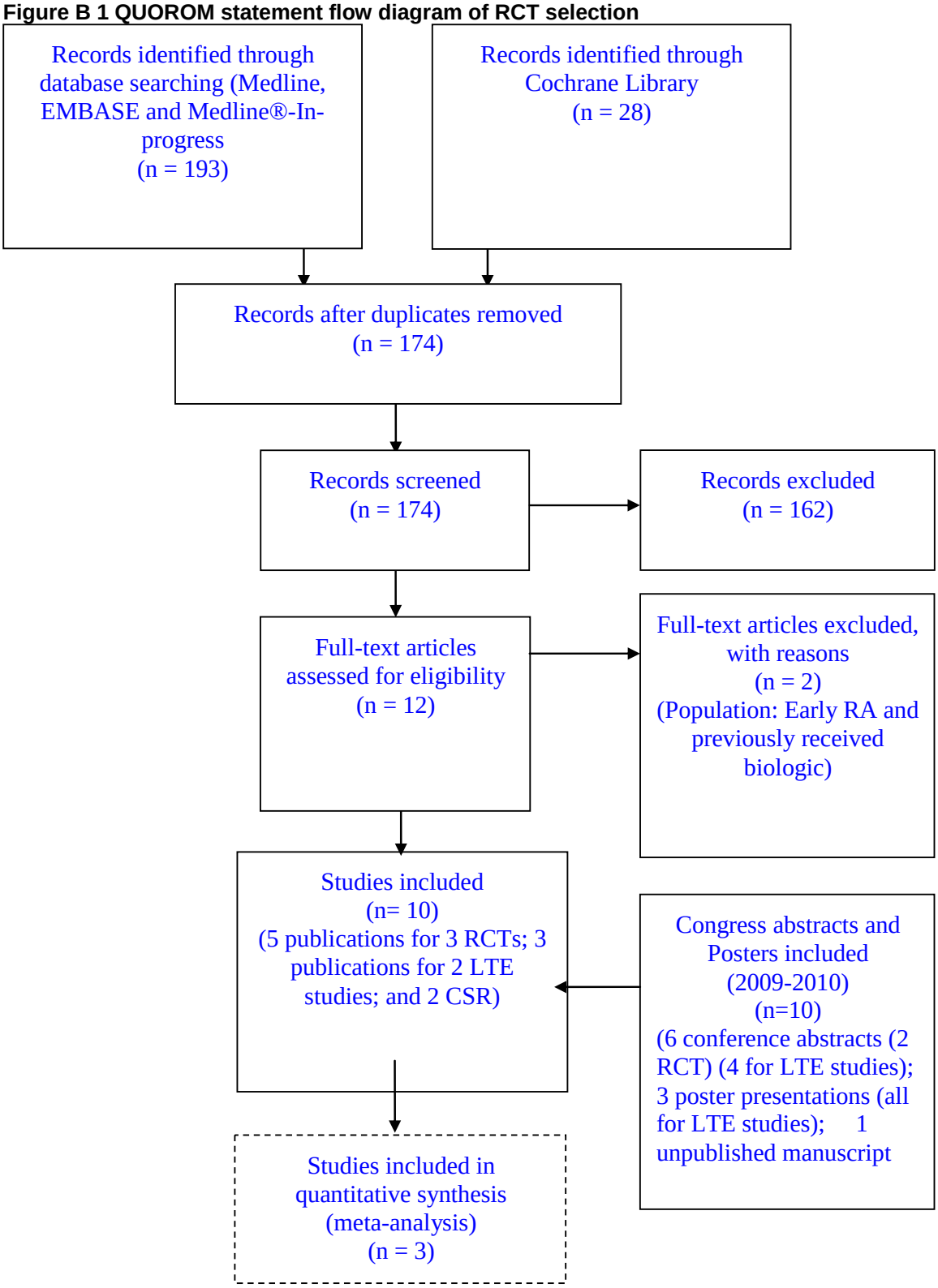
CSRs for BMS trials were included and searched for additional information if data were missing or unavailable from the published reports.

LTE studies of included RCTs were included as relevant non-RCT evidence (see Section 5.2.7).

Conference abstracts reporting on integrated analysis from abatacept trial data were also included as relevant non-RCT evidence (see Section 5.2.7).

Two additional abatacept RCTs were identified but they did not meet the inclusion criteria for the relevant patient group: Westhovens et al (2009) focuses on early RA patients and Weinblatt et al (2006) on patients receiving abatacept treatment following another biologic DMARD. One conference abstract reporting on an LTE of phase I and phase II abatacept trials for active RA patients who were either MTX-inadequate or MTX-intolerant was excluded as the enrolled patients were all Japanese and the population was considered not of interest for the UK.

Figure B 1 QUOROM statement flow diagram of RCT selection



5.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

RCTs for which more than one source was identified are referred to throughout the submission by their trial acronym or primary source (e.g. Kremer Phase 2b). Other sources are listed in column “primary and secondary study ref.” in Table B3.

Complete list of relevant RCTs

5.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

RCTs and secondary references are summarised in Table B3

Summary tables of the methodology and results of the included RCTs are presented in Sections 5.3 and 5.5. Please note that 2 conference abstracts included in Table B3 (Conaghan et al 2010, Dougados et al 2010) are not included in most summary tables due to lack of reported data. The results for these abstracts are discussed separately.

Table B 3 List of relevant RCTs with abatacept

Trial	Interventions compared (incl. dose, frequency and duration of treatment)				Comparison	Population treated	Primary and secondary study references
	Interventions	Dose	Frequency	Duration			
AIM	Placebo + MTX			1 year	Abatacept + MTX vs. Placebo + MTX	Patients with active RA despite MTX therapy (i.e. inadequate responder to MTX)	Kremer et al 2006, Russell et al 2007, and abatacept CSR Dougados et al 2010 (EULAR abstract, subgroup analysis)
	Abatacept + MTX	10 mg/kg	Days 1, 15, and 29 and every 28 days thereafter				
Kremer Phase 2b	Placebo + MTX	N/A	N/A	1 year	Abatacept + MTX vs. Placebo + MTX	Patients with active RA despite MTX therapy (i.e. inadequate responder to MTX)	Kremer et al 2005, Kremer et al 2003
	Abatacept + MTX	2 mg/kg	Day 1, 15, and 30 and every 30 days thereafter				
	Abatacept + MTX	10 mg/kg					
ATTEST	Placebo + MTX	N/A	N/A	6 months	Abatacept + MTX vs. Placebo + MTX at 6 months Infliximab + MTX vs. Placebo + MTX at 6 months Abatacept + MTX vs. Infliximab + MTX at 1 year	Patients with active RA despite MTX therapy (i.e. inadequate responder to MTX)	Schiff et al 2008 and abatacept CSR
	Infliximab + MTX	3 mg/kg	Days 1, 15, 43 and 85, and every 56 days thereafter	1 year			
	Abatacept + MTX	10 mg/kg	Days 1, 15 and 29, and every 28 days thereafter	6 months and 1 year			
IM101-119 (Phase IIIb trial)	Placebo + MTX	N/A	NR	4 months	Abatacept + MTX vs. Placebo + MTX	Patients with active RA despite MTX therapy (i.e. inadequate responder to MTX)	Conaghan et al 2010 (ACR abstract)
	Abatacept 10 mg/kg + MTX	10 mg/kg	NR				

ACR: American College of Rheumatology; CSR: clinical study report; EULAR: European League Against Rheumatism; MTX: methotrexate; N/A: not applicable; NR: not reported; RA: rheumatoid arthritis.

5.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

The decision problem states that the relevant comparators for abatacept are biological and conventional DMARDs. One RCT considers the safety and efficacy of abatacept compared with an alternative biologic for the relevant patient group. This is the ATTEST trial ('Abatacept or infliximab vs placebo, a Trial for Tolerability, Efficacy and Safety in Treating rheumatoid arthritis.

The other 3 RCTs are placebo-controlled trials and do not directly compare abatacept with a biologic and/or conventional DMARD.

5.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

No studies selected from the systematic review have been excluded from this submission.

List of relevant non-RCTs

5.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 5.8 and key details should be presented in a table; the following is a suggested format.

Table B4 provides a summary of relevant non-RCTs included in this submission. Two publications, 4 conference abstracts, 3 poster presentations, and 1 unpublished manuscript are included and provide information on long-term results for abatacept as integrated analyses or LTE studies.

The integrated safety analyses for abatacept considers the safety data from across the abatacept clinical trial programme. It includes: Kremer Phase 2b study, Phase 2 abatacept plus etanercept study (Weinblatt et al 2007), AIM, Abatacept Trial in Treatment of Anti-TNF Inadequate responders (ATTAIN), Abatacept Study of Safety in Use with other RA therapies (ASSURE), ATTEST, Abatacept Researched in RA patients with an Inadequate anti-TNF response

to Validate Effectiveness (ARRIVE) and Phase 2 Mode of Action study (Buch et al 2007). Thus not all of the patients included in the integrated safety analyses were from the correct population for the decision problem, i.e. they were not all MTX inadequate responders. However we felt that it was necessary to include this safety analyses in the submission, as it is essential to monitor long term safety and tolerability with increased drug exposure.

Summary tables of the methodology and results of the included non-RCTs are presented in Section 5.

Table B 4 List of relevant non-RCTs with abatacept

Trial	Interventions compared (incl. dose, frequency and duration of treatment)					Comparison	Population treated	Objective	Primary and secondary study references	Justification for inclusion
	Interventions	Dose	Frequency	Duration						
AIM trial	abatacept + MTX	10 mg/kg	every 4 weeks	2 years (1 year DB + 1 year LTE)	Patients who completed the 1-year, randomised, DB, placebo-controlled AIM trial (abatacept [~10 mg/kg] or placebo, plus MTX) were eligible to enter the open-label LTE period (abatacept [~10 mg/kg] plus MTX).	Results available for all patients randomised to abatacept (as-observed analysis, i.e. includes treatment switch from placebo). Safety was assessed for patients who received ≥1 dose of abatacept.	Patients with active RA despite MTX therapy (i.e. inadequate responder to MTX)	Evaluate efficacy, radiographic progression and safety of abatacept plus MTX over 2 years	Genant et al 2008 and Kremer et al 2008	LTE of the AIM trial
				3 years (1 year DB + 2 year LTE)				Evaluate efficacy, radiographic progression and safety of abatacept plus MTX over 4 years	Kremer et al (unpublished manuscript)	
				5 years (1 year DB + 4 year LTE)				Evaluate efficacy, radiographic progression and safety of abatacept plus MTX over 6 years	Genant et al 2009 (poster) Kremer et al 2009 (poster)	
						Results summarised over time by original randomisation group using point estimates for patients who received ≥1 dose of abatacept in the LTE (as-observed data).		Evaluate multi-day- and night-time aspects of HRQoL	Kremer et al 2010 (ACR abstract)	

Trial	Interventions compared (incl. dose, frequency and duration of treatment)					Comparison	Population treated	Objective	Primary and secondary study references	Justification for inclusion
	Interventions	Dose	Frequency	Duration						
Kremer Phase 2b	abatacept + MTX	10 mg/kg	every 4 weeks	1 year trial + 4 year LTE	Patients who completed the 1-year DB period (abatacept 10 and 2 mg/kg or placebo, plus MTX) were eligible to enter the open-label LTE period (abatacept [~10 mg/kg] plus MTX).	Results only available for abatacept arm, this includes treatment switch from placebo	Patients with active RA despite MTX therapy (i.e. inadequate responder to MTX)	Evaluate efficacy and safety of abatacept plus MTX over 5 years	Westhovens et al 2009a	LTE of the Kremer Phase 2b trial
				1 year trial + 6 year LTE		Results available for all patients randomised to abatacept with available data at the visit of interest (as-observed). Safety was assessed for patients who received ≥1 dose of abatacept.		Evaluate safety and efficacy of abatacept plus MTX over 8 years	Westhovens et al 2009b (poster)	
ATTEST	abatacept + MTX	10 mg/kg	every 4 weeks	1 year trial+ 1 year LTE	Patients who completed the 1 year DB period (abatacept 10mg/kg plus MTX or infliximab 3mg/kg plus MTX or placebo+MTX (6 months) then abatacept 10mg/kg plus MTX (for the second 6 months) were eligible to enter the open-label LTE period (all patients allocated to abatacept 10 mg/kg)	Results for all patients who received at least 1 dose of abatacept during the open-label period. Safety was assessed for all patients who received at least 1 dose of abatacept during the open-label period.	Patients with active RA despite MTX therapy (i.e. inadequate responder to MTX)	Evaluate safety and long-term tolerability of abatacept in patients who had completed the initial 12-month double-blind treatment period.	Schiff et al 2008 and abatacept CSR	LTE of ATTEST

Trial	Interventions compared (incl. dose, frequency and duration of treatment)					Comparison	Population treated	Objective	Primary and secondary study references	Justification for inclusion
	Interventions	Dose	Frequency	Duration						
Integrated analyses of abatacept trials	abatacept (± MTX)	NR	NR	8 abatacept RA clinical trials: 6 DB PC trials, 1 non-randomised Phase II study and 1 non-randomised Phase III study	Cumulative period included 4149 patients with 11,658 p-y of exposure; 1030 had ≥5 years' exposure.	Safety was assessed for patients who received ≥1 dose of abatacept.	RA patients	Evaluate the safety of abatacept over short- and long-term periods	Becker et al 2010 (EULAR abstract)	Integrated analysis of safety data (abatacept trials)
					Cumulative period included 4149 patients with 12,132 p-y of exposure; 1165 had ≥5 years' exposure.				Hochberg et al 2010 (ACR abstract)	
					Cumulative period included 4149 patients with 11,658 p-y of exposure.				Smitten et al 2010 (EULAR abstract)	

ACR: Amercian College of Rheumatology (conference) DB: double-blind; EULAR: European League Against Rheumatism; HRQoL: health-related quality of life; LTE: long-term extension; MTX: methrotrexate; PC: placebo-controlled; P-Y: patient-years; RA: rheumatoid arthritis.

5.3 Summary of methodology of relevant RCTs

5.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, **the information should be tabulated**.

Methods

5.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

The study designs of the three RCTs included in this submission are presented in Table B5. The AIM ('Abatacept in Inadequate responders to Methotrexate') and ATTEST trials are Phase 3 studies and the Kremer is a Phase 2b study. All three trials were randomised, double-blinded, placebo-controlled, and multicentre studies in patients with moderate to severe RA who had an inadequate clinical response to MTX. All three trials used central randomisation.

The primary objectives of the AIM study were to evaluate the proportion of patients in the abatacept + MTX group versus the placebo + MTX group with an ACR20 response at 6 months, to evaluate the proportion of patients with a clinically significant improvement in Health Assessment Questionnaire Disability Index (HAQ-DI) at 1 year, and the radiographic progression of joint erosions, as measured by Genant Modified Sharp Scores at 1 year. The primary objective of the Kremer Phase 2b study was the same as that of the AIM study in that it was to evaluate the proportion of patients that achieved an ACR20 response at 6 months for abatacept vs. placebo in combination with background MTX therapy.

The primary objective of the ATTEST trial was to demonstrate that abatacept showed a greater reduction in disease activity than placebo as measured in DAS 28 (ESR) at 6 months.

Table B 5 Comparative summary of methodology of the abatacept RCTs

Trial	AIM	Kremer Phase 2b	ATTEST
	Abatacept	**Abatacept**	**Abatacept**
Location	116 centres worldwide (USA, UK, Canada, Mexico, Poland, Belgium)	Multi-centre (NR)	86 sites worldwide (US, Europe, Canada, Australia, South America and South Africa)
Design	Randomised, double-blind, placebo-controlled trial	Randomised, double-blind, placebo-controlled trial	Randomised, double-blind, double-dummy, placebo-controlled. Treatment with placebo was limited to days 1–197. On day 198, placebo treated patients were reallocated to abatacept (with blinding maintained)
Duration of study	1 year	1 year	1 year With reallocation of placebo group to abatacept at 6 months
Method of randomisation	Central randomisation system. Stratification per site not performed. Patients randomly assigned in a 2:1 ratio	Central randomisation system. Patients were randomly assigned with use of a permuted-block size of 6. Randomly assigned in a 1:1:1 ratio	Central randomisation system. Randomised by centre in a 3:3:2 ratio to 6 months
Method of blinding (care provider, patient and outcome assessor)	Investigators were blinded to treatment group assignment throughout the 1-year study	Physicians blinded to the treatment group during the study	Assessors, physicians, and patients were blinded to the treatment group assignment for 1 year
Intervention(s) (n =) and comparator(s) (n =)	abatacept (n=433) and placebo (n=219)	abatacept 2 mg/kg (n=105), abatacept 10 mg/kg (n=115), and placebo (n=119)	abatacept (n=156), infliximab (n=165), and placebo (n=110)
Primary outcomes (including scoring methods and timings of assessments)	• ACR20 at 6 months • % patients HAQ-DI improvement of ≥ 0.3 at 1 year • CFB in joint erosion score at 1 year	• ACR20 response at 6 months	• Reduction in DAS28 (ESR) with abatacept vs. placebo at 6 months

Trial	AIM	Kremer Phase 2b	ATTEST
	Abatacept	**Abatacept**	**Abatacept**
Secondary outcomes (including scoring methods and timings of assessments)	• ACR50 and ACR70 responses at 6 months • All ACR responses, major clinical and protocol responses at 1 year • Improvements and changes DAS28, HAQ-DI, SF36 at 1 year	• ACR50 and ACR70 responses at 6 months and 1 year • Improvements in individual components of the ACR core data set at 6 months and 1 year • VAS (patient's and physician's) at 6 months and 1 year • M- HAQ at 6 months and 1 year • % patients DAS28 low disease activity and remission at 6 months and 1 year • Adverse events and immunogenicity testing at 6 months and 1 year	• Mean reduction in DAS28 (ESR) with infliximab vs. placebo at 6 months • At 6 months and 1 year included • Mean reduction in DAS28 (ESR) with abatacept vs. infliximab • DAS28 (ESR) EULAR responses • ACR20, 50 and 70 responses • HAQ-DI response rates ≥ 0.3 • Mean changes in the physical and mental component summary scores, and eight subscales of the SF-36 • % patients DAS28 low disease activity and remission at 6 months and 1 year
Duration of RCT	1 year	1 year	1 year

ACR: American College of Rheumatology; CFB: change from baseline; DAS: disease activity score; EULAR: European League Against Rheumatism; ESR: erythrocyte sedimentation rate; HAQ: health assessment questionnaire; LTE: long-term extension; NR: not reported; SF-36: short-form 36; VAS: visual analogue scale.

Participants

5.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

Table B6 provides a summary of the eligibility criteria of the three RCTs included in this submission. Overall, eligibility criteria for all three RCTs identified were comparable.

Patients were eligible if they were 18 or older and met the ACR criteria for RA. In AIM and ATTEST, patients had RA for at least one year. In all trials, at the time of randomisation, patients were required to have 10 or more swollen joints (SJC), 12 or more tender joints (TJC), and a minimum C-reactive protein (CRP) level >1 mg/dL. All eligible patients had received MTX, at a stable dose ≥15mg/wk, at least 3 months prior to trials.

Eligible patients were recruited from rheumatology centres worldwide including Europe; US, Canada, Australia, Mexico, South America, and South Africa.

Exclusion criteria were not reported for each trial but included pregnancy and nursing women in the Kremer Phase 2b trial and untreated patients with a positive tuberculin skin test in the AIM trial.

Table B 6 Eligibility criteria in the abatacept RCTs

Trial	Inclusion criteria	Exclusion criteria
AIM	• Age ≥18 years • RA for at least 1 year, RA persistent and active despite MTX treatment, met the ACR criteria for the diagnosis of RA At randomisation patients were required to have: • 10 or more swollen joints • 12 or more tender joints • CRP levels >=10.0 mg/L while receiving MTX • MTX ≥ 15mg/wk for 3 months or longer, stable dose 28 days before enrolment	Patients with a positive tuberculin skin test, unless they had completed treatment for latent tuberculosis before enrolment
Kremer Phase 2b	• Age 18-65 years • Patients met the ACR criteria for the diagnosis of RA (functional classes I, II, or III) and had active disease defined by: • ≥10 swollen joints, • ≥12 tender joints, • Had a CRP level >1 mg/dl, • Treated with MTX (10–30 mg/week) for at least 6 months with a stable dosage for 28 days prior to enrolment, • All patients continued to receive MTX and discontinued all other cDMARDs	Pregnant or nursing women were excluded from trial
ATTEST	• Age ≥18 years • Patients met the ACR criteria for RA, had RA for at least 1 year, had an inadequate response to MTX by ongoing disease activity • ≥10 swollen joints, • ≥12 tender joints, • CRP levels >1 mg/dl, • Received MTX ≥15 mg/week for ≥3 months prior to randomisation and washed out all other DMARDs, • No prior experience of abatacept or anti-TNF therapy	NR

5.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

The baseline characteristics of the patients in the three RCTs included in this submission are presented in Table B7.

Overall, the study groups were well balanced for age, gender, baseline CRP levels, TJC and SJC, previous and concomitant treatments for RA. Patients had long-standing disease, between 8 to 10 years since first diagnosis, and at least one treatment with a prior DMARD. In addition, patients' baseline assessment of pain was similar across trials, between 62.1 in Kremer Phase 2b and 65.9 in the AIM trial (out of 100mm VAS).

The proportion of patients on a biologic at the time of enrolment was slightly higher in the Kremer Phase 2b trial than in the AIM and ATTEST trials; however these patients only represented a small percentage of enrolled patients (maximum of 5.70% in low dose abatacept arm). Similarly, although a majority of patients in all three trials were RF positive, the proportion of RF positive patients was higher in Kremer Phase 2b trial.

More than 65% of patients in each trial were receiving NSAIDs and corticosteroids at the time of study enrolment.

The Health Assessment Questionnaire (HAQ) score at baseline was comparable between the AIM and ATTEST trial, between 1.7 and 1.8, but lower for the Kremer Phase 2b study. However, the latter used the modified HAQ (m-HAQ) to assess disability compared with the HAQ-Disability Index (HAQ-DI) used in the other two RCTs (see outcomes Section 5.3.5).

Similar numbers of patients were randomised to each treatment and placebo arm in the Kremer Phase 2b and ATTEST trials. In the AIM study, patients were randomised in a 2:1 ratio; this unequal allocation aiming to increase safety information on active treatment with abatacept. The demographics show that the treatment and placebo groups in the three RCTs identified were well balanced and comparable across trials with respect to baseline patients and disease characteristics. Baseline characteristics were most similar in the AIM and ATTEST trials.

Table B 7 Characteristics of participants in the abatacept RCTs across randomised groups

Trial	AIM (n=656)		Kremer Phase 2b (n=339)			ATTEST (n=431)		
	Placebo + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Placebo + MTX	Abatacept 2 mg/kg every 4 weeks + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Placebo + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Infliximab 3mg/kg every 8 weeks + MTX
	(SD) [range] unless otherwise indicated	(SD) [range] unless otherwise indicated	(SD) [range] unless otherwise indicated	(SD) [range] unless otherwise indicated	(SD) [range] unless otherwise indicated	(SD) [range] unless otherwise indicated	(SD) [range] unless otherwise indicated	(SD) [range] unless otherwise indicated
Number randomised	219	433	119	105	115	110	156	165
Gender (% of females)	82%	78%	66%	63%	75%	87%	83%	82%
Age in years, mean	50.4 (12.4)	51.5 (12.9)	54.7 [23-80]	54.4 [23-80]	55.8 [17-83]	49.4 (11.5)	49 (12.5)	49.1 (12)
Years since diagnosis, y	8.9 (7.1)	8.5 (7.3)	8.9 (8.3)	9.7 (8.1)	9.7 (9.8)	8.4 (8.6)	7.9 (8.5)	7.3 (6.2)
No. of prior DMARDs, mean	1.2 (0.58)	1.3 (0.56)	NR	NR	NR	1.8 (0.91)	1.7 (0.77)	1.7 (0.82)
% patients having received prior DMARDs	19.2%	22.2%	21%	18.1%	16.5%	55.5%	51.3%	52.7%
MTX dose, mg/wk	15.7 (3.5)	16.1 (3.6)	15.8 (4.1)	15.8 (4.5)	15.0 (4.4)	16.6 (3.7)	16.5 (3.7)	16.3 (3.6)
% patients RF+	78.50%	81.80%	90%	90%	99%	77.30%	87.20%	84.40%
% on biologics at study enrolment	0%	0.20%	2.60%	5.70%	2.60%	NR	NR	NR
% patients on NSAIDs at study enrolment	83%	85.50%	NR	NR	NR	84.50%	85.30%	86.10%
% patients on corticosteroids at study enrolment	68.50%	72.10%	67%	68%	60%	70%	75.60%	71.50%
Tender joint count	31 (13.2)	32.3 (13.6)	29.2 (13.0)	28.2 (12.0)	30.8 (12.2)	30.3 (11.7)	31.6 (13.9)	31.7 (14.5)

Trial	AIM (n=656)		Kremer Phase 2b (n=339)			ATTEST (n=431)		
	Placebo + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Placebo + MTX	Abatacept 2 mg/kg every 4 weeks + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Placebo + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Infliximab 3mg/kg every 8 weeks + MTX
	(SD) [range] unless otherwise indicated	(SD) [range] unless otherwise indicated	(SD) [range] unless otherwise indicated	(SD) [range] unless otherwise indicated	(SD) [range] unless otherwise indicated	(SD) [range] unless otherwise indicated	(SD) [range] unless otherwise indicated	(SD) [range] unless otherwise indicated
Swollen joint count	22.1 (8.8)	21.4 (8.8)	21.8 (8.8)	20.2 (8.9)	21.3 (8.4)	20.1 (7.0)	21.3 (8.6)	20.3 (8.0)
Patients assessment of pain (100-mm VAS)	65.9 (20.6)	63.3 (21.1)	65.2 (22.1)	64.5 (22.3)	62.1 (21.4)	NR	NR	NR
Patients global assessment of disease activity (100-mm VAS)	62.8 (21.6)	62.7 (21.2)	62.8 (21.6)	59.4 (23.7)	60.1 (20.7)	NR	NR	MR
Physician global assessment of disease activity (100-mm VAS)	67.4 (17.0)	68 (16.0)	63.3 (15.5)	61 (16.7)	62.1 (14.8)	NR	NR	NR
HAQ	1.7 (0.6)	1.7 (0.7)	M-HAQ 1 (0.6)	1 (0.5)	1 (0.5)	1.8 (0.7)	1.8 (0.6)	1.7 (0.7)
C-reactive protein level (mg/l)	28 (25)	33 (31)	32 (32)	32 (26)	29 (28)	27 (26)	31 (27)	33 (32)
ESR (mm/h)	NR	NR	NR	NR	NR	47 (32.6)	49.4 (31.2)	47.8 (30.4)

DMARD: disease modifying antirheumatic drug; ESR: erythrocyte sedimentation rate; HAQ: health assessment questionnaire; MTX: methotrexate; NR: not reported; NSAID: non-steroidal anti-inflammatory drugs; RF: rheumatoid factor; SD: standard deviation; VAS: visual analogue scale.

Outcomes

5.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life, and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.

Table B8 lists the primary and secondary outcomes for the three RCTs included in this submission. All the outcome measures are commonly accepted measurements of disease activity in RA.

However, considering the decision problem, the following primary and secondary outcome measures of the 3 RCTs are presented:

- ACR20/50/70 responses
- Proportion of patients with a clinically significant improvement in the Health Assessment Questionnaire Disability Index (HAQ-DI)
- Genant-modified Sharp (GMS) score
- Disease Activity Score, 28 joint count (DAS28)
- Changes in Medical Outcomes Study Short Form-36 Health Survey (SF-36)

In addition, the AIM study had the exploratory objectives reported in the CSR of:

- Patient Reported Outcomes – including Morning Stiffness, Sleep Quality and Fatigue Visual Analogue Scale (VAS)
- Patient compliance during the double blind phase

We feel that these are important to include as they assess the health outcomes associated efficacy, which may are important for patient choice and quality of life. The patient reported outcomes and patient compliance are only presented in the Non-RCT LTE section of the submission.

In considering the decision problem, the following outcomes are discussed:

- ACR 20/50/70 responses
- Proportion of patients with a clinically significant improvement in the Health Assessment Questionnaire
- Genant-modified Sharp (GMS) score
- Disease Activity Score, 28 joint count (DAS28) change from baseline (CFB)
- Patient Reported Outcomes – including Morning Stiffness, Sleep Quality and Fatigue Visual Analogue Scale (VAS)
- Patient compliance during the double blind phase

A short description is given below of the efficacy variables.

ACR response: The American College of Rheumatology (ACR) response criteria are based on a combination of the number of tender joints and swollen joints, the physician's and patient's assessment of the disease activity, the patient's assessment of pain, physical functioning (HAQ, see below) and blood tests that measure inflammatory activity. An ACR 20/50/70 response is defined as 20/50/70 percent improvement in 3 of the 5 variables listed above.

HAQ (Health Assessment Questionnaire): A questionnaire designed for patient self-assessment of physical functioning. The questionnaire has 8 sub-scales. The results are presented as a value between 0 and 3, in which 0 denotes complete and 3 denotes no functional capacity. For a clinically significant improvement, the measured difference should be at least 0.22. In the abatacept studies, the minimum clinically relevant difference was defined as a change of ≥0.3 units from the baseline value. HAQ is used less frequently than DAS in routine clinical practice. It is not part of regular assessment, but many use it less frequently with some units using it yearly to coincide with the annual multi-disciplinary review recommended by NICE RA guidelines. There are different forms of the HAQ that can be used the HAQ-DI and the m-HAQ or modified HAQ.

Genant-modified Sharp (GMS) score: Radiographic measurement, using a scale such as the Genant Modified Sharp Score, is used to measure structural damage progression. It is a measure of both erosion of bone and joint space narrowing. Radiographic scoring is recommended for monitoring therapeutic response in RA since radiographic changes are considered “a direct effect of the complex, pathological processes intrinsic to RA (Genant et al 1998).

Disease Activity Score, 28 joint count (DAS28): The DAS28 is a composite index that includes the combination of tender and swollen joint counts, patient’s global assessment of disease activity and erythrocyte sedimentation rate (ESR): ESR (or C-reactive Protein [CRP]) measure inflammatory activity. DAS28 ranges from 0-10 in which scores >5.1 = high disease activity; ≤3.2 = low disease activity; <2.6 = remission (absence of disease activity). The advantages of the DAS28 are that it has clinical utility in daily practice (Deighton et al 2010) and can be visualised as a continuous, variable measure. DAS28 is used as part of the NICE assessment criteria for anti-TNFα agent therapies.

Short Form -36: A questionnaire designed for patient self-assessment of physical and mental health for evaluation of health-related quality of life in clinical trials. The questionnaire contains 36 questions which measure health according to eight different scales, see below. Sub-scores are obtained in each of the measurements (scales), and the added scores for component scales of physical (PCS) and mental (MCS) health. Higher scores indicate a better health-related quality of life and the minimum clinically relevant difference is an improvement of ≥ 3 units. For reference, the mean value of PCS and MCS in the American adult population is 50 (standard deviation 10).

Components of the Patient Reported Outcomes

Morning stiffness: Is usually assessed by the patient, using either a scale of 0-10 (0 = no morning stiffness at all; 10 = extreme, severe morning stiffness) or as mild (0-2), moderate (3-6) or severe (7-10).

Sleep Quality: Can be measured by a number of different instruments which look across different domains such as adequacy, maintenance, initiation and day time functioning. Instruments such as insomnia severity index and sleep diaries can also be used.

Fatigue Visual Analogue Scale (VAS): The patient records their degree of tiredness on a 100mm long visual analogue scale (VAS) that ranges from 0 (no tiredness) to 100 (extreme tiredness). The minimum clinically relevant difference is 10 units.

Patient Compliance

The compliance of patients was measured by the number of missed infusions.

The common primary endpoint in the AIM and Kremer Phase 2b trials was the proportion of patients with an ACR20 response at 6 months. ACR50 and ACR70 were included as secondary outcomes measures in all three RCTs (and ACR20 in ATTEST trial).

Physical function was measured by the HAQ response. Two HAQs were used: the HAQ-DI in the AIM and ATTEST trials and the m-HAQ in the Kremer Phase 2b trial. HAQ CFB is also the outcome measure used in the *de novo* economic analysis in this submission, see Section 6.2.

Structural damage was assessed as a change from baseline in bone erosion and JSN at one year using the GMS system. The GMS score was used as a primary outcome in the AIM trial. Radiological changes were scored at baseline and Day 365.

The primary outcome in ATTEST was the reduction in disease activity, measured by DAS28 (ESR) for abatacept versus placebo at 6 months.

Other secondary outcome measures included health-related quality of life as measured by the Short-Form 36 (SF-36) scores, or global assessment scales and the number of adverse events.

Table B 8 Primary and secondary outcomes of the abatacept RCTs

Trial	Primary outcomes and measures	Secondary outcomes and measures	Validity of outcome measures
AIM	• ACR20 responses at 6 months • % patients HAQ-DI improvement of ≥ 0.3 at 1 year • change from baseline in GMS joint erosion score at 1 year	• ACR50 and ACR70 responses at 6 months and • All ACR responses at 1 year, proportions of patients achieving a major clinical response and a protocol defined extended major clinical response at 1 year • DAS28, HAQ-DI improvements and changes in SF36 at one year	All outcome measures are commonly and accepted measurements of the disease activity in RA
Kremer Phase 2b	• ACR20 response at 6 months	• ACR50 and ACR70 responses, improvements in individual components of the ACR core data set • Pain and global assessment of disease activity (patient's and physician's) • Proportions of patients having low disease activity and experiencing remission using the DAS28, physical function • Adverse events	All outcome measures are commonly and accepted measurements of the disease activity in RA
ATTEST	• Reduction in disease activity, measured by DAS28 (ESR) for abatacept vs. Placebo at 6 months	• Mean reduction in DAS28 (ESR) with Infliximab vs. Placebo at 6 months. • Mean reduction in DAS28 (ESR) with vs. Infliximab at 6 months and 1 year • DAS28 (ESR) EULAR responses at 6 months and 1 year • Proportions of patients having low disease activity and experiencing remission using the DAS28 • ACR20, 50 and 70 responses at 6 months and 1 year • HAQ-DI response rates ≥ 0.3 at 6 months and 1 year • Mean changes in the physical and mental component summary (PCS and MCS, respectively) scores, and eight subscales of the SF-36 at 6 months and 1 year	All outcome measures are commonly and accepted measurements of the disease activity in RA

ACR: American College of Rheumatology; DAS: disease activity score; ESR: erythrocyte sedimentation rate; HAQ-DI: health assessment questionnaire disability index; RA: rheumatoid arthritis; SF-36: short-form 36

Statistical analysis and definition of study groups

5.3.6 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). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

Table B9 summarises the statistical analyses in the three RCTs included in this submission.

AIM trial

The AIM trial was designed to evaluate the difference in 20% improvement in ACR at 6 months between the 2 treatment groups (abatacept + MTX vs. placebo + MTX) as well as the percentage of patients with clinically significant improvement (≥0.3) in HAQ-DI at 1 year, and radiographic progression of structural damage at 1 year, as measured by the GMS. The AIM study had 99% power to detect a difference of 20% in ACR20 between the two groups.

All efficacy and safety analyses were based on a modified intention-to-treat (ITT) population, defined as all patients randomly assigned who received at least one dose of study medication.

Sample size allowed detection of an 18% difference, with 98% power, in HAQ-DI response rate between abatacept and placebo and a 60% reduction with 90% power from placebo for CFB in the GMS score (assuming an increase of 1.27 units in placebo for the CFB).

All statistical tests in the AIM trial were two-tailed with 5% significance level. All observed data were included in analyses. Patients who discontinued were imputed as non-responders if data for ACR20 and HAQ-DI was missing. Missing annual radiographic data were imputed from linear extrapolation for discontinued patients on the basis of the GMS baseline value and the on treatment assessment at the time of discontinuation.

Sensitivity analyses were performed.

Kremer Phase 2b trial

The Kremer Phase 2b study was designed to evaluate the difference in 20% improvement in ACR at 6 months between the 3 treatment groups (abatacept 2 mg/kg every 4 weeks + MTX vs. abatacept 10 mg/kg every 4 weeks + MTX vs. placebo + MTX).

All efficacy analyses were based on the ITT population, defined as all patients who received at least 1 treatment infusion.

A sample size of 107 patients per treatment group was calculated to yield 94% power to detect a difference of 25% in ACR20 responses between the 2 abatacept groups and the placebo group.

Differences in ACR20, ACR50, and ACR70 response rates on day 360 were analysed by comparing each abatacept treatment group with the placebo group using a Dunnett-adjusted chi-square test. ACR response rates at other time points were compared between each abatacept treatment group and the placebo group using a chi-square test unadjusted for multiple comparisons. Table B9 presents more details on the statistical analyses performed for other outcomes.

All statistical tests in the Kremer Phase 2b trial were two-tailed with 5% significance level and adjusted for a discontinuation rate of 15%.

All patients who discontinued from the study due to worsening RA disease (i.e. a lack of efficacy), were imputed as non-responders subsequent to the time of discontinuation. Patients who discontinued for any other reason had their last observations carried forward.

ATTEST trial

The ATTEST trial was designed to evaluate the difference in mean CFB in DAS28 at 6 months between abatacept 10 mg/kg (every 4 weeks) + MTX vs. placebo + MTX, and Infliximab 3mg/kg (every 8 weeks) + MTX vs. placebo + MTX. This was the primary endpoint.

The ATTEST study had a 99% power to detect a 0.88 unit treatment difference in DAS28 between the abatacept and placebo group, assuming the same standard deviation and a 20% dropout rate. This study was not powered for comparisons between abatacept and infliximab.

A key secondary endpoint was ACR20, which was used to provide a basis to demonstrate internal consistency of the response rates of the active treatment groups in this study. The sample sizes of 150, 150, and 100 subjects in the abatacept, infliximab and placebo groups respectively provide 85% power to detect a difference of at

least 20% in ACR20 at 6 months between either active treatment groups and placebo, at the 5% level (two-tailed, based on a continuity-corrected Chi-square test). This calculation assumed an ACR20 placebo rate of 35%.

However, although the trial was not powered to make a formal comparison, an pre-specified analyses were carried out at 12 months between abatacept 10mg/kg (every 4 weeks) + MTX vs. infliximab 3mg/kg (every 8 weeks) + MTX using point estimates and a 95% CI.

All efficacy and safety analyses were based on a modified ITT population, using the same definition as the AIM trial.

All statistical tests in the ATTEST trial were two-tailed with 5% significance level.

All patients who discontinued the study prematurely were imputed as non-responders subsequent to the time of discontinuation for ACR20, 50 and 70 responses, good EULAR responses and clinically meaningful HAQ-DI responses. Patients who discontinued for any other reason, had last observations carried forward on their continuous measurements (such as mean changes in DAS28, SF-36, and the HAQ-DI score, low disease activity state [LDAS], and DAS28-defined remission).

Table B 9 Summary of statistical analyses in abatacept RCTs

Trial	Hypotheses, objectives	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
AIM	Hypothesis: 20% difference in ACR20 between the 2 treatment groups Objectives: Study was designed to evaluate the % of patients with 20% improvement in ACR at 6 months, % patients with clinically significant improvement (≥0.3) in HAQ-DI at one year, and radiographic progression of joint erosions at one year	• All efficacy and safety analyses on a modified ITT, defined as all patients randomly assigned who received at least 1 dose of study medication • All statistical tests on a 2-sides 5% level of significance • Co-primary analyses of ACR20 6 months and HAQ-DI response at one year: 2-sided, continue corrected chi-square test to compare response of abatacept group with those of the placebo group • To compare CFB in GMS scores treatment groups at one year between a rank-based analysis of covariance was used • HAQ-DI CFB and SF-36: analysis of covariance (ANCOVA) with LOCF to compare the CFB between the treatment groups and longitudinal linear mixed-effects model • DAS28: 2-sided, continuity corrected chi-square test to compare the responses of abatacept with those of the placebo group • AE: incidence of AE summarised and for comparison between groups 95% CIs were used	• Protocol estimated that 680 patients needed to be enrolled to randomly assign 540 patients. Sample sizes on a 5% level of significance (2-tailed) • Study had 99% power to detect a difference of 20% in ACR20 between the 2 groups • Sample size allowed to detect an 18% difference in HAQ-DI response rate between the 2 groups, with 98% power, • And a 60% reduction from placebo (assuming an increase of 1.27 units in placebo for the CFB), with 90% power, for CFB in the GMS erosion score	• ACR20 and HAQ-DI: missing data for patients who discontinued were imputed as non-responders subsequent to the discontinuation. Additional sensitivity analyses were performed. • GMS scores: primary analysis included all observed data at baseline and 12 months. • Missing annual radiographic data was imputed with linear extrapolation for discontinued patients on the basis of the baseline value and the on treatment assessment at the time of discontinuation
Kremer Phase 2b	Hypothesis: 25% difference in ACR20 responses between the 2 abatacept groups and the placebo group Objective: Study was designed to evaluate the % of patients with 20% improvement in ACR at 6 months	• All statistical analyses were carried out on the ITT population, defined as all patients who received at least 1 treatment infusion • Differences in ACR20, ACR50, and ACR70 response rates on day 360 were analysed by comparing each abatacept treatment group with the placebo group using a Dunnett-adjusted chi-square test. ACR response rates at other time points were compared between each abatacept treatment group and the Placebo group using a chi-square test unadjusted for multiple comparisons • Differences in percentage CFB to LOCF for all ACR core components were analysed using analysis of covariance with the baseline value as the covariate and without adjustment for multiple comparisons • Fishers exact tests were used to compare incidence of AEs For all other endpoints, discrete variables by t-tests unadjusted for multiple comparisons All statistical tests were conducted using a 5% significance level (2-tailed)	• A sample size of 107 patients per treatment group was calculated to yield 94% power to detect a difference of 25% in ACR20 responses between the 2 abatacept groups and the placebo group at the 5% significance level (2-tailed), adjusted for a discontinuation rate of 15%. • The ACR20 response rate in the placebo group was assumed to be 25%	• ACR responses: all patients who discontinued from the study due to worsening RA disease (lack of efficacy) were considered non-responders from that time point. • However, patients who discontinued for other reasons had their last observations carried forward.

Trial	Hypotheses, objectives	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
ATTEST	Hypothesis: There exists a difference in mean change from baseline in DAS28 Objective: Study was designed to evaluate the DAS28 improvement of abatacept is larger than placebo at 6 months	• All efficacy and safety analyses on a modified ITT, defined as all patients randomly assigned who received at least 1 dose of study medication • The abatacept and infliximab groups were compared to Placebo with respect to CFB to Day 197 in DAS28 and in the SF-36 (PCS and MCS) using an analysis of covariance (ANCOVA) model with treatment group as the effect and baseline value as the covariate. • Point estimates, 95% CIs, and p-values were computed for the treatment difference within the framework of the ANCOVA model • The proportion of patients with ACR20, 50 and 70 responses, LDAS, DAS28-defined remission, a good EULAR response, and a clinical meaningful HAQ-DI response was calculated. • The x2 test was performed to evaluate the differences (and 95% CIs) between the abatacept or infliximab groups and Placebo	• Post-hoc analysis of DAS28 in study Phase 2b demonstrated a 0.88 unit improvement in DAS28 changes at 6 months for 10 mg/kg abatacept compared with placebo, with a 1.25 unit standard deviation. • A total of 150 abatacept-treated subjects and 100 placebo-treated subjects would yield over 99% power to detect a 0.88 unit treatment difference, assuming the same standard deviation and a 20% dropout rate. If the underlying treatment difference was as modest as 0.59 units, the study was still powered at 90% for this endpoint given this sample size. The above calculations were based on a 2-tailed 5% level of significance • Prospectively, this study was not powered for pre-specified comparisons of abatacept with infliximab	• Patients who discontinued the study prematurely were considered as non-responders subsequent to the time of discontinuation for ACR20, 50 and 70 responses, good EULAR responses and clinically meaningful HAQ-DI responses • For all continuous measurements (mean changes in DAS28, SF-36 and the HAQ-DI score), LDAS and DAS28-defined remission the last observations prior to the discontinuation were carried forward (LOCF).

ACR: American College of Rheumatology; AE: adverse events; CFB: change from baseline; CI: confidence interval; DAS: disease activity score; EULAR: European League Against Rheumatism; GMS: Genant-Modified Sharp; HAQ-DI: health assessment questionnaire disability index; ITT: intention-to-treat; LDAS: low disease activity score; LOCF: last observation carried forward; MCS: mental component summary; PCS: physical component summary; RA: rheumatoid arthritis. NR: not reported

5.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

In the AIM trial, subgroup analyses were performed on; age, gender, race, geographic region, duration of RA, SJC, TJC, CRP levels, weight, GMS total score, HAQ-DI, and ACR responses at Day 169, wherever applicable.

A recent abstract by Dougados et al (2010) presents a post-hoc patient-level analysis predicting the likelihood of RA patients achieving a Low Disease Activity State (LDAS) at 1 year following treatment with abatacept in the first 6 months of the AIM trial.

This paper also reports that the majority of patients maintained or improved their treatment response or disease status from months 2 to 12, suggesting that patients who had not responded by month 3 may still achieve a clinically meaningful response over time. The sustainability of patient-level responses was also evaluated for the LTE of AIM (Westhovens et al 2009), revealing that the majority of patients who had achieved LDS, remission or normalised physical function (i.e. HAQ-DI <0.5) by year 1 sustained these outcomes through 5 years.

Additionally, summary statistics by treatment were presented for subgroups consisting of 10% or more of the total study population in the AIM and ATTEST studies, respectively.

In both the AIM and ATTEST trials, no statistical testing was performed for these subgroups. These analyses were not powered to detect any differences between the treatment groups; however, the analyses demonstrated the consistency and robustness of efficacy results across different subpopulations and compared to the entire study population.

Schiff et al 2009 reported that post-hoc analyses showed that a considerable number of infliximab non-responders (i.e. ACR20 non-responders, or patients with a high disease activity state) who switched to abatacept after 1 year achieved improved clinical responses with abatacept over the second year.

In the ATTEST trial, subgroup analyses were performed on; age, gender, race, geographic region, duration of RA, SJC, TJC, CRP levels and RF status.

No subgroup analyses were performed in the Kremer Phase 2b trial.

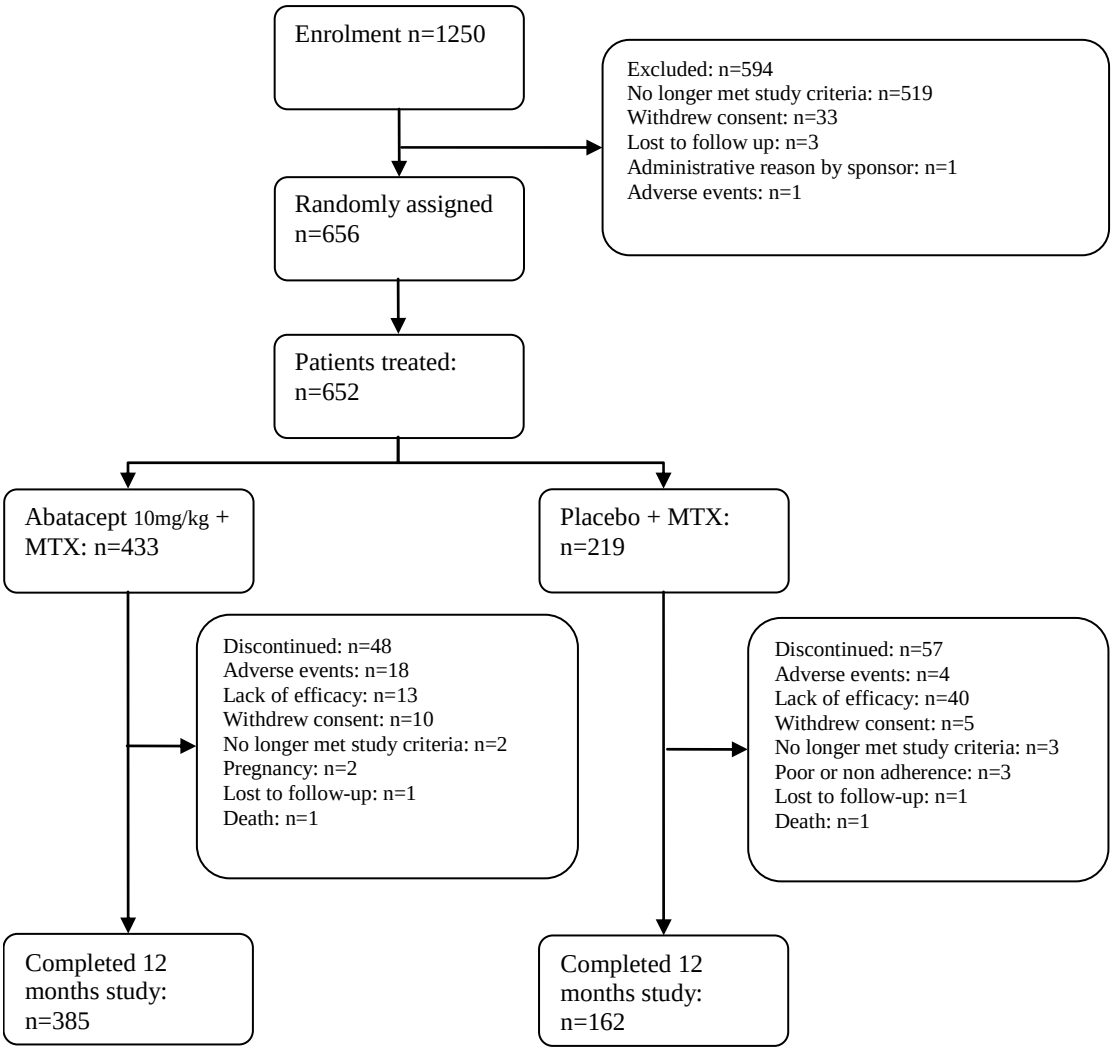
Participant flow

5.3.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

Participant flow and patient numbers are depicted in Figure B2, Figure B3 and Figure B4.

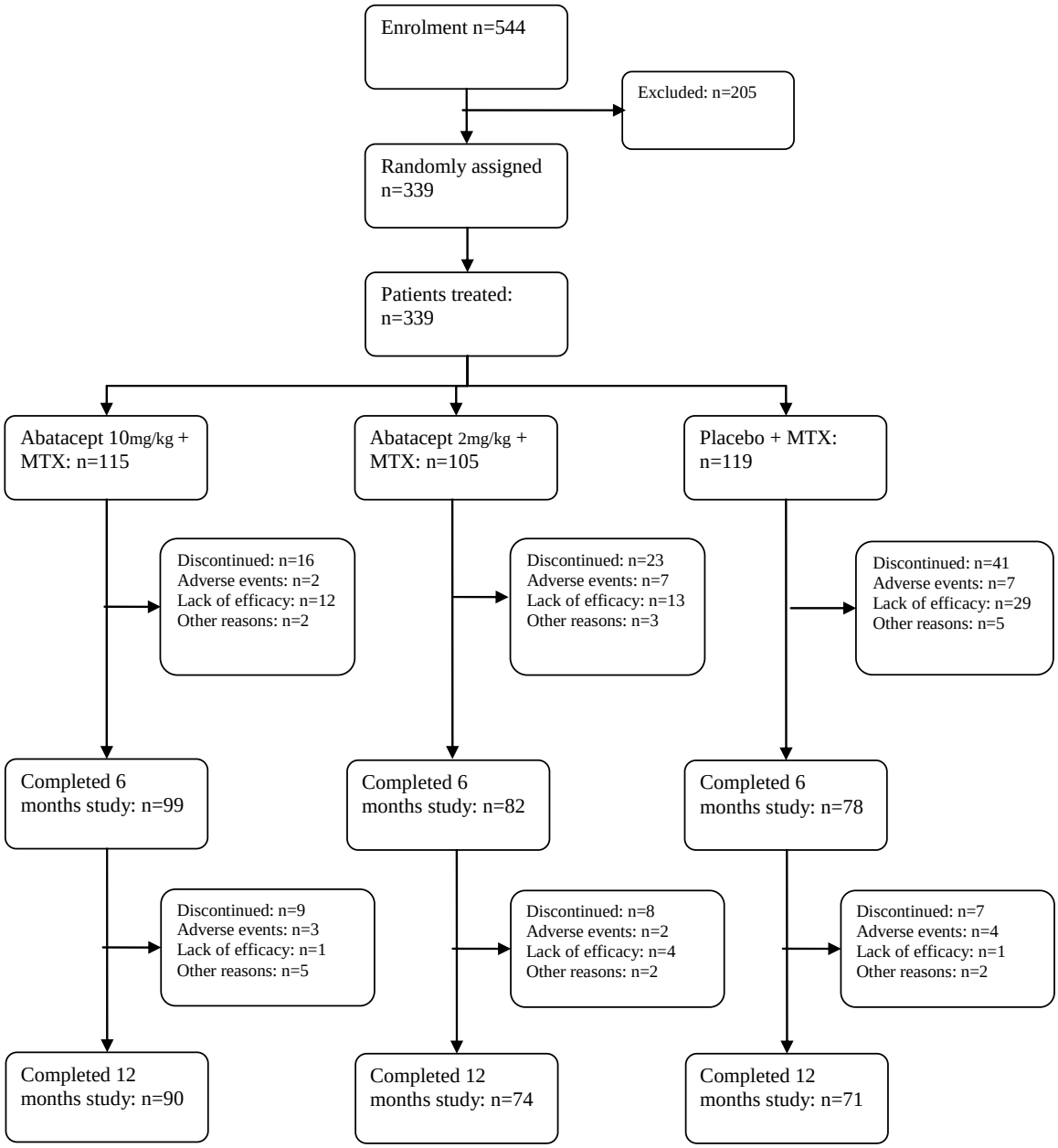
AIM trial

Figure B 2 CONSORT Participant flow in the AIM trial



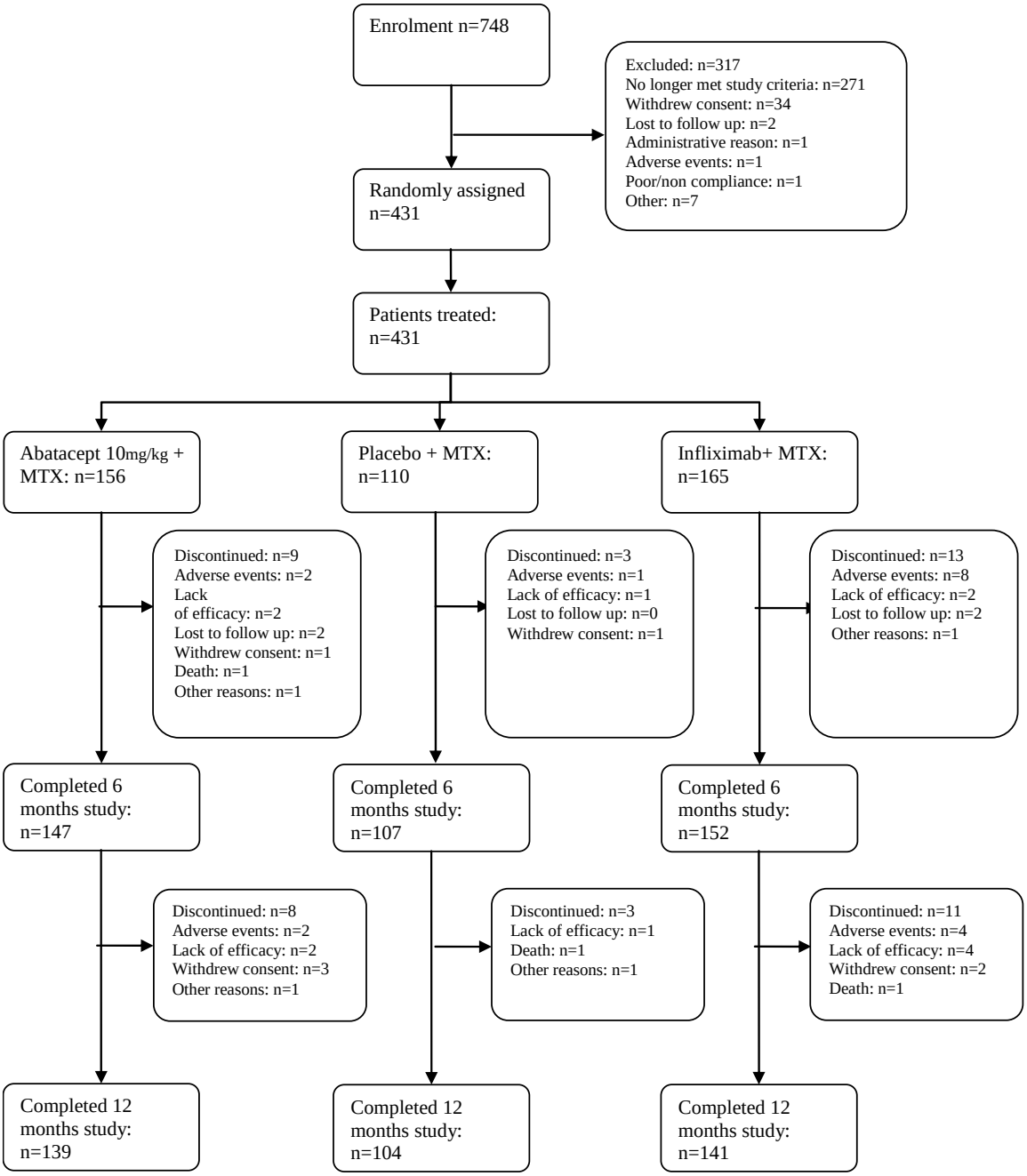
During the course of the one year trial period, a greater proportion of subjects in the placebo group (26%) compared with the abatacept group (11%) discontinued from the study. The main reason for discontinuation was lack of efficacy and adverse events.

Figure B 3 CONSORT Participant flow in the Kremer Phase 2b trial



During the initial 6 month study period, lack of efficacy was the main reason for discontinuation accounting for 75% of all discontinued patients in the abatacept 10mg/kg + MTX group, 56.5% in the abatacept 2mg/kg + MTX group; and 70.7% in the placebo group. However, in the following period (until 12 month study completion), patients discontinued treatment mainly for other reasons.

Figure B 4 CONSORT Participant flow in the ATTEST trial



Discontinuation rates were relatively low at both 6 months and one year. At 6 months, only 9 of 156 patients randomised to the abatacept group had discontinued treatment, 3 of 110 patients in the placebo group, and 13 of 165 in the infliximab group. In the latter, 8 of 13 discontinuations were due to adverse events. Of those patients that completed the 6 months study period 5.4% discontinued treatment before one year in the abatacept group, 2.8% in the placebo group, and 7.2% in the infliximab group. The main reason for discontinuation during this later trial period were adverse events, lack of efficacy, and withdrawal of consent.

5.4 Critical appraisal of relevant RCTs

5.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

- Was the method used to generate random allocations adequate?
- Was the allocation adequately concealed?
- Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?
- Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?
- Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?
- Is there any evidence to suggest that the authors measured more outcomes than they reported?
- Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

5.4.2 Please provide as an appendix a complete quality assessment for each RCT. See section 9.3, appendix 3 for a suggested format.

Quality assessment tables are presented in Appendix 3; see Section 9.3.

5.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A

suggested format for the quality assessment results is shown below.

A summary of quality assessment results for the three RCTs included in this submission is presented in Table B10.

In brief, randomisation in each of the three RCTs was performed appropriately; however, it is not clear if allocation was adequately concealed. Providers, participants and outcome assessors were blind to treatment allocation in all trials. Both treatment and placebo groups in all studies were similar at the outset of the study in terms of prognostic factors. Additionally, there is no evidence to suggest that clinical results were measured but not reported in the relevant trial publications.

Intention-to-treat analyses were performed in all studies and the statistical analyses performed were appropriate for RA trials; see Section 5.3.6 for more details.

Quality assessment was not performed for Dougados et al 2010

Table B 10 Quality assessment results for RCTs

Trial	AIM (n=656)	Kremer Phase 2b (n=339)	ATTEST (n=431)
	Grade (yes/no/not clear/N/A)	Grade (yes/no/not clear/N/A)	Grade (yes/no/not clear/N/A)
Was randomisation carried out appropriately?	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes

5.5 Results of the relevant RCTs

Overall, abatacept demonstrates superior efficacy when compared with placebo in reducing the signs and symptoms of RA, and is able to maintain this effect over 12 months. In addition to efficacy measurements of disease activity, abatacept demonstrates clinically significant improvements in patient physical functioning when compared with placebo, as well as in health-related quality-of-life, and with regard to patient reported outcomes (such as morning stiffness, sleep quality and fatigue). Abatacept is also able to show a significant inhibition of structural damage progression compare with placebo.

5.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. **If there is more than one RCT, tabulate the responses.**

Summary tables for the results of the three RCTs included in this submission are presented below.

5.5.2 The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan-Meier plots.

5.5.3 For each outcome for each included RCT, the following information should be provided.

- The unit of measurement.
- The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.
- A 95% confidence interval.

- Number of participants in each group included in each analysis and whether the analysis was by ‘intention to treat’. State the results in absolute numbers when feasible.
- When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.
- Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.
- Discuss and justify definitions of any clinically important differences.
- Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.

The results from the three RCTs included in this submission are presented below and structured as follows to capture all the short-term and long-term, primary and secondary outcomes reported in the studies:

1. ACR 20/50/70 responses 6 months and one year
2. ACR20 responses over time
3. ACR50 responses over time
4. ACR70 responses over time
5. HAQ-DI response over time
6. DAS 28 over time
7. Health-related quality of life: SF-36
8. Joint erosion score: GMS score
9. Patient reported outcomes
10. Patient compliance during the double blind period

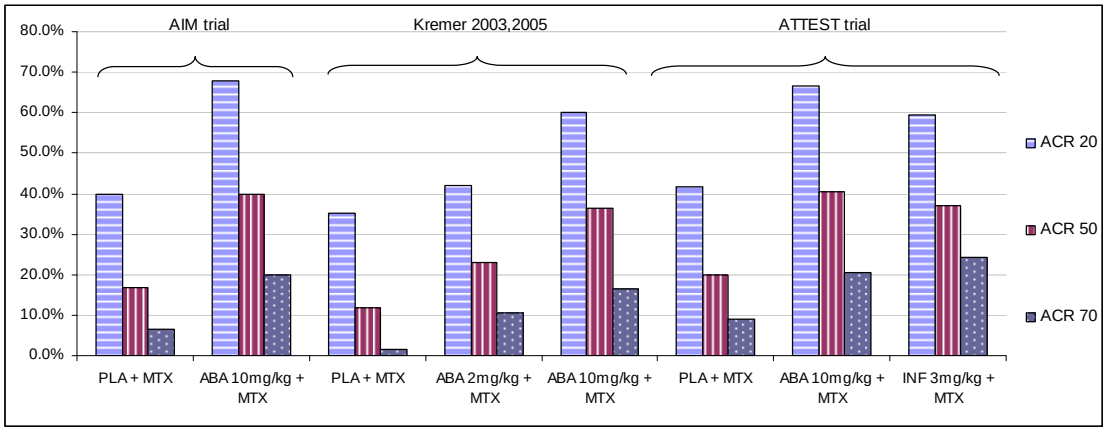
5.5.3.1 ACR 20/50/70 responses 6 months and one year

Abatacept demonstrates better efficacy than placebo in reducing the clinical manifestations of arthritis (as measured by the ACR 20/50 or 70), and this improvement is maintained for up to 12 months. A 1 year the percentage of ACR 70 responders were numerically higher with abatacept than with infliximab.

The ACR 20/50/70 responses at 6 months and one year are presented at the end of this section in Section 5.5.4 (see Table B19). ACR responses at 6 months were obtained for all patients randomised in all three trials.

A significantly higher number of ACR 20 responders in the abatacept treatment groups were seen in all RCTs at 6 months compared with placebo. Additionally in all RCTs, the proportion of patients with ACR50 and ACR70 responses was significantly larger in the abatacept group vs. placebo ($p<0.05$) at 6 months. This is illustrated in Figure B5.

Figure B 5 ACR 20/50/70 responses at 6 months in the abatacept trials



These differences were maintained at 1 year, with significant improvements for the abatacept group in ACR20, ACR50, and ACR70 responses in both the AIM and Kremer Phase 2b trial.

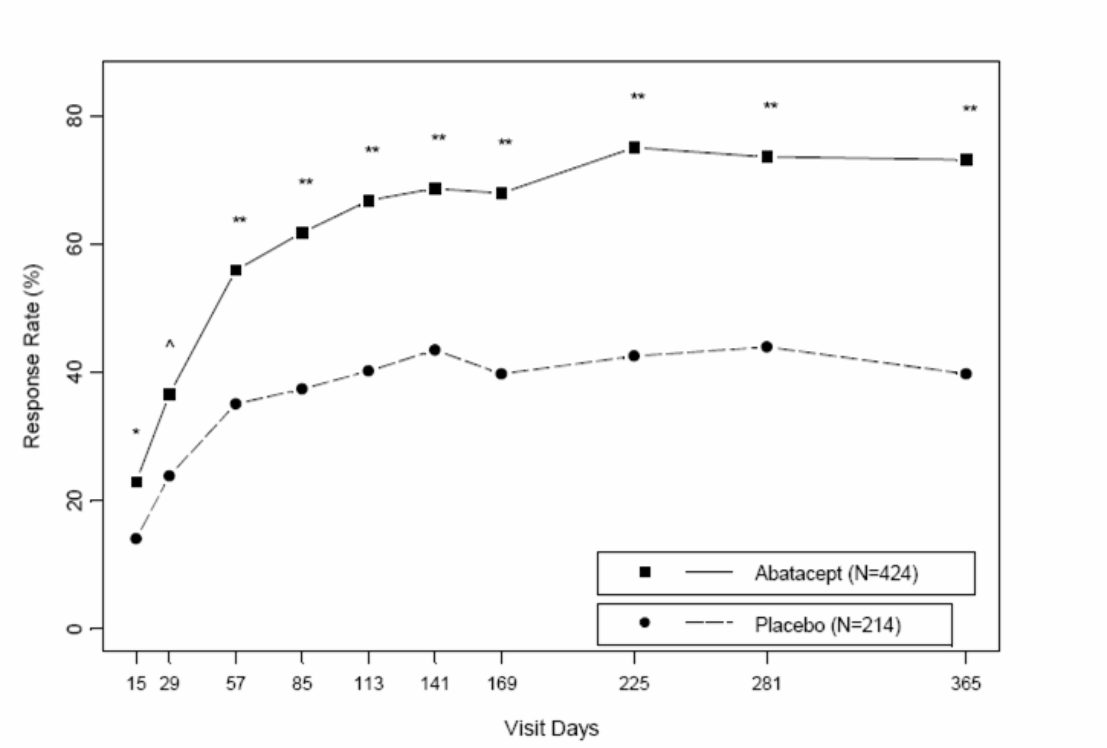
The percentage of patients displaying ACR20, ACR50 and ACR70 response in the abatacept groups was similar to the infliximab group in the ATTEST trial at 6 months (95% CI overlap).

5.5.3.2 ACR20 responses over time

The proportions of patients with ACR20 response in the AIM, Kremer Phase 2b, and ATTEST trials over time are illustrated in Figure B6, Figure B7 and Figure B8, respectively.

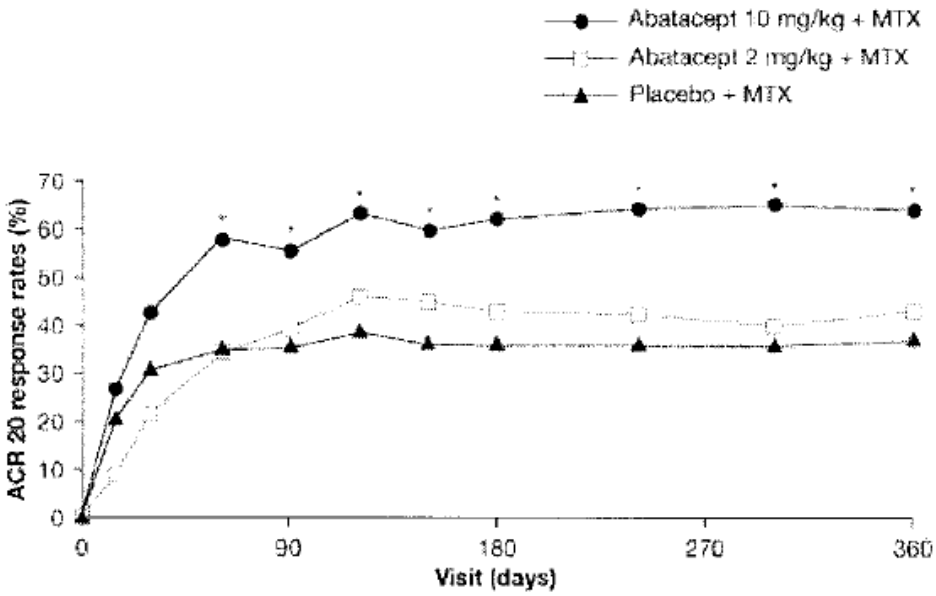
In the AIM and Kremer Phase 2b studies, ACR20 responses are higher in the abatacept group compared with placebo as depicted by the abatacept response curve. An additional longitudinal analysis in the AIM study confirmed the significant increase in ACR 20 response for abatacept vs. placebo ($p<0.001$) and more specifically at day 15 ($p=0.008$).

Figure B 6 ACR20 responses over time in the AIM trial



**p<0.001, ^p<0.01, *p<0.05: probability for testing the difference in ACR response between abatacept and placebo.

Figure B 7 ACR20 responses over time in the Kremer Phase 2b trial



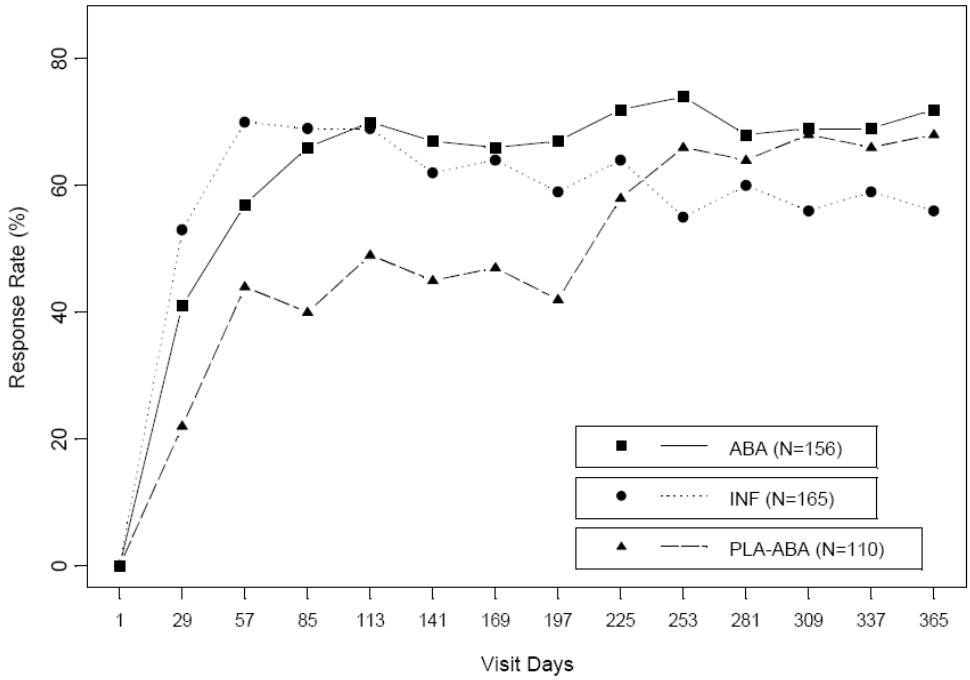
**p<0.001, ^p<0.01, *p<0.05: probability for testing the difference in ACR response between abatacept and placebo.

In the ATTEST trial, at day 197 ACR20 responses were significantly greater with abatacept versus placebo. ACR20 responses were also significantly higher in the infliximab group versus placebo.

The onset of action, as assessed by ACR20 response was generally more rapid for infliximab compared with abatacept; however, by day 85, responses were similar (Figure B8). At 6 months, abatacept and infliximab demonstrated similar responses. From 6 to 12 months, further improvements were observed with abatacept. At day 365, ACR20 responses were higher with abatacept than infliximab (ACR20: 72.4 vs 55.8%, difference of 16.7, 95% CI=5.5, 27.8).

When a clinician is choosing a biologic agent for their patient, it will sometimes be important that they have a treatment option available with a slower onset of action in situations when a fast immunosupression would not benefit the patient.

Figure B 8 ACR20 responses over time in the ATTEST trial



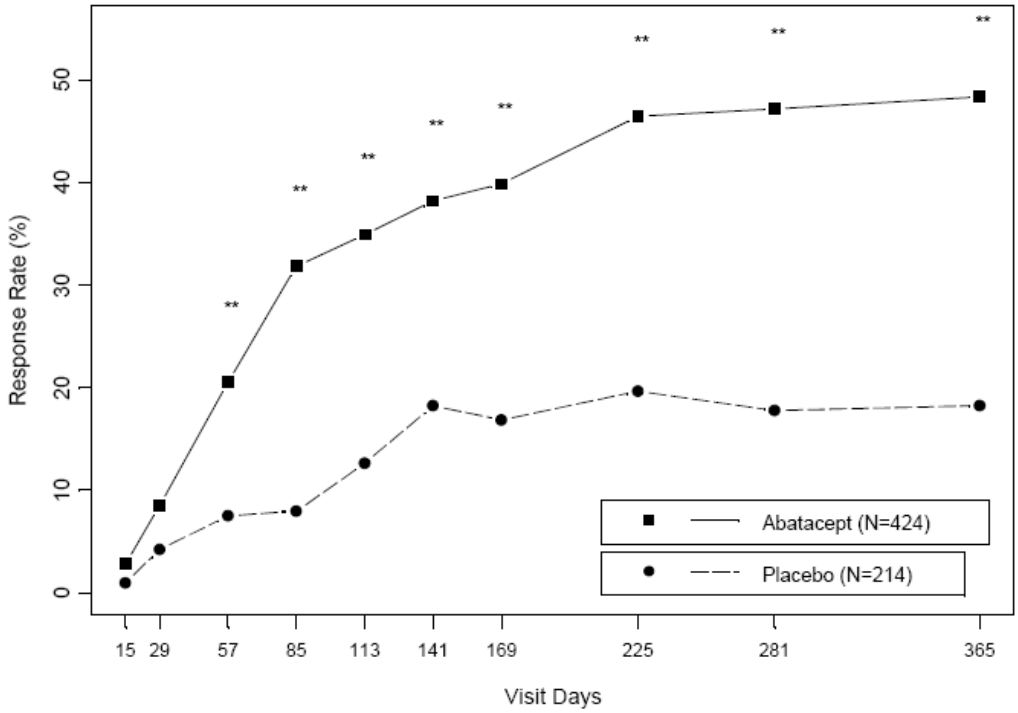
*Patients at 6 months switch from placebo to abatacept; thus the placebo + MTX treatment arm becomes abatacept + MTX.

5.5.3.3 ACR50 responses over time

The proportions of patients with ACR50 response in the AIM, Kremer Phase 2b, and ATTEST trials over time are illustrated in Figure B9, Figure B10 and Figure B11, respectively.

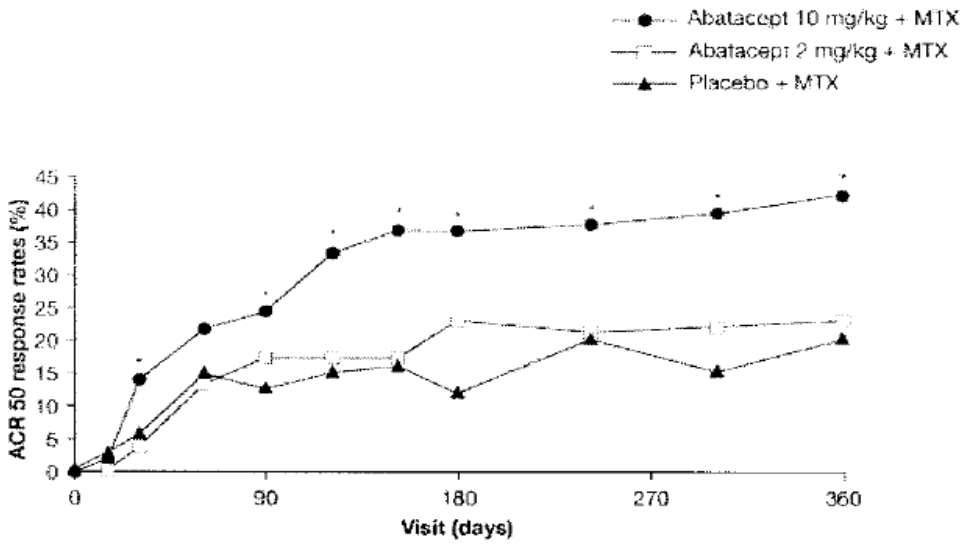
In the AIM and Kremer Phase 2b trials, ACR50 responses were higher in the abatacept groups compared to placebo.

Figure B 9 ACR50 responses over time in the AIM trial



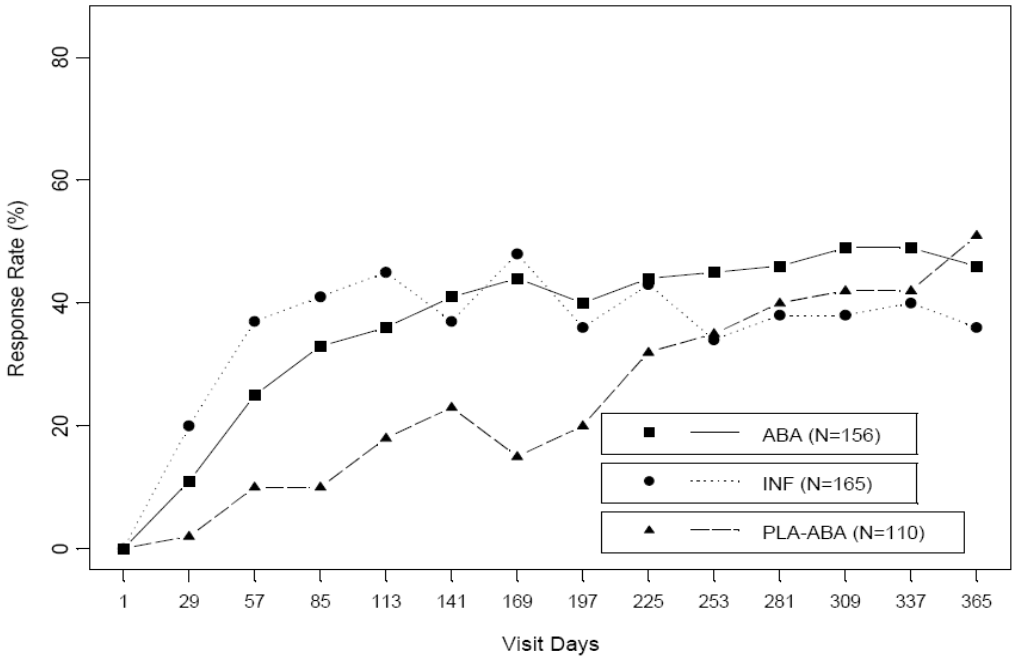
**p<0.001, ^p<0.01, *p<0.05: probability for testing the difference in ACR response between abatacept and placebo.

Figure B 10 ACR50 responses over time in the Kremer Phase 2b trial



In the ATTEST study at day 197 ACR50 responses were significantly greater with abatacept versus placebo. ACR50 responses also were significantly higher in the infliximab versus placebo group. At day 365 the percentage of ACR50 responders were numerically higher with abatacept versus infliximab treatment (with overlapping 95% CIs for the estimate of difference for ACR50 45.5 vs. 36.4%, estimate of difference [95% CI] = 9.1 [-.2, 20.5].

Figure B 11 ACR50 responses over time in the ATTEST trial*



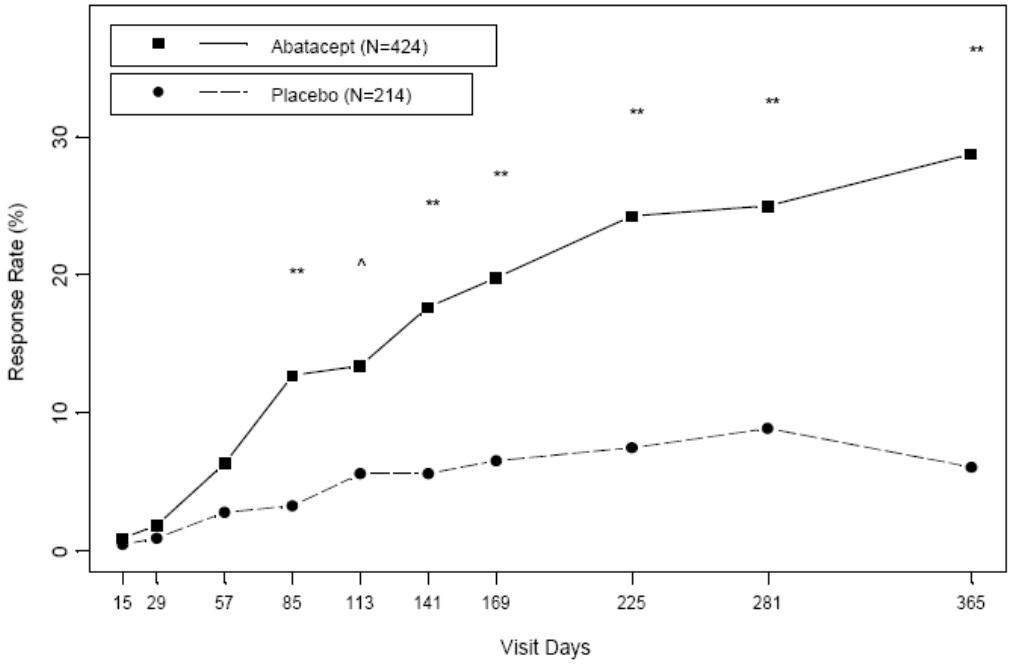
*Patients at 6 months switch from placebo to abatacept; thus the placebo + MTX treatment arm becomes abatacept + MTX.

5.5.3.4 ACR70 responses over time

The proportions of patients with an ACR70 response in the AIM, Kremer Phase 2b, and ATTEST trials over time are illustrated in Figure B12, Figure B13 and Figure B14, respectively.

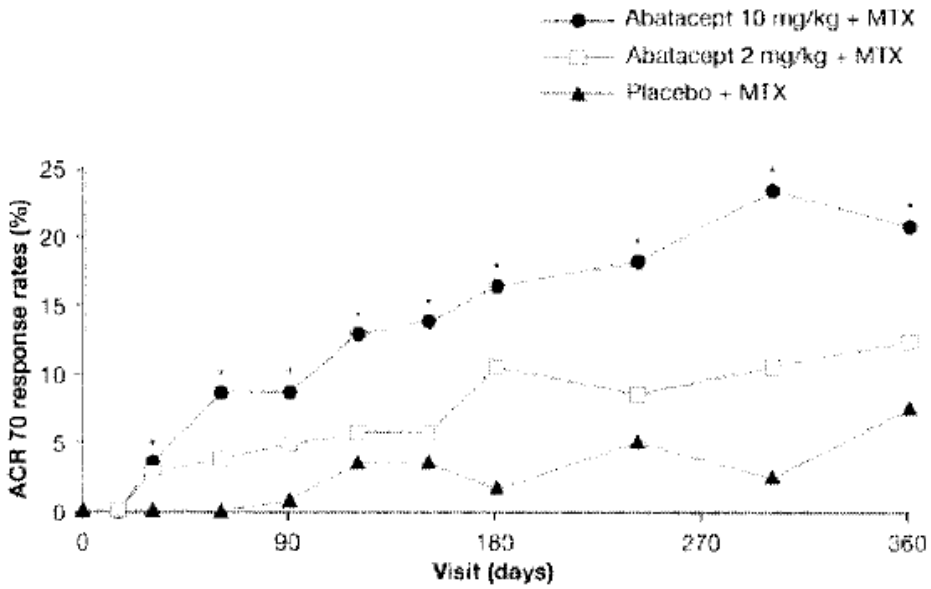
In the AIM and Kremer Phase 2b trial, ACR70 responses were higher in the abatacept group compared to placebo.

Figure B 12 ACR70 responses over time in the AIM trial



**p<0.001, ^p<0.01, *p<0.05: probability for testing the difference in ACR response between abatacept and placebo

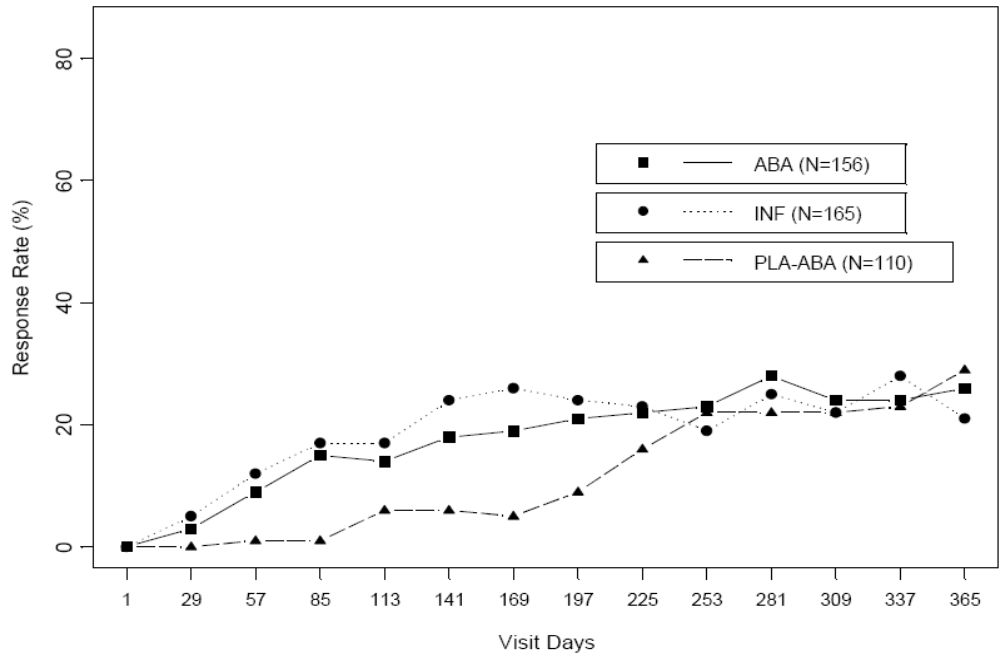
Figure B 13 ACR70 responses over time in the Kremer Phase 2b trial



**p<0.001, ^p<0.01, *p<0.05: probability for testing the difference in ACR response between abatacept and placebo

In the ATTEST trial, the abatacept group showed higher ACR70 response rates than placebo at day 197. ACR70 responses were also higher in the infliximab + MTX arm versus placebo + MTX. At day 365 the percentage of ACR70 responders were numerically higher with abatacept versus infliximab treatment (with overlapping 95% CIs for the estimate of difference for ACR70 26.3 vs. 20.6%, estimate of difference [95% CI] = 5.7 [-.4.2, 15.6].

Figure B 14 ACR70 responses over time in the ATTEST trial*



*Patients at 6 months switch from placebo to abatacept; thus the placebo + MTX treatment arm becomes abatacept + MTX.

5.5.3.5 Physical functioning: HAQ-DI response over time

Abatacept demonstrates both statistically and clinically significant improvements in the patient's physical functioning compared with placebo, and this improvement is maintained for up to 12 months. Patients receiving infliximab had a numerically lower reduction in HAQ-DI change from baseline, and a numerically lower percentage of responders, than those receiving abatacept, at both 6 months and 1 year.

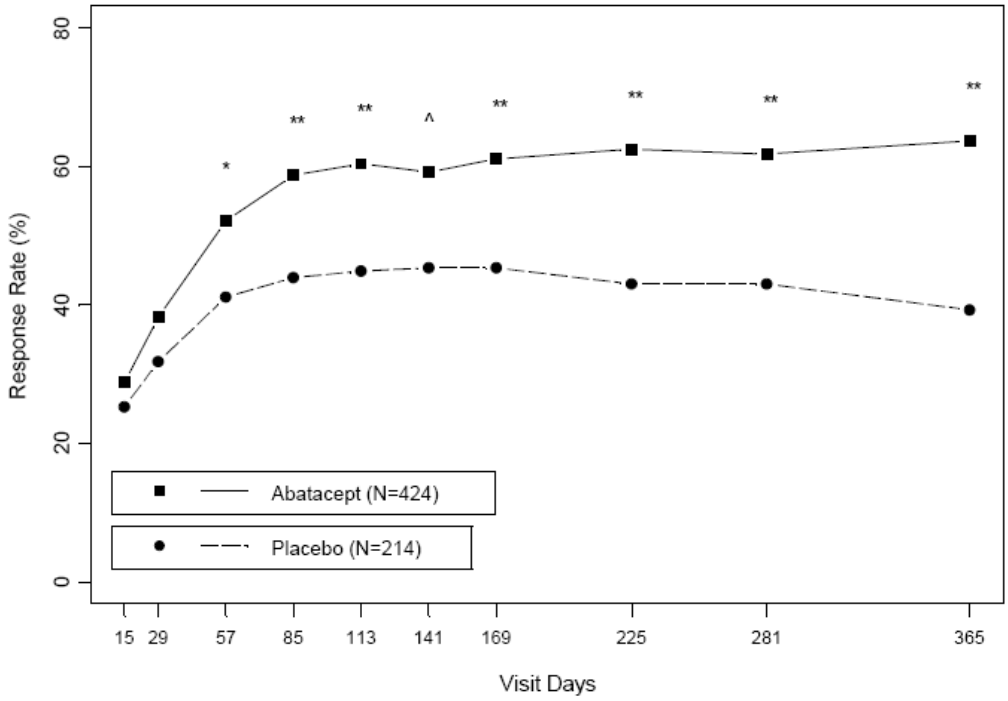
The physical function change from baseline and HAQ-DI responders at 6 months and 1 year are presented in at the end of this section in Section 5.5.4 (see Table B19).

All trials demonstrated a statistically significant difference in HAQ scores from baseline for abatacept (10 mg/kg every 4 weeks) versus placebo at 6 months.

Similar results were found at 1 year in the AIM and Kremer Phase 2b trial.

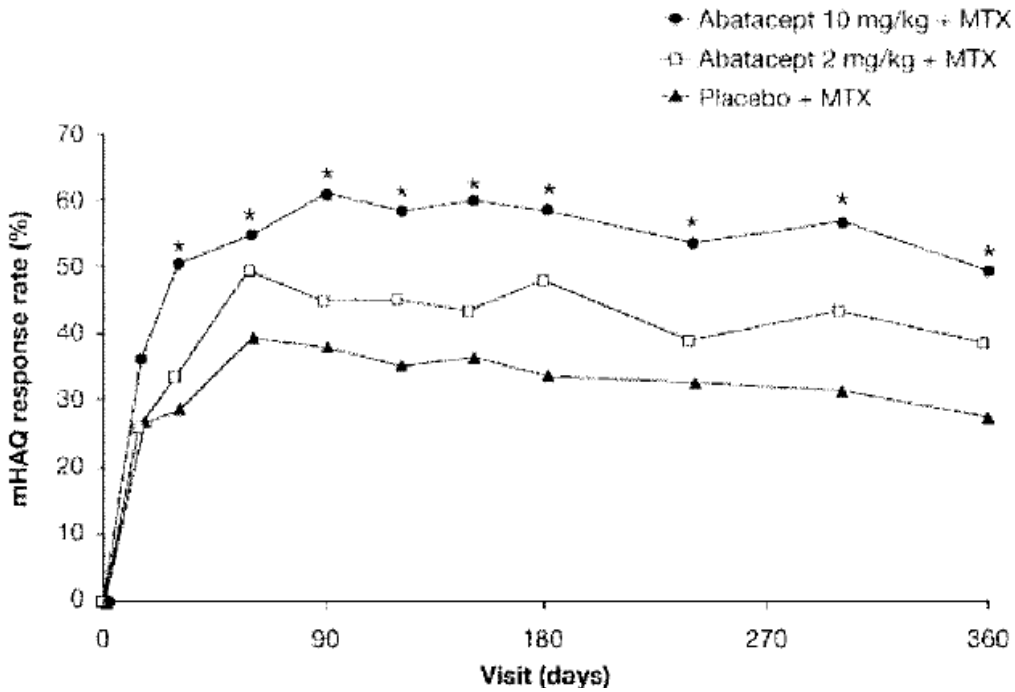
The proportions of patients with HAQ (HAQ-DI and/or m-HAQ) response over time in the AIM, Kremer Phase 2b, and ATTEST trials are shown in Figure B15, Figure B16 and Figure B17, respectively.

Figure B 15 HAQ-DI response over time AIM trial (>0.3 units)



**p<0.001, ^p<0.01, *p<0.05: probability for testing the difference in ACR response between abatacept and placebo

Figure B 16 M-HAQ response over time in the Kremer Phase 2b trial (>0.22 units)



**p<0.001, ^p<0.01, *p<0.05: probability for testing the difference in ACR response between abatacept and placebo

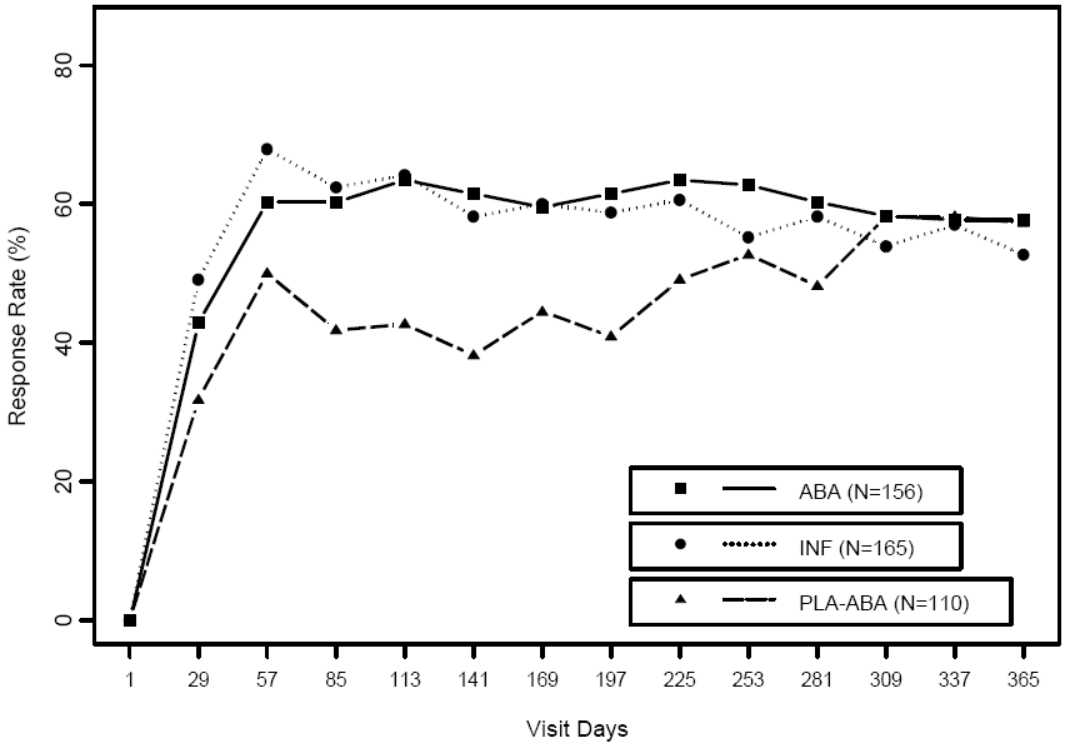
In the ATTEST trial, at day 197, significantly more patients in the abatacept group than in the placebo group demonstrated a clinically meaningful improvement in physical function (HAQ-DI responses: 61.5 vs. 40.9% p = 0.001).

Also, significantly more patients in the infliximab group than in the placebo group demonstrated a clinically meaningful improvement in physical function (HAQ-DI responses: 58.8 vs. 40.9%, p = 0.005).

At day 365, HAQ-DI responses were maintained in the abatacept and infliximab groups.

In the ATTEST trial, the infliximab group had a numerically lower reduction in HAQ-DI change from baseline and a numerically lower percentage of responders than the abatacept group at both 6 months and 1 year; however, 95% CIs of estimates of difference overlap.

Figure B 17 HAQ-DI response over time ATTEST trial (>0.3 units)*



*Patients at 6 months switch from placebo to abatacept; thus, the placebo + MTX treatment arm becomes abatacept + MTX.

5.5.3.6 Disease activity: DAS 28 scores over time

Abatacept demonstrates significant improvements in disease activity compared with placebo, and this improvement is maintained for up to 12 months. Abatacept led to a greater reduction in mean DAS 28 change from baseline at 1 year compared to infliximab. A higher percentage of patients achieved LDAS and remission at 1 year with abatacept as their treatment compared with infliximab.

The disease activity change from baseline and the number of subjects with DAS 28 responses at 6 months and 1 year are presented at the end of this section in Section 5.5.4 (Table B21). Table B21 shows, for subjects with data available, the number of subjects with improvement in DAS 28, the number of subjects in remission, and the number of subjects with low disease activity, for all trials,

DAS28 was not a reported endpoint in the Kremer Phase 2b study and thus, the results available are for AIM and ATTEST.

The DAS 28 change from baseline for the abatacept group was significantly improved compared to placebo at 6 months in the AIM and ATTEST trials. The DAS 28 reduction with abatacept was maintained in the AIM trial. At 1 year the difference (versus placebo) was statistically significant. Results from a post-hoc analysis in AIM and ATTEST trials by Kremer (2008) showed clinically meaningful responses in DAS28 score at month 1 and at month 3 at least 74% of abatacept-treated patients reached a clinically meaningful change (≥1.2 units)_in their disease activity. As this effect continued to increase over 6 months, we suggest that 3-6 months is an appropriate timeframe to properly assess response to treatment.

In addition, results from the patient-level analysis by Dougados et al (EULAR 2010) demonstrate that a proportion of MTX-IR patients who did not achieve a clinically meaningful DAS28 response in the first 6 months of the AIM trial could achieve a LDAS at 1 year.

In the ATTEST study, at 6 months (day 197) reductions in DAS28 were also greater in the infliximab arm v placebo.

In the ATTEST trial, similar results were observed at 6 months between abatacept and infliximab; abatacept led to a greater reduction in mean DAS 28 change from baseline at 1 year compared to infliximab; since 95% CI of difference did not overlap ((–2.88 vs. –2.25; estimate of difference (95% CI) = –0.62 (–0.96, –0.29)).

These results showed that at 1 year 35.3% of patients receiving abatacept achieved an LDAS (DAS28 ≤3.2) compared to 22.4% of patients that had received infliximab (estimate of difference [95% CI] = 12.9 [2.1,3.7]). In addition, 18.7% of patients that had received abatacept achieved remission (DAS28 <2.6) compared to 12.2% of infliximab patients (estimate of difference [95% CI] = 18.7 [-2.2,15.2]). These results are very important, when contextualized into the UK setting. The DAS28, is the most widely used efficacy measurement in the UK clinical environment, the difference between abatacept and infliximab shown at 1 year in the ATTEST study, must be considered when making a choice between these agents.

5.5.3.7 Health related Quality of Life: SF-36

Abatacept demonstrates significant improvements in health related quality-of-life compared with placebo, and this improvement is maintained for up to 12 months. At 1 year, greater numerical improvements from baseline in the PCS and MCS were observed with abatacept compared with infliximab.

The HRQoL at 6 months and 1 year is presented at the end of this section in Section 5.5.4 (Table B22).

In the AIM and ATTEST trials, the abatacept groups showed significant improvement in SF-36 scores at 6 months and 1 year compared with the placebo group, both in the physical and mental components of SF-36 domains.

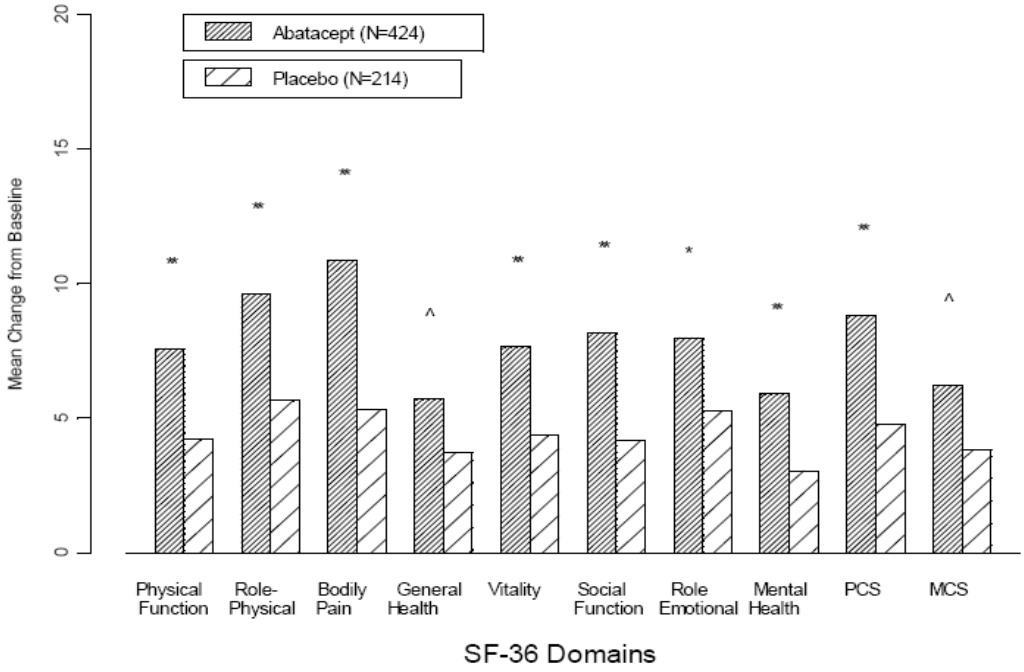
Also, at 6 months in the ATTEST study patients in the infliximab group also experienced significantly greater improvements from baseline in the PCS and MCS compared to placebo.

The ATTEST trial also reported similar mean SF-36 scores for abatacept compared with infliximab at 6 months, in both the physical and the mental components of SF-36 domains. At 1 year, greater improvement from baseline in the PCS were observed with abatacept versus infliximab (difference of 1.93; 95% CI=0.08;3.84). Improvement in the MCS (difference of 1.92; 95% CI=-0.30;4.15) was also numerically higher with abatacept versus infliximab although 95% CI overlaps.

Kremer Phase 2b provided little insight into the HRQoL of enrolled patients, but they reported a greater reduction in mean SF-36 CFB for abatacept, of 17.3% for the 2 mg/kg every 4 weeks group and 41.5% for the 10 mg/kg every 4 weeks group, compared to placebo, (14.1%).

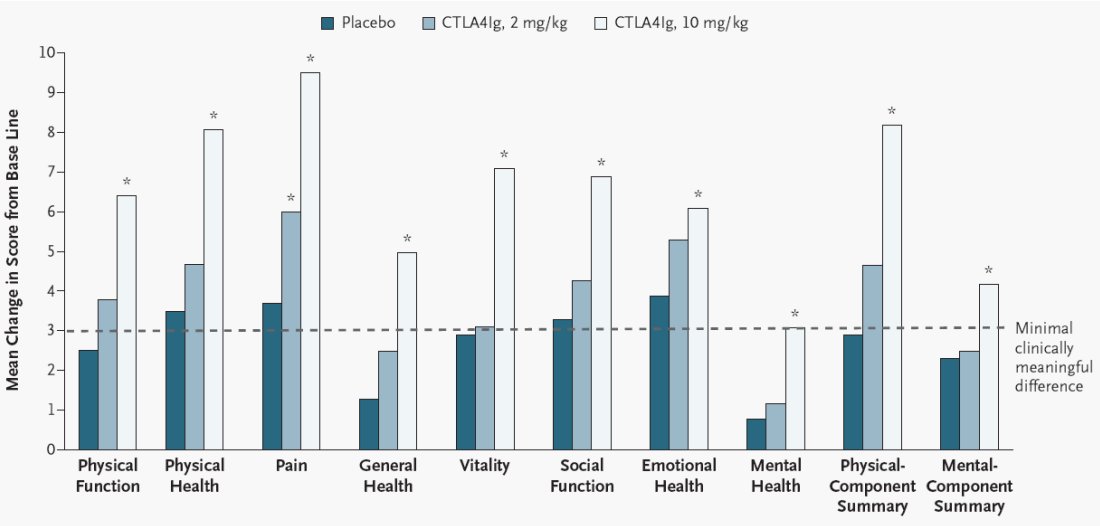
The mean CFB in physical and mental components of SF-36 domains by treatment groups for the AIM, Kremer Phase 2b and ATTEST trials at 6 months are illustrated in Figure B18, Figure B19 and Figure B20, respectively, and for the AIM and ATTEST trials at 1 year in Figure B21 and Figure B22, respectively

Figure B 18 Mean change from baseline in SF-36 CFB subscales at 6 months AIM trial



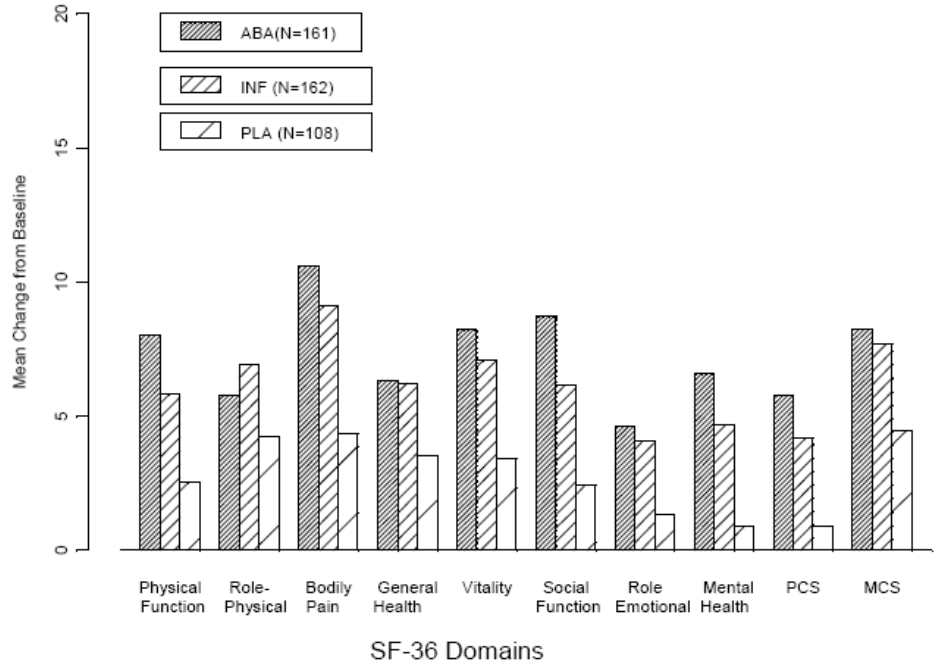
**p<0.001, ^p<0.01, *p<0.05: probability for testing the difference in ACR response between abatacept and placebo

Figure B 19 Mean change from baseline in SF-36 CFB subscales at 6 months Kremer Phase 2b



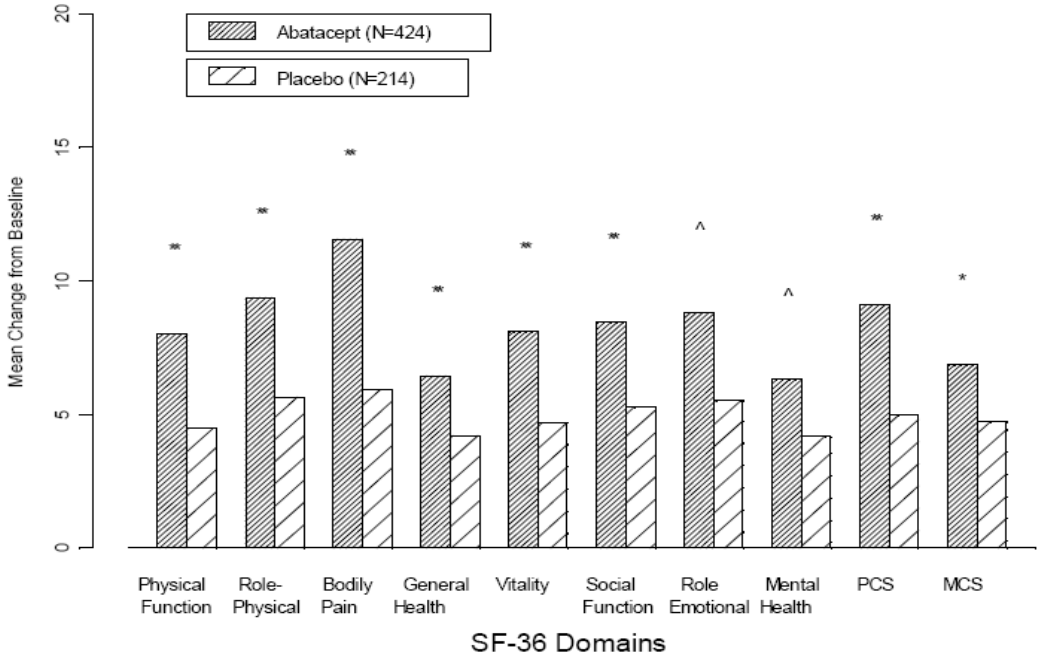
**p<0.001, ^p<0.01, *p<0.05: probability for testing the difference in ACR response between abatacept and placebo

Figure B 20 Mean change from baseline in SF-36 CFB subscales at 6 months ATTEST trial



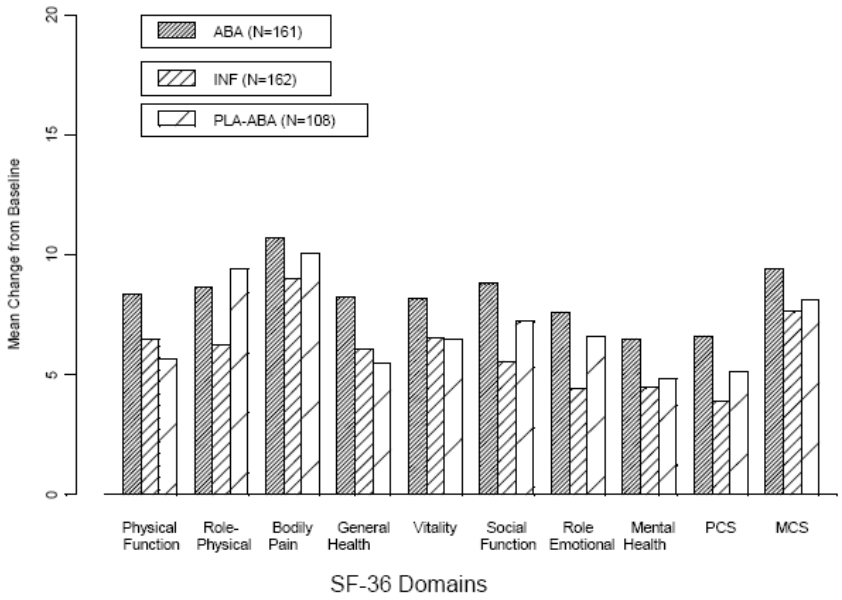
**p<0.001, ^p<0.01, *p<0.05: probability for testing the difference in ACR response between abatacept and placebo

Figure B 21 Mean change from baseline in SF-36 CFB subscales at one year AIM trial



**p<0.001, ^p<0.01, *p<0.05: probability for testing the difference in ACR response between abatacept and placebo

Figure B 22 Mean change from baseline in SF-36 CFB subscales at one year ATTEST trial



5.5.3.8 Joint erosion score: Genant Modified Sharp Scores

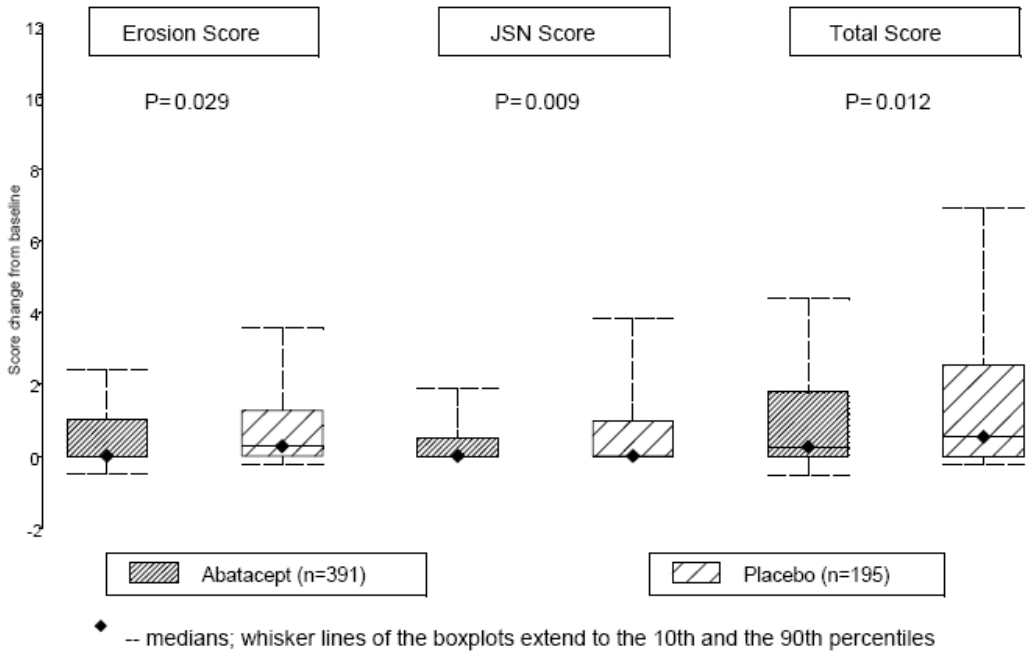
Abatacept demonstrates statistically significant benefits regarding joint erosion compared with placebo.

The AIM study is the only RCT that evaluated radiographic outcomes, and thus radiographic data is only presented from the AIM study. The joint erosion count and the CFB in GMS scores at 1 year for the AIM trial are illustrated in Figure B23.

The difference in positive change in GMS scores from baseline was statistically different between the abatacept treatment group and the placebo group.

At the end of the double blind period, a significant inhibition of structural damage progression was seen with abatacept compared to placebo, with approximately 50% reduction in change from baseline in GMS scores compared with placebo.

Figure B 23 Mean CFB in GMS scores at one year AIM trial



5.5.3.9 Patient Reported Outcomes

Patients who received abatacept reported less morning stiffness, better sleep quality and less fatigue after both 6 months and 12 months of treatment.

The patient reported outcomes of morning stiffness, sleep quality and fatigue were only evaluated in the AIM study, and thus data from the AIM study only is reported in this section.

In considering the decision problem, the following patient reported outcomes (PROs) are discussed:

- morning stiffness mean CFB
- sleep quality mean CFB
- fatigue mean CFB

The PROs at 6 months and 1 year for the AIM trial are presented in Table B11.

Table B 11 Patient reported outcomes in the AIM trial

Parameter	Placebo + MTX (SE) [95% CI] unless otherwise indicated	Abatacept 10 mg/kg every 4 weeks + MTX (SE) [95% CI] unless otherwise indicated
Number of randomised patients	n=219 (214)	n=433 (424)
Morning stiffness at 6 months	n=176	n=393
baseline mean (SD)	84.09 (59.98)	97.48 (61.09)
CFB, mean (SE)	-45.4 (3.29)	-71.7 (2.20)
difference vs. placebo, mean [95%CI]		-26.3 [-34.1, -18.5]
Morning stiffness at one year	n=161	n=382
baseline mean (SD)	83.45 (59.10)	97.34 (61.36)
CFB, mean (SE)	-55.4 (3.11)	-74.3 (2.01)
difference vs. placebo, mean [95%CI]		-18.9 [-26.2, -11.6]
Sleep quality at 6 months	n=211	n=420
baseline mean (SD)	43.95 (19.06)	43.04 (20.42)
CFB, mean (SE)	-7.80 (1.03)	-10.2 (0.73)
difference vs. placebo, mean [95%CI]		-2.39 [-4.88, 0.09]
Sleep quality at one year	n=212	n=423
Baseline Mean (SD)	44.05 (19.07)	43.11 (20.51)
CFB, mean (SE)	-6.75 (1.01)	-10.4 (0.72)
difference vs. placebo, mean [95%CI]		-3.60 [-6.04, -1.17]
Reduction of fatigue (VAS) at 6 months	n=211	n=420
Baseline Mean (SD)	65.92 (22.81)	63.42 (23.08)
CFB, mean (SE)	-17.2 (1.75)	-25.3 (1.24)
difference vs. placebo, mean (95%CI)		-8.13 [-12.3, -3.91]
Reduction of fatigue (VAS) at one year	n=212	n=423
Baseline Mean (SD)	65.87 (22.77)	63.38 (23.06)
mean CFB (SE)	-16.4 (1.74)	-26.5 (1.23)
difference vs. placebo, mean [95%CI]		-10.1 [-14.3, -5.91]

CFB: change from baseline; CI: confidence interval; MTX: methotrexate; SD: standard deviation; SE: standard error; VAS: visual analogue scale.

The AIM trial reported greater reductions for abatacept compared with placebo, for morning stiffness and fatigue, as well as a mean improvement in sleep quality, both at 6 months and 1 year.

Greater numeric reductions in morning stiffness were seen at 1 year in the abatacept + MTX group compared to the placebo group.

Greater numeric reductions in sleep problem index (SPI) score were seen in patients that were treated with abatacept + MTX compared to placebo at 1 year.

Patients treated with abatacept + MTX experienced greater numerical improvements in fatigue over 1 year than those treated with placebo + MTX. This was measured by the fatigue visual analogue scale.

Thus, improvements in morning stiffness, sleep quality and fatigue were clinically meaningful were seen in the abatacept + MTX group at 1 year. Lesser improvements in these outcomes were achieved with placebo + MTX at 1 year.

Improvements in HRQoL are important in this patient group. RA significantly impairs patients quality of life and limits their ability to participate in daily activities, thus these results show that abatacept has a significant clinically meaningful impact on the day and night time aspects of HRQoL of patients with established RA.

5.5.3.10 Patient compliance during the double-blind period

Patients comply well with the abatacept 30 minutes IV infusion treatment regimen.

The compliance of patients as measured by the number of missed infusions, for the AIM and ATTEST trials, are presented in Table B12.

Both trials reported low numbers of missed infusions with a median of 0.2 infusions missed and a mean of 0 in all arms of the ATTEST trial.

These results are important as compliance is an important issue in a chronic disease population of patients. The failure to complete treatment regimens as prescribed has significant negative health impacts on RA patients, as well as implications on their carers, the relationship between the patient and their health care professionals and cost implications, not only from wasted drug but also disease exacerbation and thus unplanned admissions and the requirement for further medications and appointments.

Table B 12 Patient compliance during the double-blind period in the abatacept trials (number of missed infusions)

Missed infusions	AIM (n=656)		ATTEST (n=431)		
	Placebo + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Placebo + ABA	Abatacept 10 mg/kg every 4 weeks + MTX	Infliximab 3mg/kg every 8 weeks + MTX
Number of randomised patients	n=219 (214)	n=433 (424)	n=110	n=156	n=165
Number of missed infusions, mean (SD)	NR	NR	0.2 (0.44)	0.2 (0.45)	0.2 (0.39)
Number of missed infusions, median (range)	NR	NR	0.0 (0.0-2.0)	0.0 (0.0-2.0)	0.0 (0.0-2.0)
Number of subjects that missed 0 infusion s (%)	195 (89%)	367 (84.8%)	95 (86.4%)	132 (84.6%)	138 (83.6%)
Number of subjects that missed 1 infusion (%)	20 (9.1%)	61 (14.1%)	12 (10.9%)	20 (12.8%)	26 (15.8%)
Number of subjects that missed 2 infusions (%)	4 (1.8%)	5 (1.2%)	3 (2.7%)	4 (2.6%)	1 (0.6%)

MTX: methotrexate; NR: not reported; SD: standard deviation.

5.5.3.11 IM1001119 study

Abatacept is associated with improvements in synovitis and bone erosion compared with placebo although, most likely because of the small sample size, the differences did not reach statistical significance. Such improvements are consistent with the benefits seen in the other abatacept clinical trials using more conventional clinical endpoints

IM101119 study

We have decided to present the IM100119 study data separately from the other RCTs as this study has a set of unique clinical endpoints which complement the standard clinical endpoints discussed in the previous RCTs.

There is increasing evidence that joint destruction occurs early in RA. Magnetic resonance imaging (MRI) provides the unique ability to study the primary site of inflammation (synovitis) as well as measuring bone damage (erosion) with increased sensitivity over radiographic methods. There is a direct relationship between MRI-detected synovitis and the subsequent development of MRI-detected erosions. MRI, uniquely, has also detected bone marrow oedema leision (osteitis), which is highly predictive of subsequent erosion development. Therefore, changes can be detected much earlier by MRI, and with a smaller number of patients, compared

with conventional radiography. The wrist is the most commonly imaged site used in RA MRI studies.

The details of the study design, and the clinical analyses, have been taken from the latest CSR.

IM10119 details

Table B 13 IM101119 trial details

Trial	Interventions compared (incl. dose, frequency and duration of treatment)				Comparison	Population treated	Primary and secondary study references
	Interventions	Dose	Frequency	Duration			
IM101-119 (Phase IIIb trial)	Placebo + MTX	N/A	Day 1, 15, 29 and every 28 days up to and including Day 113	4 months	abatacept + MTX vs. Placebo + MTX	Patients with active RA despite MTX therapy (i.e. inadequate responder to MTX)	Conaghan et al 2010 (ACR abstract)
	abatacept 10 mg/kg + MTX	10 mg/kg	Day 1, 15, 29 and every 28 days up to and including Day 113				

ACR: American College of Rheumatology; MTX: methotrexate; RA: rheumatoid arthritis.

IM101119 was a multinational, multicentre, randomised, double-blind, placebo-controlled, 2-arm, parallel group study, of 4 months duration, to assess short-term changes in synovitis and structural damage outcomes in patients with active RA and inadequate response to MTX with abatacept versus placebo on a background of therapy with MTX.

The primary endpoint of this study was to assess the changes in wrist synovitis in patients with active RA and inadequate response to MTX, as measured by MRI, and using the OMERACT 6 RA MRI score, after 4 months of treatment with abatacept or placebo, on a background therapy with MTX. Secondary endpoints included: changes in bone lesions (i.e. bone oedema, bone erosions) in hand/wrists; changes in biochemical markers in bone, cartilage and synovial fluid metabolism; safety and tolerability. Exploratory clinical efficacy analyses included DAS28.

Main criteria for inclusion

- Active RA despite MTX treatment
- DAS28 (CRP) > 3.2
- ≥6 tender TSJ
- CRP above upper limit or normal
- Clinically detectable synovitis of at least 1 wrist at screening and at baseline

- 1 erosion present (shown by X-ray) or positive for anti-CP or RF

A total of 50 patients (27 on abatacept + MTX and 23 on PLA + MTX) were randomised (1:1) and treated in this study. One patient in the abatacept + MTX discontinued the study during the double-blind period as they no longer met the study criteria due to hyperparathyroidism.

An additional 13 patients were enrolled but not randomised (10 subjects no longer met the study criteria and 1 subject withdrew consent, 1 subject was not randomised due to administrative reasons, and 1 subject was not randomised due to other reasons (MRI out of screening period).

Table B 14 Patients disposition and Baseline Characteristics

Table 1: Subject Disposition

Number (%)	ABA+MTX	PLA+MTX	Overall
No. of Subjects Enrolled	27	23	50
No. of Subjects Treated	27	23	50
No. of Subjects Completed DB	26	23	49
No of Subject excluded from analysis	0	0	0
No. of Subjects Discontinued	1 (3.7)	0	1 (2.0)
No longer met study criteria	1 (3.7)	0	1 (2.0)

Abbreviations: ABA = abatacept; DB = double-blind; MTX = methotrexate; PLA = placebo

Table B 15 Demographic and clinical characteristics

Table 2: Demographic and Clinical Characteristics

	ABA+MTX N=27	PLA+MTX N=23	Overall N=50
Age, Mean years (SD)	51.7 (11.2)	52.5 (11.5)	2.1 (11.2)
Gender, Female	16 (59.3%)	16 (69.6%)	32 (64.0%)
Race, White	26 (96.3%)	19 (82.6%)	45 (90.0%)
Duration of RA, Mean months (SD)	25.7 (18.0)	28.2 (17.0)	26.8 (17.4)
Tender joints, Mean (SD)	12.9 (7.1)	13.3 (7.2)	13.1 (7.1)
Swollen joints, Mean (SD)	11.3 (6.6)	8.5 (4.1)	10.0 (5.7)
RF Status Positive	15 (55.6%)	19 (82.6%)	34 (68.0%)
Anti-CCP2 Status Positive	13 (48.1%)	17 (73.9%)	30 (60.0%)
DAS28-CRP, Mean (SD)	5.3 (1.1)	5.3 (0.9)	5.3 (1.0)

Abbreviations: ABA = abatacept; CCP = cyclic citrullinated peptides; DAS = Disease Activity Score; MTX = methotrexate; PLA = placebo; RA = rheumatoid arthritis; RF = rheumatoid factor; SD = standard deviation

Most baseline and demographic characteristics were similar for both treatment groups; however there was an imbalance between groups with regard seropositivity at baseline.

IM101119 Clinical endpoints at 4 months

Efficacy results

Table B 16 Summary of efficacy results at 4 months (Day 113)

Table 4: Summary of Efficacy Results at 4 Months (Day 113; End of Double-Blind Treatment Period)

	ABA+MTX N=25	PLA+MTX N=23	Adjusted mean difference (95% CI)	p-value
Synovitis Score (non-parametric model): Mean change (SD) from baseline to Day 113	-0.44 (1.47)	0.52 (1.38)	---	0.103
Erosion Score: Adjusted mean change (SE) from baseline to Day 113	0.45 (0.43)	0.95 (0.45)	-0.50 (-1.77, 0.76)	---
Edema/Osteitis Score: Adjusted mean change (SE) from baseline to Day 113	-1.94 (0.86)	1.54 (0.90)	-3.48 (-6.00, -0.96)	---
RAMRIS Score: Adjusted mean change (SE) from baseline to Day 113	-1.82 (1.13)	2.89 (1.18)	-4.71 (-8.00, -1.42)	---
Number of newly involved joints: Bone erosion				
0	20/25 (80)	16/23 (69.6)	---	---
≥ 1	5/25 (20)	7/23 (30.4)		
Edema/osteitis				
0	18/25 (72)	16/23 (69.6)	---	---

Table B 17 Summary of efficacy results at 4 months (Day 113)

Table 4: Summary of Efficacy Results at 4 Months (Day 113; End of Double-Blind Treatment Period)

	ABA+MTX N=25	PLA+MTX N=23	Adjusted mean difference (95% CI)	p-value
≥ 1	7/27 (28)	7/23 (30.4)		
Synovitis				
0	23/25 (92)	20/23 (87)	---	---
≥ 1	2/25 (8)	3/23 (13)		

Abbreviations: ABA = abatacept; MTX = methotrexate; PLA = placebo; RAMRIS = rheumatoid arthritis MRI scores; SD = standard deviation; SE = standard error

The primary endpoint of mean change from baseline in total wrist synovitis did not show a significant difference between the two treatment groups.

However, the mean wrist MRI synovitis (3 sites) improved from baseline to Day 113 for the abatacept + MTX group compared with the placebo + MTX group which showed deterioration. The

abatacept + MTX group also showed an improvement in MRI wrist + hand osteitis score, and in total MRI RAMIS score (both compared to the placebo + MTX group). Finally, the MTX + MTX group showed a smaller deterioration in MRI wrist + hand erosion score compared with the placebo + MTX group.

Exploratory clinical efficacy analyses reported:

- DAS28(CRP)

The mean change from baseline over time during the double-blind period (4 months-Day 113) was:

in the abatacept + MTX group: -1.68 (95% CI: -2.15, -1.21)

and in the PLA + MTX group: -0.55 (95% CI: -0.95, -0.16)

At all timepoints from Day 15 to Day 113, a higher proportion of subjects in the abatacept + MTX group had a response to treatment based on DAS-derived criteria than the PLA + MTX group. On Day 113, low disease activity was noted for 50.0% of subjects in the abatacept + MTX group (95% CI: 30.8, 69.2) and 13.6% of subjects in the PLA + MTX group (95% CI: 0.0, 28.0). Remission was noted for 15.4% (95% CI: 1.5, 29.3) of subjects in the abatacept + MTX group and no subjects in the PLA + MTX group (95% CI: 0.0, 0.0).

Safety results

No deaths were reported during the double blind period of the study

Table B 18 with Adverse Events

Table 8.1: Summary of Subjects with Adverse Events Reported During Double-Blind Period of Treatment: All Treated Subjects

	Number (%) of Subjects					
	Abatacept N=27		Placebo N=23		Total N=50	
Deaths	0		0		0	
SAEs	0		2	(8.7)	2	(4.0)
Related SAEs	0		0		0	
Discontinued due to SAEs	0		0		0	
AEs	20	(74.1)	14	(60.9)	34	(68.0)
Related AEs	8	(29.6)	6	(26.1)	14	(28.0)
Discontinued due to AEs	0		0		0	

SAEs include hospitalizations for elective surgical procedures.
Related AE or SAE defined as AE or SAE with Certain, Probable, Possible, or Missing relationship to study medication.
Includes data up to 56 days post the last dose of double-blind period or start of the first dose of open-label period, whichever occurred first.
Includes all deaths reported during the double-blind period including those that occurred > 56 days after the last dose.

During the double-blind period, there were no SAEs reported for any patient in the abatacept group, while there were 2 SAEs reported in the placebo group (atrial fibrillation and overdose). Neither of these was considered related to the study drug.

No serious infections, malignancies, auto-immune events or discontinuation related to an adverse event or serious adverse

event was reported in either group. No patient discontinued the study in the double blind period.

The overall incidence of AEs was 74.1% in the abatacept + MTX group compared with 60.9% in the placebo + MTX group. Most AEs were mild in intensity.

5.5.4 Summary clinical efficacy tables

The summary clinical efficacy tables for ACR20/50/70, HAQ-DI, DAS28 and SF-36 for the RCTs presented in Section 5.5.3 are presented below.

Table B 19 ACR20/50/70 responses at 6 months and one year in the abatacept trials

Trial	AIM (n=656)		Kremer Phase 2b (n=339)			ATTEST (n=431)		
	Placebo + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Placebo + MTX	Abatacept 2 mg/kg every 4 weeks + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Placebo + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Infliximab 3mg/kg every 8 weeks + MTX
	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated
Number randomised	219 (214)	433 (424)	119	105	115	110	156	165
ACR responses at 6 months	214	424	119	105	115	110	156	165
ACR20, number of responders (%)	87 (39.7%)	294 (67.9%)	42 (35.2%)	44 (41.9%)	69 (60%)	46 (41.8%)	104 (66.7%)	98 (59.4%)
difference vs. placebo, mean [95%CI]		28.2 [19.8, 36.7] *p<0.001*		NR	NR *p<0.001*		24.8 [12.0, 37.7] *p<0.001*	17.6 [4.8, 30.4] *p<0.006*
difference ABA vs. active treatment mean [95%CI]*							7.3 [-3.9, 18.5]	
ACR50, number of responders (%)	37 (16.8%)	173 (39.9%)	14 (11.8%)	24 (22.9%)	42 (36.5%)	22 (20%)	63 (40.4%)	61 (37%)
difference vs. placebo mean [95%CI]		23.0 [15.0-31.1] *p<0.001*		NR *p<0.05*	NR *p<0.001*		20.4 [8.2-32.5] *p<0.001*	17.0 [5.1, 28.8] *p<0.004*
difference ABA vs. active treatment, mean [95%CI]*							3.4 [-7.9, 14.7]	
ACR70, number of responders (%)	14 (6.5%)	86 (19.8%)	2 (1.7%)	11 (10.5%)	19 (16.5%)	10 (9.1%)	32 (20.5%)	40 (24.2%)
difference vs. placebo, mean [95%CI]		13.3 [7.0, 19.5] *p<0.001*		NR *p<0.05*	NR *p<0.001*		11.4 [1.7, 21.1] *p<0.019*	15.2 [5.1, 25.2] *p<0.002*
ACR responses at one year	214	424	119	105	115	109	156	164

Trial	AIM (n=656)		Kremer Phase 2b (n=339)			ATTEST (n=431)		
	Placebo + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Placebo + MTX	Abatacept 2 mg/kg every 4 weeks + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Placebo + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Infliximab 3mg/kg every 8 weeks + MTX
	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated
ACR20, number of responders (%)	87 (39.7%)	317 (73.1%)	43 (36.1%)	41 (39%)	72 (62.6%)	75 (68.3%)	113 (72.4%)	92 (55.8%))
difference vs. placebo, mean [95%CI]		33.4 [25.1-41.7] *p<0.001*		NR *p<0.05*	NR *p<0.05*		NA	NA
difference ABA vs. active treatment, mean [95%CI]*							16.8 [5.3, 28.3]	
ACR50, number of responders (%)	40 (18.2%)	209 (48.3%)	24 (20.2%)	24 (22.9%)	48 (41.7%)	56 (50.9%)	71 (45.5%)	60 (36.4%)
difference vs. placebo, mean [95%CI]		30.1 [21.8-38.5] *p<0.001*		NR *p<0.05*	NR *p<0.05*		NA	NA
difference ABA vs. active treatment mean [95%CI]*							10.1 [-1.0, 21.2]	
ACR70, number of responders (%)	13 (6.1%)	124 (28.8%)	9 (7.6%)	13 (12.5%)	24 (20.9%)	32 (29.1%)	41 (26.3%)	34 (20.6%)
difference vs. placebo, mean [95%CI]		22.7 [15.6-29.8] *p<0.001*		NR *p<0.05*	NR *p<0.05*			
difference ABA vs. active treatment, mean [95%CI]*							6.1 [-3.3-15.5]	

*No trial was powered to detect a statistical difference between abatacept vs. active treatment.
ABA: abatacept; ACR: American College of Rheumatology; CI: confidence interval; MTX: methotrexate; NA: not applicable since patients that were randomised to placebo were no longer treated with placebo and thus switched to abatacept reported

Table B 20 HAQ-DI: change from baseline and responders at 6 months and one year in the abatacept trials

Trial	AIM trial (n=656)		Kremer Phase 2b (n=339)			ATTEST (n=431)		
	Placebo + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Placebo + MTX	Abatacept 2 mg/kg every 4 weeks + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Placebo + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Infliximab 3mg/kg every 8 weeks + MTX
	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated
Number randomised	219 (214)	433 (424)	119	105	115	110	156	165
HAQ-DI CFB at 6 months	211	420	119	105	115	110	156	165
HAQ-DI CFB, mean (SE)	-0.40 (0.04)	-0.59 (0.03)	-0.14	-0.17	-0.42	-0.31 (0.06)	-0.69 (0.05)	-0.61 (0.05)
difference vs. placebo, mean [95%CI]		-0.19 [-0.29, -0.10] *p<0.001*			NR p<0.05		-0.38 [-0.53, -0.23] *p<0.001*	-0.30 [-0.45, -0.15] *p<0.001*
clinically meaningful HAQ-DI response (>0.3), number of responders (%)	97 (45.3%)	259 (61.1%)	40 (33.6%) **response >0.22**		67 (58.3%) **response >0.22**	45 (40.9%)	96 (61.5%)	97 (58.8%)
difference vs. placebo mean [95%CI]		15.8 [7.2, 24.3] *p<0.001*					20.6 [7.7, 33.6] *p=0.001*	17.9 [5.1, 30.7] *p=0.005*
difference ABA vs. active treatment, mean [95%CI]*							2.8 [-8.6, 14.1]	
HAQ-DI at one year	212	422	119	105	115	PLA-ABA 110	156	165
mean HAQ-DI CFB (SE)	-0.37 (0.04)	-0.66 (0.03)	-0.10	-0.25	-0.47	-0.56 (0.06)	-0.67 (0.05)	-0.59 (0.05)
difference vs. placebo mean [95%CI]		-0.29 [-0.38, -0.19] *p<0.001*		NR *p<0.087*	NR *p<0.001*		NA	NA
difference ABA vs. active treatment, mean [95%CI]*							-0.08 [-0.22, 0.06]	
clinically meaningful HAQ-DI response (>0.3), number of responders (%)	84 (39.3%)	270 (63.7%)	33 (27.7%) **response >0.22**		57 (49.6%) **response >0.22**	63 (57.3%)	90 (57.7%)	87 (52.7%)

Trial	AIM trial (n=656)		Kremer Phase 2b (n=339)			ATTEST (n=431)		
	Placebo + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Placebo + MTX	Abatacept 2 mg/kg every 4 weeks + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Placebo + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Infliximab 3mg/kg every 8 weeks + MTX
	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated
difference vs. placebo mean [95%CI]		24.4 [15.9, 32.9] *p<0.001*					NA	NA
difference ABA vs. active treatment, mean [95%CI]							5.0 [-6.5, 16.5]	

*No trial was powered to detect a statistical difference between abatacept vs. active treatment.
ABA: abatacept; ACR: American College of Rheumatology; CI: confidence interval; HAQ-DI: health assessment questionnaire disability; index; MTX: methotrexate; NR: not reported; SE: standard error.

Table B 21 DAS 28 at 6 months and one year in the abatacept trials

Trial	AIM (n=656)		Kremer Phase 2b (n=339)			ATTEST (n=431)		
	Placebo + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Placebo + MTX	Abatacept 2 mg/kg every 4 weeks + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Placebo + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Infliximab 3mg/kg every 8 weeks + MTX
	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated
Number randomised	219 (214)	433 (424)	119	105	115	110	156	165
DAS 28 at 6 months	179	366	119	105	115	102	150	156
DAS 28 (ESR) CFB, mean (SE)	-1.33 (0.10)	-2.48 (0.07)	NR	NR	NR	-1.48 (0.15)	-2.53 (0.12)	-2.25 (0.12)
difference vs. placebo, mean [95%CI]		-1.15 [-1.38, -0.91] *p<0.001*		NR	NR		-1.04 [-1.42, -0.67] *p<0.001*	-0.77 [-1.14, -0.39] *p<0.001*
difference abatacept vs. active treatment mean, [95%CI]*							-0.28 [-0.61, 0.06]	
subjects with improvement (DAS 28change ≥1.2), number of subjects (%)	91 (50.8%)	301 (82.2%)				53 (52%)	123 (82%)	113 (72.4%)
difference abatacept vs. active treatment, mean [95%CI]*							9.6 [-0.5, 19.6]	
subjects with low disease activity (DAS 28 change ≤3.2), number of subjects (%)	7 (3.9%)	82 (22.4%)	23 (19.3%)	32 (30.5%)	46 (40%)	11 (10.8%)	31 (20.7%)	40 (25.6%)
difference abatacept vs. active treatment, mean [95%CI]*							-5.0 [-15.1, 5.1]	
subjects in remission (DAS 28 <2.6), number of subjects (%)	1 (0.6%)	35 (9.6%)	11 (9.2%)	19 (18%)	30 (26.1%)	3 (2.9%)	17 (11.3%)	20 (12.8%)
difference abatacept vs. active treatment, mean [95%CI]*							-1.5 [-9.4, 6.5]	

Trial	AIM (n=656)		Kremer Phase 2b (n=339)			ATTEST (n=431)		
	Placebo + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Placebo + MTX	Abatacept 2 mg/kg every 4 weeks + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Placebo + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Infliximab 3mg/kg every 8 weeks + MTX
	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated	(%) [95% CI] unless otherwise indicated
DAS 28 at one year	183	375				PLA-ABA 102	155	155
DAS 28 (ESR) CFB, mean (SE)	-1.46 (0.10)	-2.85 (0.07)				-2.68 (0.15)	-2.88 (0.12)	-2.25 (0.12)
difference vs. placebo, mean [95%CI]		-1.39 [-1.63, -1.16] *p<0.001*					-0.62 [-0.96, -0.29]	
Subjects with improvement (DAS 28change ≥1.2), number of subjects (%)	108 (59%)	328 (87.5%)				81 (79.4%)	129 (86%)	117 (75%)
difference abatacept vs. active treatment, mean [95%CI]							11 [1.4, 20.6]	
Subjects with low disease activity (DAS 28 change ≤3.2), number of subjects (%)	7 (3.8%)	103 (27.5%)	26 (21.9%)	30 (28.6%)	57 (49.6%)	30 (29.4%)	53 (35.3%)	35 (22.4%)
difference abatacept vs. active treatment, mean [95%CI]							12..9 [2.1, 23.7]	
Subjects in remission (DAS 28 <2.6), number of subjects (%)	4 (2.2%)	65 (17.3%)	12 (10.1%)	25 (24%)	40 (34.8%)	16 (15.7%)	28 (18.7%)	19 (12.2%)
difference abatacept vs. active treatment, mean [95%CI]							6.5 [-2.2, 15.2]	

*No trial was powered to detect a statistical difference between abatacept vs. active treatment.
ABA: abatacept; ACR: American College of Rheumatology; CFB: change from baseline; CI: confidence interval; DAS: disease activity score; MTX: methotrexate; NR: not reported; PLA: placebo; SE: standard error

Table B 22 SF-36 physical functioning and mental component at 6 months and one year in the abatacept trials

Trial	AIM (n=656)		Kremer Phase 2b (n=339)			ATTEST (n=431)		
	Placebo + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Placebo + MTX	Abatacept 2 mg/kg every 4 weeks + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Placebo + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Infliximab 3mg/kg every 8 weeks + MTX
	(SE) [95%CI] unless otherwise indicated	(SE) [95%CI] unless otherwise indicated	(SE) [95%CI] unless otherwise indicated	(SE) [95%CI] unless otherwise indicated	(SE) [95%CI] unless otherwise indicated	(SE) [95%CI] unless otherwise indicated	(SE) [95%CI] unless otherwise indicated	(SE) [95%CI] unless otherwise indicated
Number randomised	219 (214)	433 (424)	119	105	115	110	156	165
SF-36 at 6 months (physical component)	207	416				109	154	163
SF-36 CFB, mean (SE)	4.77 (0.59)	8.82 (0.42)				4.34 (0.82)	8.36 (0.69)	7.66 (0.67)
difference vs. placebo, mean [95%CI]		4.06 [2.64, 5.47] *p<0.001*					4.02 [1.92, 6.12] *p<0.001*	3.32 [1.25, 5.40] *p=0.002*
difference ABA vs. active treatment, mean [95%CI]*							0.70 [-1.19, 2.58]	
SF-36 at one year (physical component)	207	417				PLA-ABA 109	154	163
SF-36 CFB, mean (SE)	4.97 (0.61)	9.12 (0.43)				8 (0.83)	9.52 (0.70)	7.59 (0.68)
difference vs. placebo mean [95%CI]		4.15 [2.69, 5.62] *p<0.001*						
difference ABA vs. active treatment, mean [95%CI]*							1.93 [0.02, 3.84]	
SF-36 at 6 months (mental component)	207	416				109	154	163
SF-36 CFB, mean (SE)	3.83 (0.70)	6.22 (0.49)				1.64 (0.93)	5.14 (0.79)	4.32 (0.76)
difference vs. placebo mean [95%CI]		2.39 [0.70, 4.07] *p=0.005*					3.51 [1.10, 5.91] *p=0.004*	2.68 [0.31, 5.05] *p=0.027*
difference ABA vs. active treatment, mean [95%CI]*							0.83 [-1.33, 2.98]	
SF-36 at one year (mental component)	207	417				PLA-ABA 109	154	163
SF-36 CFB, mean (SE)	4.73 (0.69)	6.86 (0.48)				5.85 (0.97)	5.96 (0.81)	4.03 (0.79)
difference vs. placebo, mean		2.13 [0.48, 3.78]						

Trial	AIM (n=656)		Kremer Phase 2b (n=339)			ATTEST (n=431)		
	Placebo + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Placebo + MTX	Abatacept 2 mg/kg every 4 weeks + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Placebo + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Infliximab 3mg/kg every 8 weeks + MTX
	(SE) [95%CI] unless otherwise indicated	(SE) [95%CI] unless otherwise indicated	(SE) [95%CI] unless otherwise indicated	(SE) [95%CI] unless otherwise indicated	(SE) [95%CI] unless otherwise indicated	(SE) [95%CI] unless otherwise indicated	(SE) [95%CI] unless otherwise indicated	(SE) [95%CI] unless otherwise indicated
[95%CI]		*p=0.011*						
difference ABA vs. active treatment, mean [95%CI]*							1.92 [-0.30, 4.15]	

*No trial was powered to detect a statistical difference between abatacept vs. active treatment.

ABA: abatacept; ACR: American College of Rheumatology; CI: confidence interval; DAS: disease activity score; HRQOL: health related quality of life; MTX: methotrexate; NR: not reported; PLA: placebo; SE: standard error; SF-36: short-form 36.

5.6 Meta-analysis

- Abatacept + MTX is better than placebo + MTX in reducing ACR 20/50/70 scores
- Abatacept + MTX is better than placebo + MTX in reducing DAS28 scores
- Abatacept + MTX is better than placebo + MTX in achieving a DAS28 defined remission
- Abatacept + MTX is better than placebo + MTX in reducing HAQ score at 26 and 52 weeks.

5.6.1 The following steps should be used as a minimum when presenting a meta-analysis.

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.
- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).
- Provide an adequate description of the methods of statistical combination and justify their choice.
- Undertake sensitivity analysis when appropriate.
- Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).

A meta-analysis was performed for 3 RCTs evaluating the efficacy of abatacept in combination with MTX relative to placebo in combination with MTX. The results of the meta-analysis are presented in Tables B24 to B30 and graphically represented in forest plots.

Data from the abatacept (10mg/kg) + MTX arms and placebo + MTX arms were pooled; these included 1152 patients in total, of whom 704 were treated with abatacept.

The results of the meta-analysis are structured as follows.

Mean differences are calculated for the continuous outcomes

- HAQ CFB 24/26 weeks (Table B24)
- HAQ CFB at one year (Table B25)
- DAS 28 CFB at 24/28 weeks (Table B26)

Odds ratios and relative risks are calculated for binary outcomes

- ACR20 at 24/28 weeks (Table B27)
- ACR50 at 24/28 weeks (Table B28)
- ACR70 at 24/28 weeks (Table B29)
- DAS28 improvement at 24/28 weeks (Table B30)

The outcomes presented are the most commonly used measures for continuous and binary outcomes. Relative measures are presented instead of absolute measures, as they relate directly to the treatment effect of abatacept.

5.6.1.1 Methods of statistical combination

The weighting methods used in the meta-analysis for both continuous and binary data are shown in Table B23 below.

Table B 23 Weighting methods per type of outcome

Type of outcome	Weighting method
Continuous outcomes	Inverse-variance (IV) fixed effect method Inverse-variance random effect method*
Binary outcomes	Mantel-Haenszel (MH) method (fixed effect) Der Simonian Laird (SL) (random effect)*

*when evidence of heterogeneity is found

The Mantel-Haenszel method is often considered as the default fixed-effect method of meta-analysis. Mantel-Haenszel has been shown to have better statistical properties when there are few events. In other situations, Mantel-Haenszel and inverse-variance fixed effect method give similar estimates.

In a fixed-effect model the assumption is made that the true effect of the intervention, in both magnitude and direction, is the same value in every study (i.e. fixed across studies). This assumption implies that the observed differences among study results are due solely to the play of chance (i.e. that there is no statistical heterogeneity).

When there is evidence of heterogeneity, a random-effects model is preferred.

The random-effects method (Der Simonian Laird) is based on the inverse-variance approach which adjusts the study weights according to the extent of variation, or heterogeneity, of the intervention effects.

It should be noted that the random-effects method and the fixed-effect method will give identical results when there is no heterogeneity among the studies.

5.6.1.2 Statistical assessment of heterogeneity

Three heterogeneity assessments were performed:

- **Q test**: assesses whether observed differences in results are compatible with chance alone.
- **A low P value** (or a large chi-squared statistic relative to its degree of freedom) provides evidence of heterogeneity of intervention effects (variation in effect estimates beyond chance).
- **H statistic**: describes the relative excess in Q over its degrees of freedom.
- **I-squared statistic**: measures the extent of true heterogeneity dividing the difference between the result of the Q test and its degrees of freedom (k – 1) by the Q value itself, and multiplied by 100.

  The I-squared statistic index can be interpreted as the percentage of the total variability in a set of effect sizes due to true heterogeneity, that is, to between-studies variability. The I-squared statistic index is more easily interpreted that the H statistic.

If the *p*-value of the Q-test is less than 0.10 and/or the I-squared statistic index is above 50%, we assume that there is some evidence of heterogeneity and a random effect model is performed.

5.6.1.3 Results

Results of the meta- analyses are shown in Tables B24 to B30.

Please note there is no comparative for abatacept versus placebo at 52 weeks.

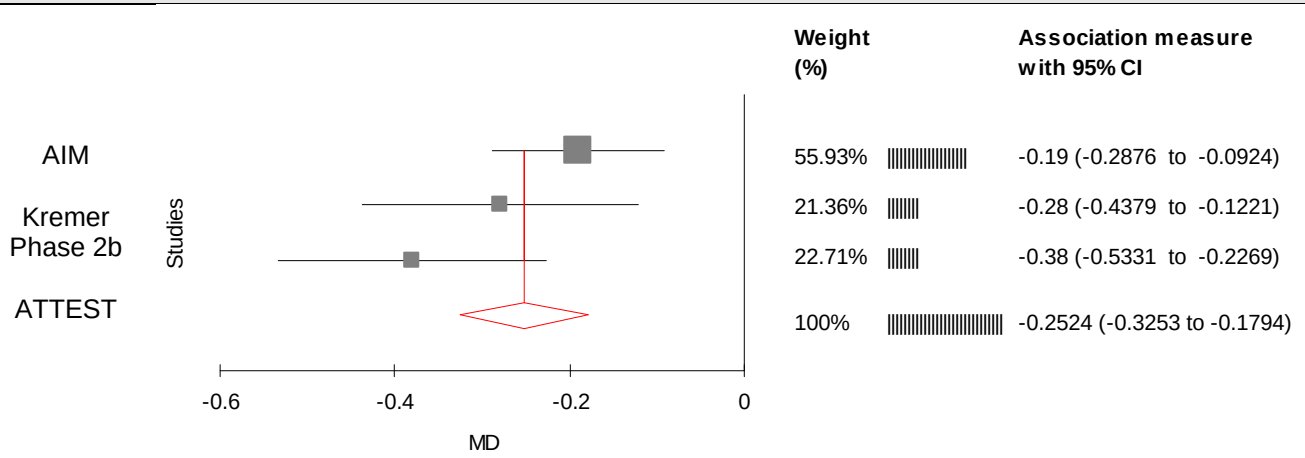
In terms of improvement in functional status as measured by HAQ change from baseline, abatacept + MTX is more efficacious than placebo + MTX at reducing the HAQ score at 24/26 weeks (-0.2524 [95%CI: -0.3253 to -0.1794] (fixed effects)) and 52 weeks (-0.3105 [95%CI: -0.3934 to -0.2275]).

Abatacept + MTX is more efficacious than placebo + MTX in reducing the DAS28 score at 24/28 weeks (mean difference -1.123 [-1.3275 to -0.9186]) and ACR20/50/70 response criteria. The OR ratio for an ACR responders was estimated to be 2.9961 for ACR20, 3.2811 for ACR50 and 3.7555 for ACR70 at weeks 24/28. The results expressed in relative risks were in the same range.

Finally, abatacept + MTX showed to be more efficacious than placebo + MTX in achieving a DAS28 defined remission (OR=3.4182 [2.589 to 4.548]).

Table B 24 HAQ CFB 24/26 weeks (NB: relative change from baseline in addition to placebo + MTX effect

Fixed effect model – Mean Difference (MD)	
Meta-analysis outcome	-0.2524
95% CI lower limit	-0.3523
95% CI upper limit	-0.1794
z	6.7802
p-value (two-tailed)	< 0.0001
Heterogeneity	
Q *p*-value (two-tailed)	4.3584 (0.1131)
H 95% CI lower limit 95% CI upper limit	1.4762 1 2.7593
I^2 95% CI lower limit 95% CI upper limit	54.11% 0% 86.87%



Random effect model – Mean Difference (MD)	
Meta-analysis outcome	-0.271
95% CI lower limit	-0.3854
95% CI upper limit	-0.1567
z	4.6459
p-value (two-tailed)	< 0.0001

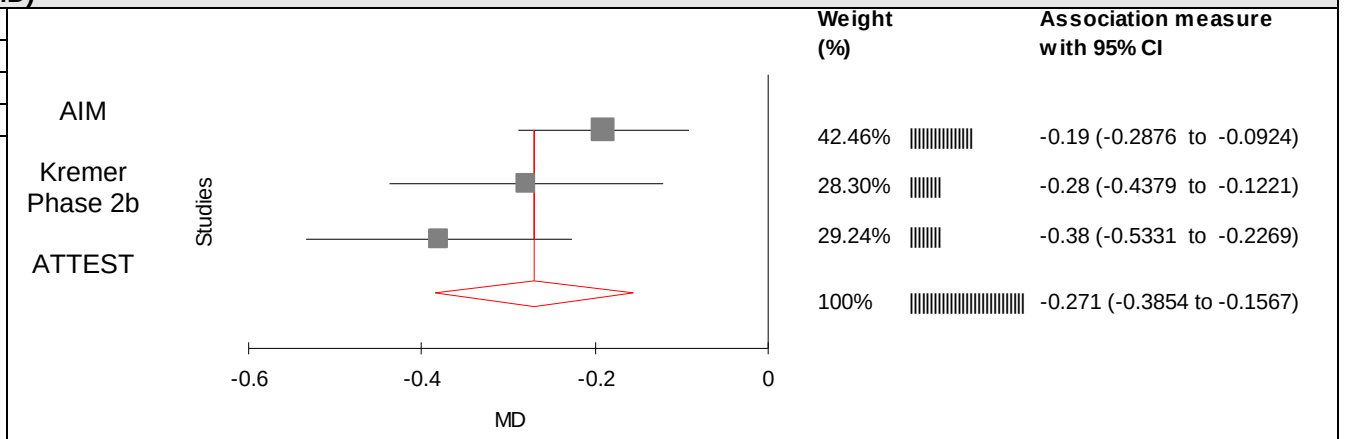


Table B 25 HAQ CFB at one year

Fixed effect model – Mean Difference (MB)	
Meta-analysis outcome	-0.3105
95% CI lower limit	-0.3934
95% CI upper limit	-0.2275
z	7.3353
p-value (two-tailed)	< 0.0001
Heterogeneity	
Q *p*-value (two-tailed)	0.5925 (0.4415)
H 95% CI lower limit 95% CI upper limit	1 n/a n/a
I^2 95% CI lower limit 95% CI upper limit	0% n/a n/a

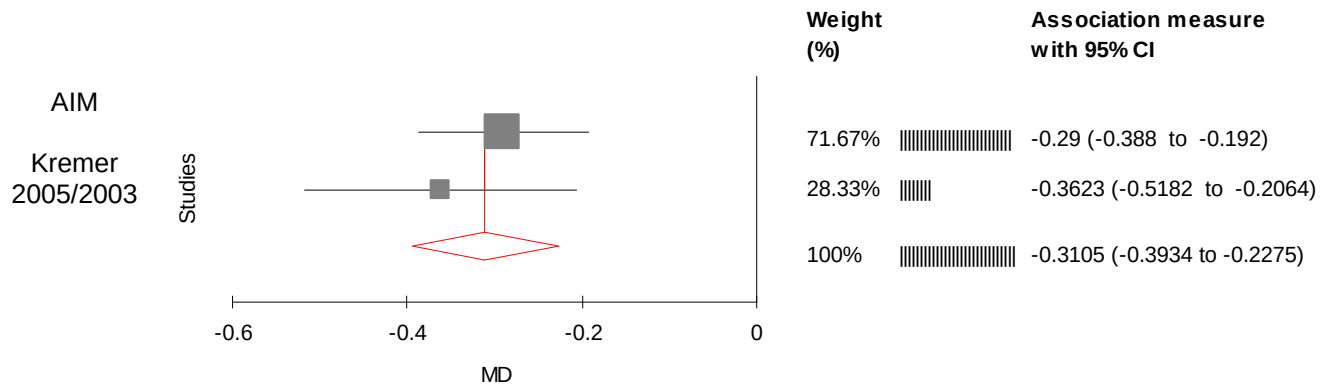


Table B 26 DAS 28 CFB at 24/28 weeks

Fixed effect model – Mean Difference (MD)	
Meta-analysis outcome	-1.123
95% CI lower limit	-1.3275
95% CI upper limit	-0.9186
z	10.7663
p-value (two-tailed)	< 0.0001
Heterogeneity	
Q *p*-value (two-tailed)	0.1811 (0.6705)
H 95% CI lower limit 95% CI upper limit	1 n/a n/a
I^2 95% CI lower limit 95% CI upper limit	0% n/a n/a

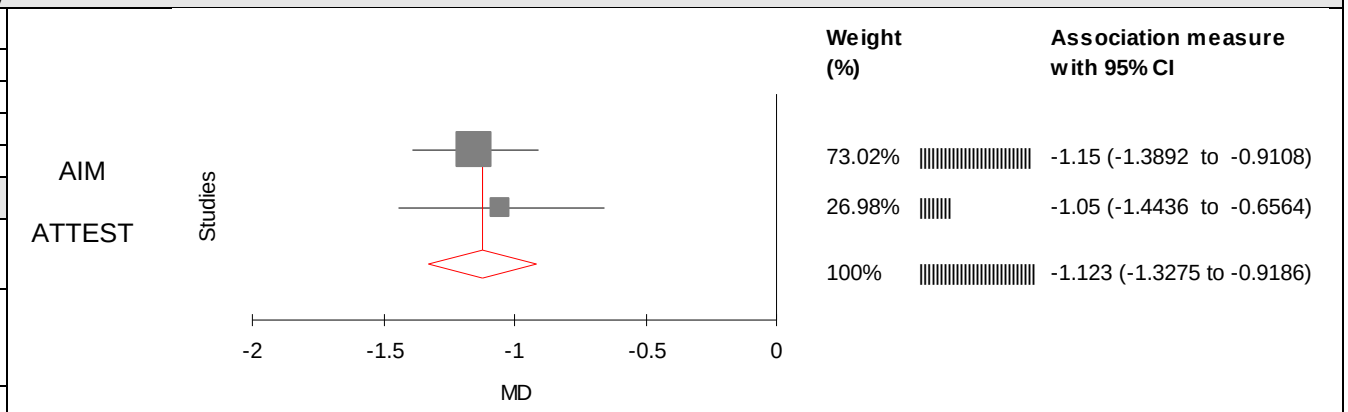
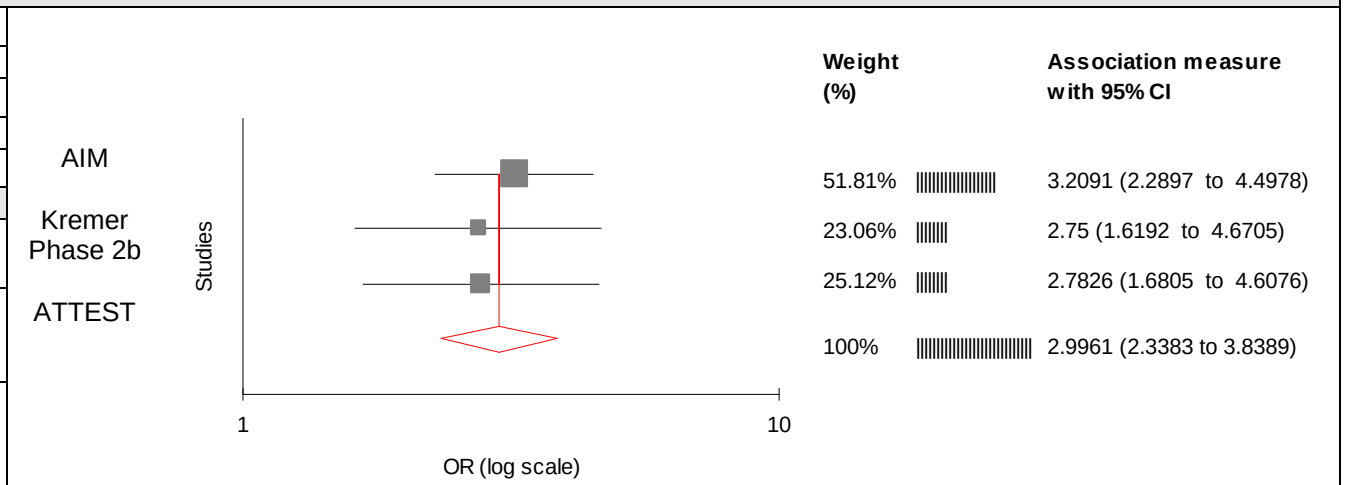


Table B 27 ACR20 at 24/28 weeks

Fixed effect model – Odds Ratio (OR)	
Meta-analysis outcome	2.9961
95% CI lower limit	2.3383
95% CI upper limit	3.8389
z	8.6764
p-value (two-tailed)	< 0.0001
Heterogeneity	
Q *p*-value (two-tailed)	0.3422 (0.8427)
H 95% CI lower limit 95% CI upper limit	1 1 3.1006
I^2 95% CI lower limit 95% CI upper limit	0% 0% 89.6%



Fixed effect model – Relative Risk (RR)	
Meta-analysis outcome	1.6779
95% CI lower limit	1.5211
95% CI upper limit	1.851
z	10.3355
p-value (two-tailed)	< 0.0001
Heterogeneity	
Q *p*-value (two-tailed)	0.2158 (0.8977)
H 95% CI lower limit 95% CI upper limit	1 1 3.1006
I^2 95% CI lower limit 95% CI upper limit	0% 0% 89.6%

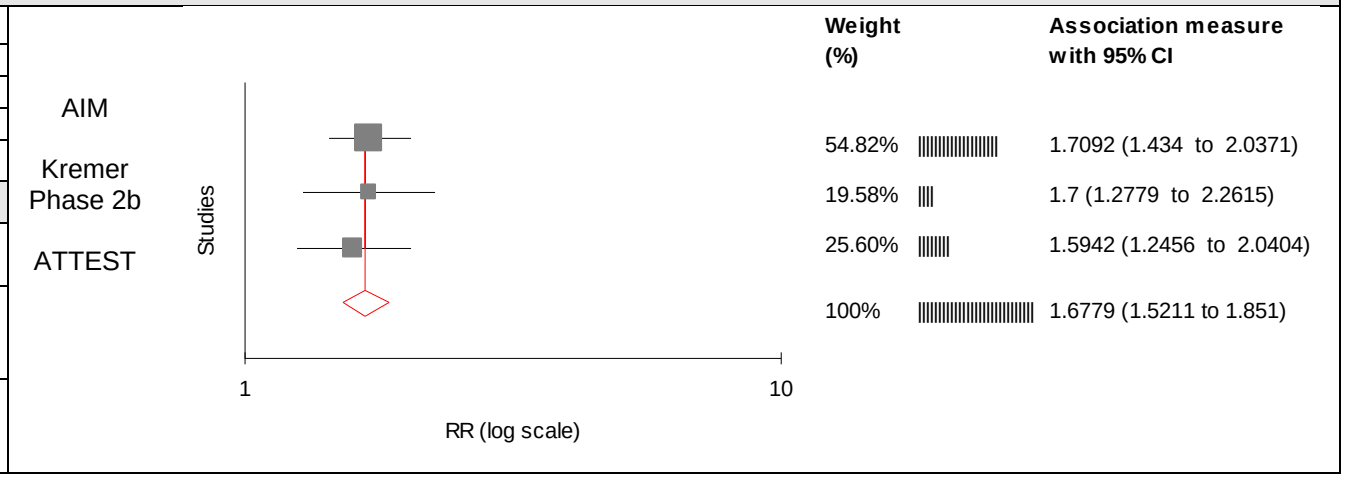
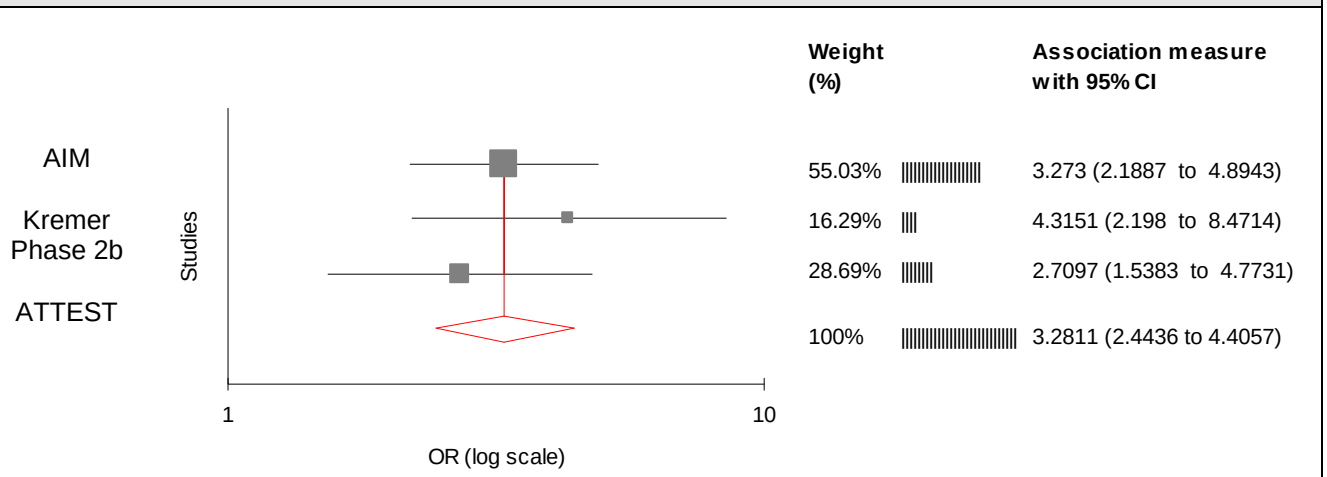


Table B 28 ACR50 at 24/28 weeks

Fixed effect model – Odds ratio (OR)	
Meta-analysis outcome	3.2811
95% CI lower limit	2.4436
95% CI upper limit	4.4057
z	7.9019
p-value (two-tailed)	< 0.0001
Heterogeneity	
Q	1.0724
p-value (two-tailed)	(0.585)
H	1
95% CI lower limit	1
95% CI upper limit	3.1006
I^2	0%
95% CI lower limit	0%
95% CI upper limit	89.6%



Fixed effect model – Relative Risk (RR)	
Meta-analysis outcome	2.379
95% CI lower limit	1.971
95% CI upper limit	2.8715
z	9.0276
p-value (two-tailed)	< 0.0001
Heterogeneity	
Q	1.4944
p-value (two-tailed)	(0.4737)
H	1
95% CI lower limit	1
95% CI upper limit	3.1006
I^2	0%
95% CI lower limit	0%
95% CI upper limit	89.6%

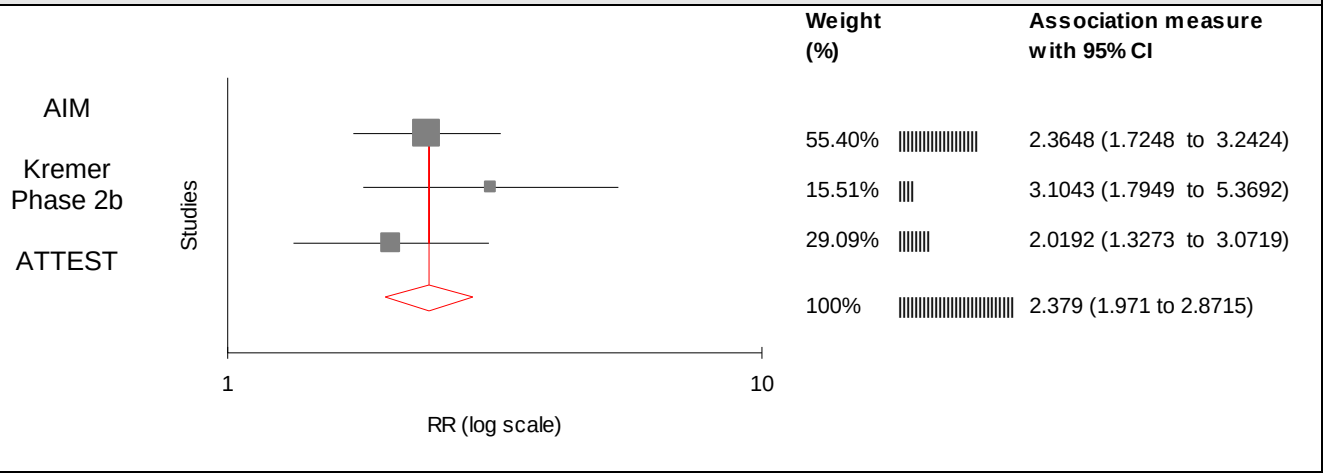
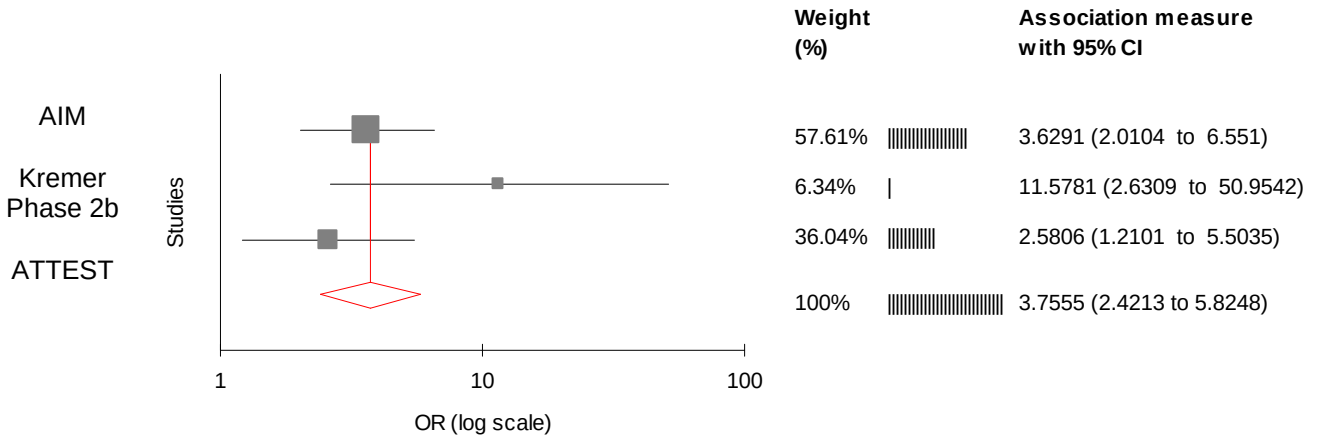


Table B 29 ACR70 at 24/28 weeks

Fixed effect model – Odds ratio (OR)	
Meta-analysis outcome	3.7555
95% CI lower limit	2.4213
95% CI upper limit	5.8248
z	5.9089
p-value (two-tailed)	< 0.0001
Heterogeneity	
Q *p*-value (two-tailed)	3.1733 (0.2046)
H 95% CI lower limit 95% CI upper limit	1.2596 1 2.2378
I^2 95% CI lower limit 95% CI upper limit	36.98% 0% 80.03%



Fixed effect model – Relative Risk (RR)	
Meta-analysis outcome	3.2073
95% CI lower limit	2.2496
95% CI upper limit	4.5727
z	6.44
p-value (two-tailed)	< 0.0001
Heterogeneity	
Q *p*-value (two-tailed)	3.4242 (0.1805)
H 95% CI lower limit 95% CI upper limit	1.3085 1 2.3735
I^2 95% CI lower limit 95% CI upper limit	41.59% 0% 82.25%

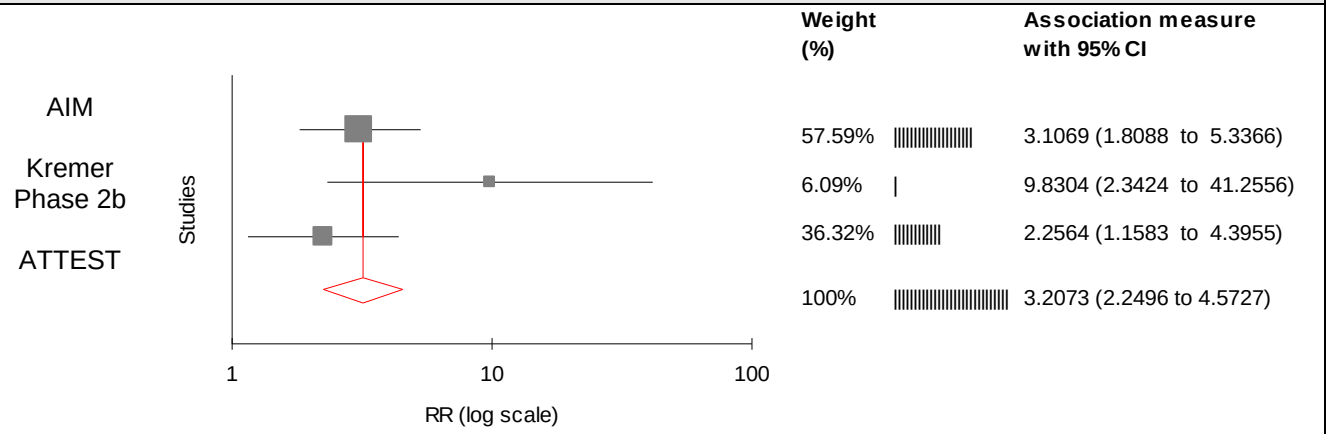
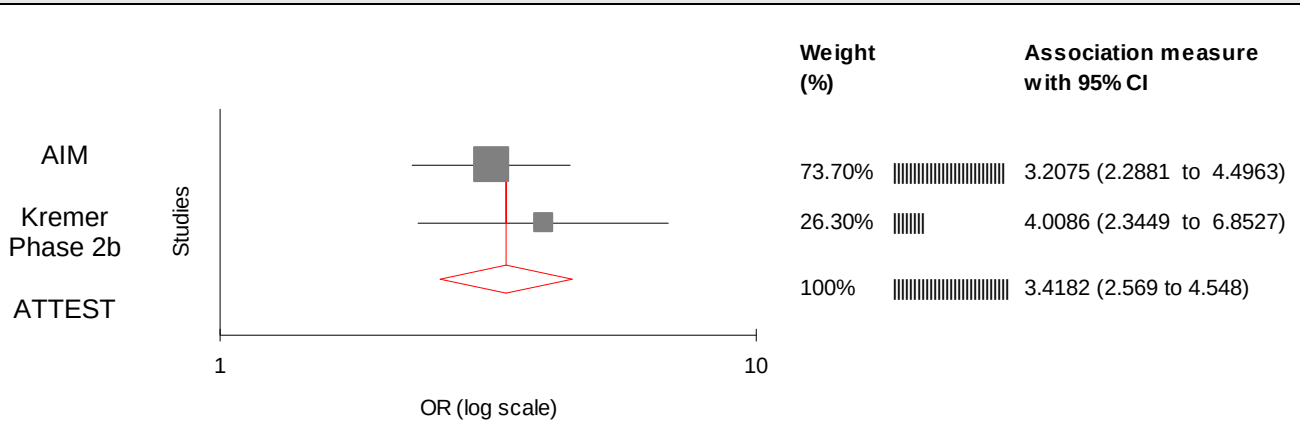
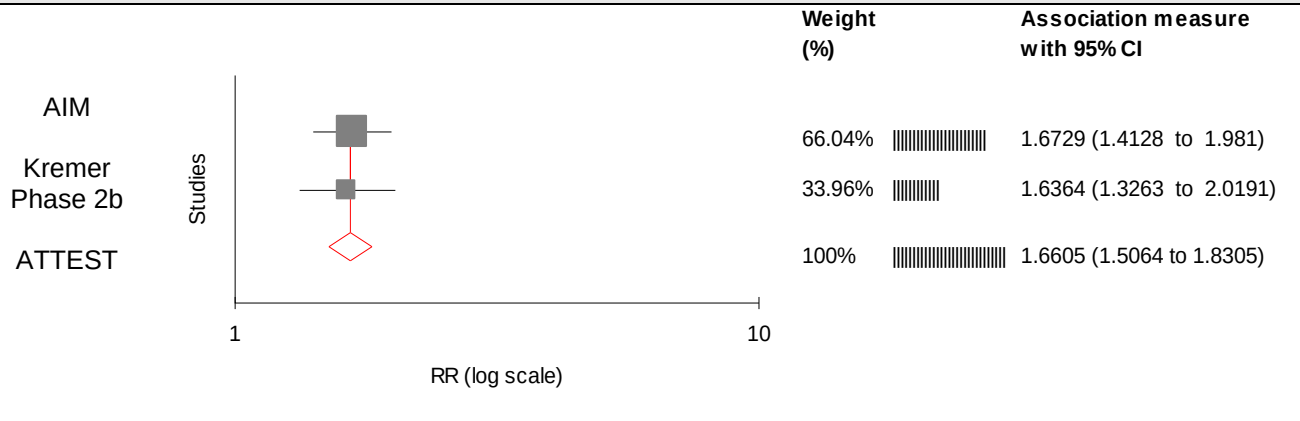


Table B 30 DAS 28 improvement at 24/28 weeks

Fixed effect model – Odds ratio (OR)	
Meta-analysis outcome	3.4182
95% CI lower limit	2.569
95% CI upper limit	4.548
z	8.4354
p-value (two-tailed)	< 0.0001
Heterogeneity	
Q *p*-value (two-tailed)	0.4755 (0.4905)
H 95% CI lower limit 95% CI upper limit	0 0 0
I^2 95% CI lower limit 95% CI upper limit	0% 0% 0%



Fixed effect model – Relative Risk (RR)	
Meta-analysis outcome	1.6605
95% CI lower limit	1.5064
95% CI upper limit	1.8305
z	10.2023
p-value (two-tailed)	< 0.0001
Heterogeneity	
Q *p*-value (two-tailed)	0.261 (0.8718)
H 95% CI lower limit 95% CI upper limit	1 N/A N/A
I^2 95% CI lower limit 95% CI upper limit	0% N/A N.A



5.6.2 If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

Not applicable.

5.6.3 If any of the relevant RCTs listed in response to section 5.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.

No studies selected from the systematic review have been excluded from the meta-analysis.

5.7 Indirect and mixed treatment comparisons

The mixed treatment comparison results support the outcomes from the RCTs discussed previously: abatacept is more efficacious than placebo in terms of ACR response.

In addition, abatacept is expected to have a level of clinical efficacy that is comparable to that of other biologic DMARDs.

5.7.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 9.4, appendix 4.

A similar search and two-step study selection process to that used in Section 5.1 was used to identify relevant evidence for the mixed treatment comparison. Medline, Medline-In-Process, Embase, and the Cochrane Library were searched (see Appendix 4 for details).

ACR and EULAR conference websites were searched to identify the latest and any additional results not available in retrieved publications. In addition a hand search of NICE STA reports was performed.

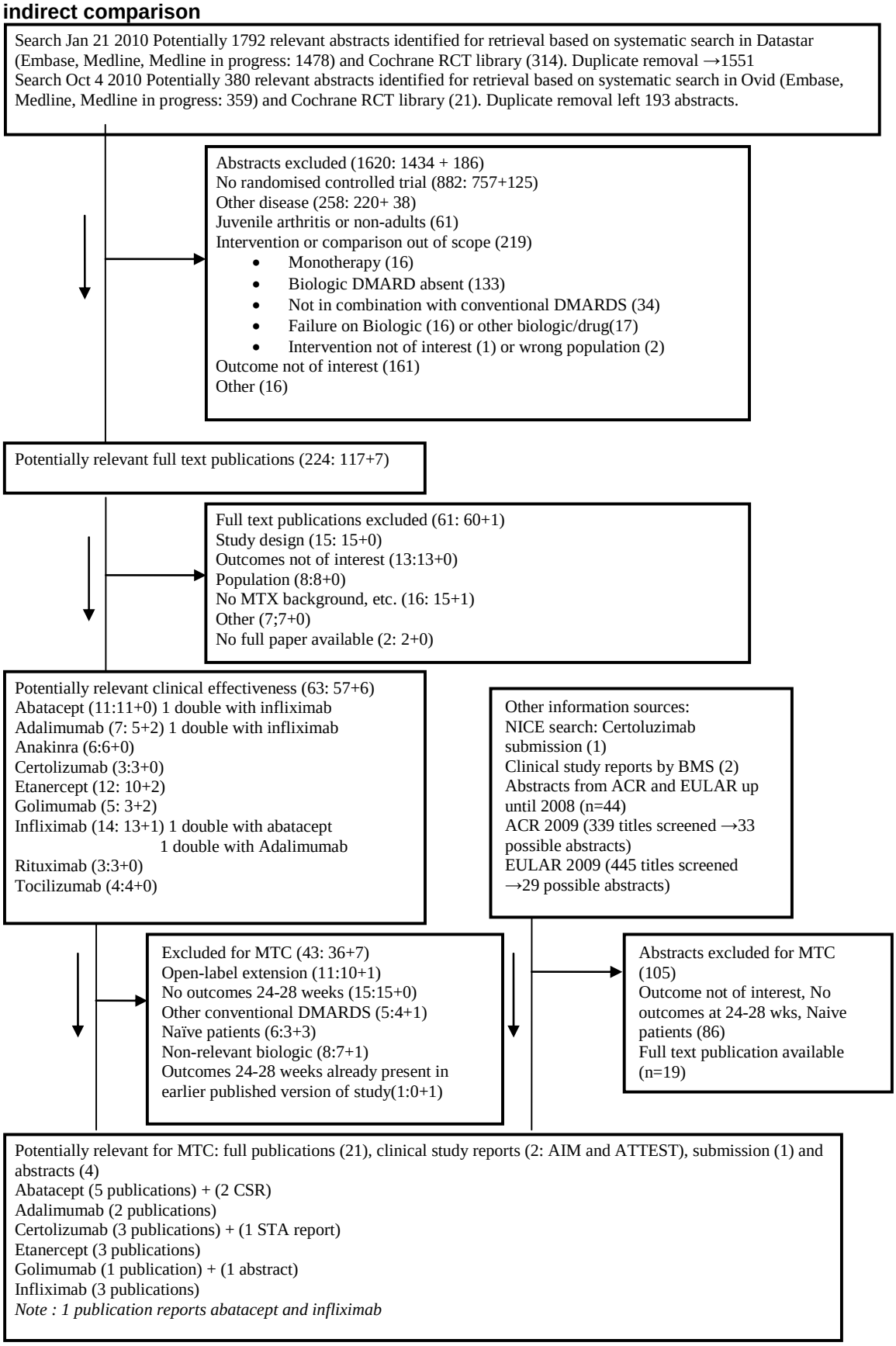
One NICE submission and 4 relevant abstracts were included in the mixed treatment comparison (MTC) analyses.

As described in Section 5.1, the original search was performed on January 21, 2010 and an updated search based on the final scope was performed on October 4, 2010.

The flow of study selection process, including both searches, is summarised in Figure B24.

All Phase II and Phase III studies undertaken as part of the drug development plan for abatacept by BMS were considered and CSRs obtained for review. CSRs for BMS trials (AIM and ATTEST) were included and searched for additional information if data was missing or unavailable from published report(s). Conference abstracts were also searched for complementary data, if relevant.

Figure B 24 Selection flow chart of publications and congress reports included in the indirect comparison



5.7.2 Please follow the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 9.5, appendix 5, a complete quality assessment for each comparator RCT identified.

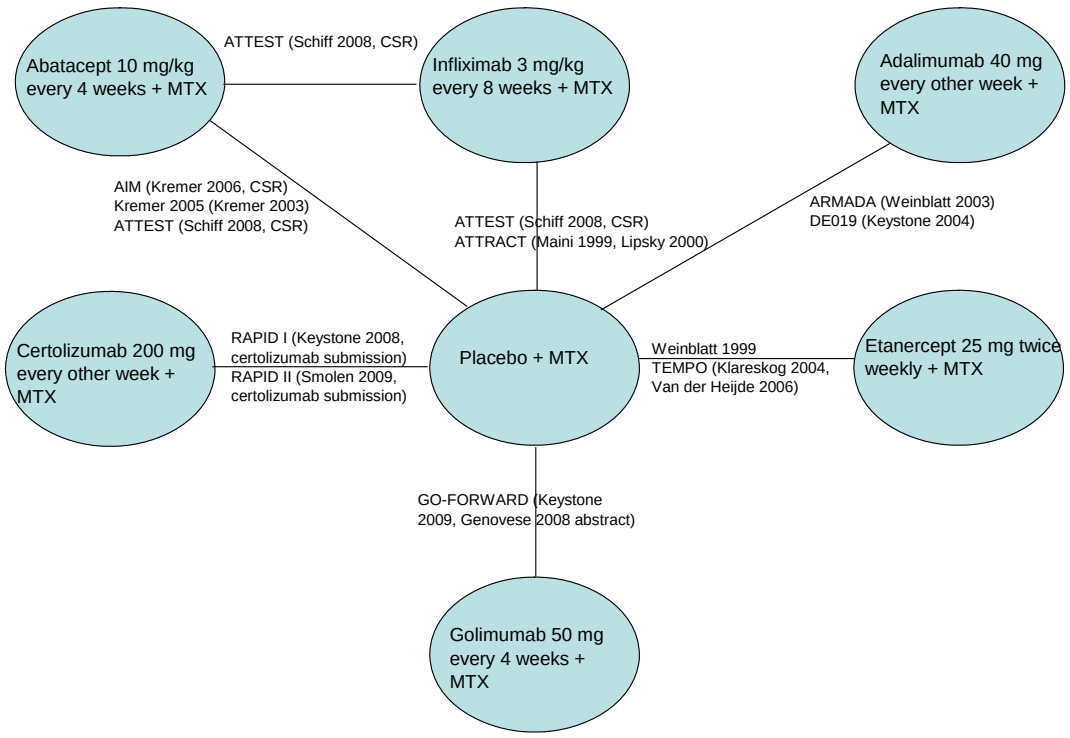
A similar approach to summarise the trials was used as in Section 5.2 and 5.3. Table B31, Table B32 and Table B33 in Section 5.7.3 summarise the intervention and study population, study methodology, and baseline population and disease characteristics, respectively, for each trial included in the MTC.

Quality assessment tables are presented in Appendix 5, see Section 9.5.

5.7.3 Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

The network of studies included in the indirect treatment comparison base case analysis is summarised in Figure B25.

Figure B 25 Network of Studies (base case analysis)



The 28 documents (21 publications, 2 CSRs, 1 STA submission, 4 abstracts) identified by the literature search covered 11 individual studies.

All the other studies compared the combination of a biologic DMARD and MTX to placebo + MTX. Please note that the ATTEST trial included both a direct comparison for abatacept versus placebo as well as infliximab versus placebo.

Placebo + MTX is therefore the common comparator for the analyses. Each comparison is supported by at least one pivotal trial. The network of studies is sufficient to perform an indirect treatment comparison, but is characterised by the absence of 'closed loops' (except for abatacept vs. infliximab which is evaluated in the ATTEST trial, and supported by abatacept vs. placebo comparison in combination with infliximab vs. placebo comparison). This implies that for most comparisons, the direct evidence from trials is not supported by indirect evidence.

The following comparability issues were identified.

TEMPO ('Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes') evaluated etanercept in combination with MTX trial and so may have included a different study population to the other studies, as the patient population included was not composed of inadequate responders to MTX, but to conventional DMARDs.

Thus, in the placebo treatment group, patients effectively changed their treatment from one of the conventional DMARDs to MTX (which is seen as a more efficacious treatment) potentially explaining the high placebo response observed.

A summary of the trials used to conduct the indirect treatment comparison is presented in Table B31.

Table B 31 Summary of the trials used to conduct the indirect comparison (interventions and study population)

Trial	Interventions compared (incl. dose, frequency and duration of treatment)				Comparison	Population treated	Primary and secondary study references
	Interventions	Dose	Frequency	Duration			
Abatacept studies							
AIM	Placebo + MTX	N/A	N/A	1 year	Abatacept + MTX vs. Placebo + MTX	Active RA despite MTX treatment	Abatacept CSR, Kremer *et al* 2006 and Russell *et al* 2007
	Abatacept + MTX	10 mg/kg	Days 1, 15, and 29 and every 28 days thereafter				
Kremer Phase 2b	Placebo + MTX	N/A	N/A	1 year	Abatacept + MTX vs. Placebo + MTX	RA that has remained active despite MTX therapy.	Kremer *et al* 2005, Kremer *et al* 2003
	Abatacept 2 mg/kg every 4 weeks + MTX	2 mg/kg	Day 1, 15, and 30 and every 30 days thereafter				
	Abatacept 10 mg/kg every 4 weeks + MTX	10 mg/kg					
ATTEST	Placebo + MTX	N/A	N/A	6 months	Abatacept + MTX vs. Placebo + MTX at 6 months only Infliximab + MTX vs. Placebo + MTX at 6 months only Abatacept + MTX vs. Infliximab + MTX	RA and an inadequate response to MTX	Abatacept CSR and Schiff *et al* 2007
	Infliximab + MTX	3 mg/kg	Days 1, 15, 43 and 85, and every 56 days thereafter	12 months			
	Abatacept + MTX	10 mg/kg	Days 1, 15 and 29, and every 28 days thereafter	6 and 12 months			
Adalimumab studies							
ARMADA	Placebo + MTX	N/A	N/A	24 weeks	Adalimumab + MTX vs. Placebo + MTX	Active RA despite treatment with MTX	Weinblatt *et al* 2003
	Adalimumab + MTX	20 mg	Every other week				
	Adalimumab + MTX	40 mg					

Trial	Interventions compared (incl. dose, frequency and duration of treatment)				Comparison	Population treated	Primary and secondary study references
	Interventions	Dose	Frequency	Duration			
	Adalimumab + MTX	80 mg					
DE019	Placebo + MTX	N/A	N/A	52 weeks	Adalimumab + MTX vs. Placebo + MTX	Active RA receiving with an inadequate response to MTX.	Keystone *et al* 2004
	Adalimumab + MTX	20 mg	Weekly				
	Adalimumab + MTX	40 mg	Every other week				
Certolizumab studies							
RAPID 1	Placebo + MTX	N/A	N/A	1 year	Certolizumab + MTX vs. Placebo + MTX	Active RA with an inadequate response to MTX	Keystone *et al* 2008 and Strand *et al* 2009
	Certolizumab + MTX	200 mg	Every other week				
	Certolizumab + MTX	400 mg	Every other week				
RAPID II	Placebo + MTX			24 weeks	Certolizumab + MTX vs. Placebo + MTX	Active RA despite >= 6 months MTX treatment	Smolen *et al* 2009
	Certolizumab + MTX	200 mg	Every other week				
	Certolizumab + MTX	400 mg					
Etanercept studies							
TEMPO	Placebo + MTX	N/A	N/A	52 weeks to 2 years	Etanercept + MTX vs. Placebo + MTX	Active RA with an inadequate response to MTX	Heijde van der *et al* 2004, Heijde van der *et al* 2006 (PRO), Heijde van der *et al* 2006 (2-
	Etanercept	25 mg	Twice weekly				

Trial	Interventions compared (incl. dose, frequency and duration of treatment)				Comparison	Population treated	Primary and secondary study references
	Interventions	Dose	Frequency	Duration			
	Etanercept + MTX	25 mg					yr), Heijde van der *et al* 2007
Weinblatt *et al* 1999	Placebo + MTX	N/A	N/A	24 weeks	Etanercept + MTX vs. Placebo + MTX	Active RA despite >= 6 months of MTX	Weinblatt *et al* 1999
	Etanercept + MTX	25 mg	Twice weekly				
Golimumab studies							
GO-FORWARD	Placebo + MTX	N/A	N/A	24 weeks	Golimumab + MTX vs. Placebo + MTX	Active RA with an inadequate response to MTX	Keystone *et al* 2009
	Golimumab + placebo	100 mg	Every 4 weeks				
	Golimumab + MTX	50 mg					
	Golimumab + MTX	100 mg					
Infliximab studies							
ATTRACT	Placebo + MTX	N/A	N/A	30 weeks to 2 years	Infliximab + MTX vs. Placebo + MTX	Active RA with an inadequate response to MTX	Maini *et al* 2004 (2-yr), Lipsky *et al* 2000 and Maini *et al* 1999
	Infliximab + MTX	3 mg/kg	Every 8 weeks				
	Infliximab + MTX	3 mg/kg	Every 4 weeks				
	Infliximab + MTX	10 mg/kg	Every 8 weeks				
	Infliximab + MTX	10 mg/kg	Every 4 weeks				

MTX: methotrexate; N/A: not applicable; RA: rheumatoid arthritis

Table B32 presents an overview of study designs and methodologies of the trials included in the indirect treatment comparison.

All studies were randomised, double-blind, placebo-controlled, and reported outcomes at 24/28 weeks.

Four studies included an early escape for non-responders (DE019 [Keystone 2004], RAPID I, RAPID II, GO-FORWARD). RAPID I and RAPID II studies withdrew patients who did not show an ACR20 response at both weeks 12 and 14. The GO-FORWARD study provided rescue therapy for patients who did not achieve at least 20% improvement in both TJC and SJC by week 16.

Three studies (ARMADA [Weinblatt et al 2003]; RAPID II [Smolen et al 2009]; Weinblatt et al 1999); did not have a follow up at 48/52 weeks and could therefore not be included in the 48/52 weeks analyses.

No data for the outcomes of interest could be identified for the GO-FORWARD study (Keystone et al 2009, Genovese et al 2008).

Across the studies, selected patients were those with active RA despite treatment with MTX. These patients received treatment with MTX for at least a 3 or 6 months prior to study enrolment, with a stable dose of at least 4 weeks prior to randomisation. All studies included in the analysis met these criteria, except for patients selected in the TEMPO trial. Patients selected for the TEMPO trial included patients with RA who had failed previous DMARD treatment other than MTX. Patients could have previously been treated with MTX (but not in the previous 6 months), as long as they did not present with clinically significant toxic effects, or lack of response.

Table B 32 Summary of the trials used to conduct the indirect comparison (study methodology)

Trial	Design	Patient population	Inclusion criteria	Exclusion criteria	Primary endpoints	Duration	Year of study
Abatacept studies							
AIM	Multicentre, randomised, double-blind, placebo-controlled trial	Active RA despite MTX treatment	Met the ACR criteria, active disease, ≥18 years, RA for ≥ 1 year, RA persistent and active despite MTX, ≥10 swollen joints, ≥12 tender joints, CRP level ≥10.0 mg/L, treated with MTX (≥ 15mg/week) for ≥ 3 months with stable dosage for 28 days prior to enrolment	Positive tuberculin skin test	ACR20 at 6 months, HAQ-DI(≥ 0.3), and CFB in joint erosion score at 1 year	52 weeks	November 2002 to October 2004
Kremer Phase 2b	Multicentre, randomised, double-blind, placebo-controlled study	RA that has remained active despite MTX therapy	Met the ACR criteria, active disease, ≥10 swollen joints, ≥12 tender joints, CRP level >1 mg/dl, treated with MTX (10–30 mg/week) for ≥ 6 months with stable dosage for 28 days prior to enrolment	Pregnant or nursing women were excluded from trial	ACR20 response at 6 months	52 weeks and 6 months	NR
ATTEST	Randomised, double-blind, double-dummy, placebo- and active (infliximab)-controlled	RA and an inadequate response to MTX	ACR criteria for RA, ≥ 18 years, RA for ≥ 1 year, IR to MTX, >10 swollen joints, >12 tender joints, CRP levels >1 mg/dl, MTX >15 mg/week for >3 months prior to randomisation and washed out all other DMARDs, No prior experience of abatacept or anti-TNF therapy	NR	Reduction in disease activity, measured by DAS28 with abatacept vs. placebo at 6 months	52 weeks	NR
Adalimumab studies							
ARMADA	Randomised, double-blind, placebo-controlled study	Active RA despite treatment with MTX	≥18 years, ACR criteria for RA, > 9 tender joints, > 6 swollen joints, MTX for ≥ 6 months and stable weekly	Had received treatment with anti-CD4 therapy or TNF-alpha antagonists, had a history of active	ACR20 response	24 weeks	NR

Trial	Design	Patient population	Inclusion criteria	Exclusion criteria	Primary endpoints	Duration	Year of study
			dose for ≥ 4 weeks before enrolment, failed treatment with ≥ 1 DMARD besides MTX, but no > 4 DMARDs	listeriosis or mycobacterial infection, had a major episode of infection			
DE019	Multicentre, randomised, double-blind, placebo-controlled study	Active RA receiving concomitant treatment with MTX	≥18 years, ACR criteria for RA, ≥9 tender joints, ≥ 6 swollen joints, CRP level >1 mg/dl, either rheumatoid factor positivity or ≥ 1 joint erosion on radiographs of the hands and feet, MTX therapy for ≥3 months at stable dose of 12.5–25 mg/week for ≥4 weeks	Prior use of anti-CD4 antibody therapy or TNF antagonists, history of other active inflammatory arthritide, history of active listeriosis or mycobacterial infection, history of lymphoma or leukaemia within 5 years, major episode of infection	ACR20 response at week 24	52 weeks	NR
Certolizumab Pegol studies							
RAPID I	Phase III, multicentre, randomised, double-blind, placebo controlled	Active RA with inadequate response to MTX therapy alone	≥ 18 years, active RA for ≥ 6 months and <15 years prior to screening ≥9 tender and 9 swollen joints at screening and baseline with either ESR ≥30 m/hour or CRP>15 mg/l MTX for ≥6 months with a stable dosage of ≥10 mg/week for ≥ 2 months prior to baseline	History of tuberculosis, PPD positive skin test, history of malignancy, had received any biologic therapy within 6 months of baseline, had previously failed to respond to treatment with an anti-TNF agent	ACR20 response rate at week 24 and the mean change from baseline in the modified total Sharp score at week 52	52 weeks	Between February 2005 and October 2006
RAPID II	Phase III, multicentre, double-blind,	Active RA despite ≥ 6 months MTX treatment	>18 years, RA defined by ACR 1987 criteria of >6 months duration but < 15	Biological agent for RA within 6 months before enrolment, previously treated with a	ACR20 response at week 24	24 weeks Patients who did not show an	Between June 2005 to September 2006

Trial	Design	Patient population	Inclusion criteria	Exclusion criteria	Primary endpoints	Duration	Year of study
	randomised, placebo-controlled		years, had to have received prior MTX for >6 months (stable dose >10 mg/week for >2 months before baseline)	biological agent resulting in a severe hypersensitivity or anaphylactic reaction, not initially responded to previous anti-TNF therapy, history of tuberculosis, PPD positive skin test		ACR20 response at both weeks 12 and 14 were to be withdrawn from the study, designated ACR20 non-responders in the primary analysis.	
Etanercept studies							
Weinblatt *et al* 1999	Double-blind, randomised	Persistently active RA despite ≥ 6 months of MTX	≥ 18 years, ACR criteria for RA, ≥ 6swollen joints, ≥ 6 tender joints, MTX for ≥ 6 months, and at a stable dose of 15-25 mg/week for the last 4 weeks, discontinued sulfasalazine and hydroxychloroquine ≥ 2 weeks before starting the study drug and DMARDs other than MTX ≥ 4 weeks before	NR	ACR20 at 24 weeks	24 weeks	NR
TEMPO	Randomised, double-blind, parallel group study	Patients with RA who had failed previous DMARDs treatment other than MTX	≥ 18 years, active disease of 6 months to 20 years, ACR criteria for RA, > 10 swollen joints, > 12 painful joints, IR to ≥1 DMARD other than MTX, previously treated with MTX if no clinically important toxic effects or lack of response, not treated with MTX within 6 months of enrolment	Previously received etanercept or other TNF antagonists, previous immunosuppressive drugs within 6 months of screening; investigational drug or biological agent within 3 months screening, any other DMARDs or corticosteroid within 4 weeks of baseline visit, presence of relevant co morbidity	ACR response (ACR-N) area under the curve (AUC) over the first 24 weeks	52 weeks	Between October 2000 and July 2001

Trial	Design	Patient population	Inclusion criteria	Exclusion criteria	Primary endpoints	Duration	Year of study
Golimumab studies							
GO-FORWARD	Phase III, multicentre, randomised, double-blind, placebo controlled trial.	Active RA despite MTX therapy	> 18 years, ACR criteria for RA ≥ 3 months before screening, stable MTX dose of 15-25 mg/week during 4 weeks before screening, tolerated ≥15 mg/week of MTX for ≥3 months before screening, ≥4 swollen joints, ≥4 tender joints, met the tuberculosis screening criteria	Hypersensitivity to components of golimumab, previous use of any anti-TNF agent, rituximab, natalizumab, cytotoxic agents, no anakinra, DMARDs other than MTX, corticosteroids within 4 weeks before the study agent, alefacept or efalizumab within 3 months before the study agent	ACR20 response at week 14 and improvement from baseline in HAQ-DI score at week 24	52 weeks. At week 16, patients in groups 1, 2 or 3 with < 20% CFB in both TJC and SJC had their study medication adjusted in a double-blind fashion	Between 19 December 2005 and 17 September 2007
Infliximab studies							
ATTRACT	Phase III, Multi-centre, randomised, double-blind, placebo-controlled	Active RA despite receiving MTX	ACR criteria for RA, active disease despite MTX ≥6 swollen and tender joints, MTX for ≥ 3 months with no break in treatment of more than 2 weeks during this period, MTX at stable dose >12·5 mg/week for ≥ 4 weeks before screening, oral corticosteroids or NSAIDs on a stable dose for ≥ 4 weeks before screening	DMARD other than MTX or corticosteroids other than oral in the 4 weeks before screening, any other agent to reduce tumour necrosis factor or previous use of alkylating agents, known allergies to murine proteins, serious infections in the previous 3 months, chronic infectious disease	ACR20 at the week 30 visit	54 weeks	NR

ACR: American College of Rheumatology. HAQ: Health Assessment Questionnaire, TNF: Tumor Necrosis Factor, CFB: Change from Baseline, MTX: Methotrexate

Table B33 presents an overview of baseline population and disease characteristics for the trials included in the MTC.

Across the studies similar demographics and HAQ scores at baseline were reported, except for the study by Kremer et al (2005) which presented a lower mean HAQ baseline value. The most likely reason for this low value is that the study used the m-HAQ instead of the traditional HAQ-DI. However, HAQ and m-HAQ scores are strongly correlated with a Pearson correlation coefficient of 0.88 (Uhlig et al 2006) and therefore could be used in the analyses.

The studies are not completely homogeneous in terms of patient and disease duration characteristics. Some studies (GO-FORWARD, RAPID I, RAPID II and TEMPO) reported shorter disease duration with a mean of between 4.5 and 6.8 years, while the other studies reported longer disease durations (with means between 7.3 and 13 years).

In terms of patient characteristics, the GO-FORWARD study included patients with a SJC of 11-13 compared with 16.9-23 for the other studies, and lower CRP levels (8-10 mg/l compared to 13-40 mg/l for the other studies).

In addition, patient eligibility criteria in the ARMADA (adalimumab), Weinblatt et al (etanercept), and ATTRACT (infliximab) trials only required patients to have a SJC and TJC of ≥6, respectively. These criteria are less severe than in other trials, and may reflect a less advanced state of RA (for example, in the AIM trial, eligible patients required ≥10 swollen joints and ≥12 tender joints).

These differences could explain potential differences in the observed relative treatment effects; however, the random effects approach was used to this heterogeneity take into account across trials.

Table B 33 Summary of the trials used to conduct the indirect comparison (baseline population and disease characteristics)

Trial (reference)	Treatment arm	RF status (% + ve)	Gender (%F)	Mean Age (y)	Mean Years since diag-nosis	Mean number of prior DMARDs	% pts with previous DMARD use other than MTX	%pts on NSAIDs	%pts on corticoid steroids	Mean TJC	Mean SJC	Mean Pts pain [1]	Mean Pts GA [2]	Mean Phs GA [3]	Mean HAQ-DI	Mean CRP (mg/l)	Mean ESR (mm/h)
Abatacept studies																	
AIM	Abatacept 10 mg/kg every 4 weeks +MTX	81.8	77.8	51.5	8.5	1.3		85.5	72.1	31.0	21.4	63.3	62.7	68.0	1.70	33	NR
	Placebo + MTX	78.5	81.7	50.4	8.9	1.2		82.6	68.5	32.3	22.1	65.9	62.8	67.4	1.70	28	
Kremer Phase 2b	Placebo + MTX	90.0	66.0	54.7	8.9	NR	21.0	NR	67.2	29.2	21.8	65.2	62.8	63.3	1.00	32	NR
	Abatacept 2 mg/kg every 4 weeks + MTX	90.0	63.0	54.4	9.7		18.1		67.6	28.2	20.2	64.5	59.4	61.0	1.00	32	
	Abatacept 10 mg/kg every 4 weeks + MTX	99.0	75.0	55.8	9.7		16.5		60.0	30.8	21.3	62.1	60.1	62.1	1.00	29	
ATTEST	Abatacept 10 mg/kg every 4 weeks + MTX	87.2	83.3	49.0	7.9	1.7		85.3	75.6	31.6	21.3	NR	NR	NR	1.80	31	49.4

[1] Patients assessment of pain (Pts Pain) 100 mm VAS
[2] Patients global assessment of disease activity (Pts GA) 100 mm VAS
[3] Physician global assessment of disease activity (Phs GA) 100 mm VAS

Trial (reference)	Treatment arm	RF status (% + ve)	Gender (%F)	Mean Age (y)	Mean Years since diag-nosis	Mean number of prior DMARDs	% pts with previous DMARD use other than MTX	%pts on NSAIDs	%pts on corticoid steroids	Mean TJC	Mean SJC	Mean Pts pain [1]	Mean Pts GA [2]	Mean Phs GA [3]	Mean HAQ-DI	Mean CRP (mg/l)	Mean ESR (mm/h)
	Placebo + MTX	77.3	87.3	49.4	8.4	1.8		84.5	70.0	30.3	20.1				1.80	27	47.0
	Infliximab 3mg/kg every 8 weeks + MTX	84.8	82.4	49.1	7.3	1.7		86.1	71.5	31.7	20.3				1.70	33	47.8
Adalimumab studies																	
ARMADA	Placebo + MTX	NR	82.3	56.0	11.1	3.0	NR	NR	NR	28.7	16.9	57.2	58.0	58.9	1.64	31	NR
	Adalimumab 20 mg every other week + MTX		75.4	53.5	13.1	3.0				28.5	17.6	55.1	57.6	60.5	1.52	28	
	Adalimumab 40 mg every other week + MTX		74.6	57.2	12.2	2.9				28.0	17.3	53.0	56.9	58.7	1.55	21	
	Adalimumab 80 mg every other week + MTX		75.3	55.5	12.8	3.1				30.3	17.0	55.0	58.8	62.6	1.55	28	
DE019	Adalimumab 40 mg every other week + MTX	81.6	76.3	56.1	11.0	2.4	NR	NR	NR	27.3	19.3	55.9	52.7	62.0	1.45	18	NR

Trial (reference)	Treatment arm	RF status (% + ve)	Gender (%F)	Mean Age (y)	Mean Years since diag-nosis	Mean number of prior DMARDs	% pts with previous DMARD use other than MTX	%pts on NSAIDs	%pts on corticoid steroids	Mean TJC	Mean SJC	Mean Pts pain [1]	Mean Pts GA [2]	Mean Phs GA [3]	Mean HAQ-DI	Mean CRP (mg/l)	Mean ESR (mm/h)
	Adalimumab 20 mg weekly + MTX	81.2	75.5	57.3	11.0	2.4				27.9	19.6	55.2	51.9	61.6	1.44	14	
	Placebo + MTX	89.5	73.0	56.1	10.9	2.4				28.1	19.0	56.3	54.3	61.3	1.48	18	
Certolizumab Pegol studies																	
RAPID I	Placebo + MTX	82.8	83.9	52.2	6.2	1.4	NR	NR	NR	29.8	21.2	NR	NR	NR	1.70	16	45.0
	CZP 200 mg every other week + MTX	79.6	82.4	51.4	6.1	1.3				30.8	21.7				1.70	16	43.5
	CZP 400 mg every other week + MTX	83.6	83.6	52.4	6.2	1.3				31.1	21.5				1.70	14	42.5
RAPID II	Placebo + MTX	78.2	84.3	51.5	5.6	1.2	NR	NR	NR	30.4	21.9	59.9	59.9	65.7	1.60	14	40.8
	CZP 200 mg every other week + MTX	77.5	83.7	52.2	6.1	1.2				30.1	20.5	61.8	62.4	64.3	1.60	14	43.7
	CZP 400 mg every other week + MTX	75.5	78.0	51.9	6.5	1.3				30.0	21.0	60.5	61.1	62.8	1.60	13	39.1
Etanercept studies																	

Trial (reference)	Treatment arm	RF status (% + ve)	Gender (%F)	Mean Age (y)	Mean Years since diag-nosis	Mean number of prior DMARDs	% pts with previous DMARD use other than MTX	%pts on NSAIDs	%pts on corticoid steroids	Mean TJC	Mean SJC	Mean Pts pain [1]	Mean Pts GA [2]	Mean Phs GA [3]	Mean HAQ-DI	Mean CRP (mg/l)	Mean ESR (mm/h)
Weinblatt *et al* 1999	Placebo + MTX	90.0	73.0	53.0	13.0	2.8	NR	80.0	70.0	28.0	17.0	56.0	60.0	65.0	1.50	26	36.0
	Etanercept 25 mg twice weekly + MTX	84.0	90.0	48.0	13.0	2.7		75.0	53.0	28.0	20.0	50.0	60.0	60.0	1.50	22	25.0
TEMPO	Placebo + MTX	71.0	79.0	53.0	6.8	2.3		86.0	64.0	33.1	22.6	NR	NR	NR	NR	26	NR
	Etanercept 25 mg twice weekly	75.0	77.0	53.2	6.3	2.3		88.0	57.0	35.0	23.0					32	
	Etanercept 25 mg twice weekly + MTX	76.0	74.0	52.5	6.8	2.3		88.0	62.0	34.2	22.1					30	
Golimumab studies																	
GO-FORWARD	Placebo + MTX	81.2	82.0	52.0	6.5	NR	70.7	NR	NR	21.0	12.0	57.0	53.0	56.5	1.25	8	NR
	Golimumab 100 mg every 4 weeks	83.5	78.9	51.0	5.9		75.9			22.0	11.0	60.0	56.0	58.0	1.38	9	
	Golimumab 50 mg every 4 weeks + MTX	86.5	80.9	52.0	4.5		78.7			26.0	13.0	61.0	60.0	61.0	1.38	10	

Trial (reference)	Treatment arm	RF status (% + ve)	Gender (%F)	Mean Age (y)	Mean Years since diag-nosis	Mean number of prior DMARDs	% pts with previous DMARD use other than MTX	%pts on NSAIDs	%pts on corticoid steroids	Mean TJC	Mean SJC	Mean Pts pain [1]	Mean Pts GA [2]	Mean Phs GA [3]	Mean HAQ-DI	Mean CRP (mg/l)	Mean ESR (mm/h)
	Golimumab 100 mg every 4 weeks + MTX	84.3	80.9	50.0	6.7		75.3			23.0	12.0	64.0	59.0	61.0	1.38	9	
Infliximab studies																	
ATTRACT	Placebo + MTX	77.0	80.0	51.0	8.9	2.5	NR	72.0	64.0	24.0	19.0	67.0	62.0	65.0	1.80	30	NR
	Infliximab 3 mg/kg every 8 weeks +MTX	84.0	81.0	56.0	8.4	2.8		79.0	63.0	32.0	19.0	70.0	66.0	61.0	1.80	31	
	Infliximab 3 mg/kg every 4 weeks +MTX	80.0	77.0	51.0	7.2	2.6		76.0	53.0	31.0	20.0	69.0	57.0	62.0	1.80	20	
	Infliximab 10 mg/kg every 8 weeks +MTX	82.0	77.0	55.0	9.0	2.5		77.0	57.0	30.0	20.0	67.0	64.0	64.0	1.80	25	
	Infliximab 10 mg/kg every 4 weeks +MTX	82.0	73.0	52.0	8.7	2.5		68.0	65.0	35.0	23.0	66.0	60.0	60.0	1.50	24	

CRP: C-reactive protein; DMARD: disease-modifying antirheumatic drug; ESR: erythrocyte sedimentation rate; GA: global assessment; HAQ-DI: health assessment questionnaire - disability index; MTX: methotrexate; NSAID: non-steroidal anti-inflammatory drug; NR: not reported; Phs: physicians; Pts: patients; SJC: swollen joint count; TJC: tender joint count.

5.7.4 For the selected trials, provide a summary of the data used in the analysis.

The data used in the MTC analyses are presented below:

5.7.4.1 HAQ-DI CFB 24/26 weeks

The HAQ-DI CFB at 24/26 weeks for all the studies included in the MTC analyses are presented by treatment arm in Table B34.

5.7.4.2 ACR20 response 24/28 weeks

The ACR20 responses at 24/28 weeks for all the studies included in the MTC analyses are presented by treatment arm in Table B35.

5.7.4.3 ACR50 response 24/28 weeks

The ACR50 responses at 24/28 weeks for all the studies included in the MTC analyses are presented by treatment arm in Table B36.

5.7.4.4 ACR70 response 24/28 weeks

The ACR70 responses at 24/28 weeks for all the studies included in the MTC analyses are presented in Table B37.

Table B 34 HAQ-DI change from baseline at 24/26 weeks (input)

Trial	Placebo + MTX			Adalimumab + MTX			Certolizumab Pegol + MTX			Etanercept + MTX			Golimumab + MTX			Infliximab + MTX			Abatacept + MTX		
Treatment	**mean HAQ CFB**	**SD**	**No pts**	**mean HAQ CFB**	**SD**	**No pts**	**mean HAQ CFB**	**SD**	**No pts**	**mean HAQ CFB**	**SD**	**No pts**	**mean HAQ CFB**	**SD**	**No pts**	**mean HAQ CFB**	**SD**	**No pts**	**mean HAQ CFB**	**SD**	**No pts**
AIM	-0.40	0.59	219																-0.59	0.62	433
Kremer Phase 2b	-0.14	0.49	119																-0.42	0.49	115
ATTEST	-0.29	0.22	110													-0.53	0.29	165	-0.68	0.22	156
ARMADA	-0.27	0.57	62	-0.62	0.63	67															
DE019	-0.24	0.52	200	-0.56	0.52	207															
RAPID I	-0.17	0.56	199				-0.58	0.59	393												
RAPID II	-0.14	0.45	127				-0.50	0.47	246												
Weinblatt 1999	-0.40	0.49	30							-0.70	0.49	59									
TEMPO	-0.63	1.08	228							-0.89	1.08	231									
GO-FORWARD	-0.13	0.58	133										-0.47	0.55	89						
ATTRACT	-0.19	0.49	88													-0.31	0.49	86			

Note: r is the number of responders and n the total number of patients enrolled in the trial. MTX: methotrexate

Table B 35 ACR20 responses (input) at 24/28 weeks

Trial / Treatment	Placebo + MTX		Adalimumab + MTX		Certolizumab Pegol + MTX		Etanercept + MTX		Golimumab + MTX		Infliximab + MTX		Abatacept + MTX	
	r	*n*	*r*	*n*	*r*	*n*	*r*	*n*	*r*	*n*	*r*	*n*	*r*	*n*
AIM	87	219											294	433
Kremer Phase 2b	42	119											69	115
ATTEST	46	110									98	165	104	156
ARMADA	9	62	45	67										
DE019	59	200	131	207										
RAPID I	27	199			231	393								
RAPID II	11	127			141	246								
Weinblatt 1999	8	30					42	59						
TEMPO	167	228					188	231						
GO-FORWARD	37	133							53	89				
ATTRACT	18	88									42	86		

Note: *r* is the number of responders and *n* the total number of patients enrolled in the trial**.** MTX: methotrexate.

Table B 36 ACR50 responses (input) at 24/28 weeks

Trial	Placebo + MTX		Adalimumab + MTX		Certolizumab Pegol + MTX		Etanercept + MTX		Golimumab + MTX		Infliximab + MTX		Abatacept + MTX	
treatment	***r***	***n***	***r***	***n***	***r***	***n***	***r***	***n***	***r***	***n***	***r***	***n***	***r***	***n***
AIM	37	219											173	433
Kremer Phase 2b	14	119											42	115
ATTEST	22	110									61	165	63	156
ARMADA	5	62	37	67										
DE019	19	200	81	207										
RAPID I	15	199			146	393								
RAPID II	4	127			80	246								
Weinblatt 1999	1	30					23	59						
TEMPO	92	228					136	231						
GO-FORWARD	18	133							33	89				

Note: r is the number of responders and n the total number of patients enrolled in the trial. MTX: methotrexate

Table B 37 ACR70 responses (input) at 24/28 weeks

Trial	Placebo + MTX		Adalimumab + MTX		Certolizumab Pegol + MTX		Etanercept + MTX		Golimumab + MTX		Infliximab + MTX		Abatacept + MTX	
treatment	***r***	***n***	***r***	***n***	***r***	***n***	***r***	***n***	***r***	***n***	***r***	***n***	***r***	***n***
AIM	14	219											86	433
Kremer Phase 2b	2	119											19	115
ATTEST	10	110									40	165	32	156
ARMADA	3	62	18	67										
DE019	5	200	43	207										
RAPID I	6	199			84	393								
RAPID II	1	127			39	246								
Weinblatt 1999	0	30					9	59						
TEMPO	34	228					82	231						
GO-FORWARD	7	133							18	89				

Note: r is the number of responders and n the total number of patients in the trial. MTX: methotrexate

5.7.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

The data from the included studies were combined with Bayesian MTC techniques.

Before synthesising the evidence, an assessment of the evidence base for each analysis was made. The feasibility of the MTC was evaluated by means of a qualitative assessment of the comparability of the studies in terms of study design, treatments evaluated and patient population, and an evaluation of the quality of the network of studies.

All analyses were performed using a fixed effect and a random effects model. The optimal approach was dependent on the evidence base and the observed heterogeneity across the studies, (see Section 5.7.7). In addition, the choice for a fixed effect and random effects was justified using statistical measures based on the goodness of fit of the model to the data.

All analyses were performed with WinBUGS 1.4 statistical software. The programming codes used in the analyses are provided in Appendix 4, Section 9.4.8.

5.7.6 Please present the results of the analysis.

The results from the indirect comparison are presented below.

In summary, the analysis of HAQ CFB at 24/26 weeks showed that abatacept + MTX is expected to be more efficacious than placebo + MTX and is expected to show a comparable efficacy relative to most other biologic DMARDs, with numerical differences ranging from -0.11 versus infliximab to 0.09 versus certolizumab pegol (See Section 5.7.6.1, Table B38). For biologic agents in combination with MTX, the absolute CFB is expected to range from -0.46 (infliximab) to 0.65 (certolizumab) (See Section 5.7.6.2, Table B39).

From our analysis, we can expect all biologic agents considered in this appraisal to result in comparable proportions of ACR20/50/70 responders, although the findings show that certolizumab pegol is expected to have a slightly higher ACR20 response rate than other biologic DMARDs. (See Section 5.7.6.3 to 5.7.6.8, Tables B40-45)

The TEMPO trial appeared to have included a slightly different patient population and reported different placebo responses than the other trials. Excluding the TEMPO trial from the analyses did improve the results for etanercept for the ACR50 analysis, but did

not lead to a difference in the interpretation of the results. (results not reported)

5.7.6.1 HAQ CFB results at 24/26 weeks

Table B38 presents an overview of the relative efficacy of treatments versus abatacept + MTX for the HAQ CFB at 24/26 weeks.

Table B 38 Relative efficacy versus abatacept + MTX for the HAQ change from baseline at 24/26 weeks

Treatment effect relative to abatacept + MTX	Relative difference in mean HAQ CFB	2.5% CrL	97.5% CrL
Placebo + MTX	-0.30	-0.42	-0.16
Adalimumab + MTX	0.03	-0.17	0.26
Certolizumab Pegol + MTX	0.09	-0.11	0.29
Etanercept + MTX	-0.02	-0.25	0.22
Golimumab + MTX	0.04	-0.23	0.32
Infliximab + MTX	-0.11	-0.30	0.10

Note: based on a random effects model. CrL: Credibility limit

5.7.6.2 Adjusted mean HAQ CFB at 24/26 weeks

Table B39 presents an overview of the adjusted mean HAQ CFB for all treatments at 24/26 weeks.

Table B 39 Adjusted mean HAQ change from baseline at 24/26 weeks

Treatment	Adjusted mean HAQ CFB	2.5%CrL	97.5%CrL
Placebo + MTX	-0.27	-0.30	-0.24
Adalimumab + MTX	-0.60	-0.78	-0.43
Certolizumab Pegol + MTX	-0.65	-0.81	-0.50
Etanercept + MTX	-0.55	-0.74	-0.36
Golimumab + MTX	-0.61	-0.85	-0.36
Infliximab + MTX	-0.46	-0.62	-0.30
Abatacept + MTX	-0.57	-0.69	-0.43

Note: random effects model. CrL: Credibility limit

5.7.6.3 ACR20 responses at 24/28 weeks

Table B40 presents an overview of the relative efficacy of treatments versus abatacept + MTX for ACR20 at 24/28 weeks

Table B 40 Relative efficacy for abatacept versus alternatives for ACR20 at 24/28 weeks

Treatment effect relative to abatacept + MTX	Relative risk	2.5% CrL	97.5% CrL	Odds ratio	2.5% CrL	97.5% CrL
Placebo + MTX	1.90	1.24	2.57	3.00	1.37	6.42
Adalimumab + MTX	0.77	0.46	1.17	0.49	0.12	1.51
Certolizumab Pegol + MTX	0.67	0.42	0.96	0.27	0.07	0.88
Etanercept + MTX	1.06	0.57	1.91	1.14	0.28	3.53
Golimumab + MTX	0.90	0.51	2.00	0.77	0.16	3.64
Infliximab + MTX	1.06	0.59	1.94	1.13	0.31	3.66

Note: random effects model. CrL: Credibility limit

5.7.6.4 Adjusted proportion for ACR20 at 24/28 weeks

Table B41 presents an overview of the adjusted proportion for ACR20 for all treatments at 24/28 weeks.

Table B 41 Adjusted proportion for ACR20 at 24/28 weeks

Treatment	Adjusted % patients with ACR20 response	2.5%CrL	97.5%CrL
Placebo + MTX	28.5%	25.5%	31.6%
Adalimumab + MTX	71.3%	50.0%	87.7%
Certolizumab Pegol + MTX	81.9%	63.3%	92.1%
Etanercept + MTX	51.6%	29.9%	76.0%
Golimumab + MTX	61.0%	27.9%	85.6%
Infliximab + MTX	51.9%	28.9%	74.0%
Abatacept + MTX	54.8%	34.6%	71.3%

Note: random effects model.

5.7.6.5 ACR50 responses at 24/28 weeks

Table B42 presents an overview of the relative efficacy of treatments versus abatacept + MTX for ACR50 at 24/28 weeks

Table B 42 Relative efficacy for abatacept versus alternatives for ACR50 at 24/28 weeks

Treatment effect relative to Abatacept + MTX	Relative risk	2.5% CrL	97.5% CrL	Odds ratio	2.5% CrL	97.5% CrL
Placebo + MTX	2.62	1.24	4.95	3.36	1.28	9.22
Adalimumab + MTX	0.59	0.23	1.43	0.40	0.07	1.79
Certolizumab Pegol + MTX	0.55	0.22	1.32	0.34	0.06	1.59
Etanercept + MTX	1.00	0.28	2.46	0.99	0.12	3.60
Golimumab + MTX	0.92	0.30	4.24	0.88	0.12	6.57
Infliximab + MTX	1.22	0.37	6.33	1.33	0.20	10.19

Note: random effects model

5.7.6.6 Adjusted proportion for ACR50 at 24/28 weeks

Table B43 presents an overview of the adjusted proportion for ACR 50 for all treatments at 24/28 weeks.

Table B 43 Adjusted proportion for ACR50 at 24/28 weeks

Treatment	Adjusted % patients with ACR50 response	2.5%CrL	97.5%CrL
Placebo + MTX	11.7%	9.1%	14.2%
Adalimumab + MTX	53.5%	24.7%	80.0%
Certolizumab Pegol + MTX	57.0%	27.3%	81.8%
Etanercept + MTX	31.4%	14.2%	69.7%
Golimumab + MTX	34.1%	7.6%	73.0%
Infliximab + MTX	25.5%	5.0%	62.0%
Abatacept + MTX	31.3%	13.5%	52.7%

Note: random effects model

5.7.6.7 ACR70 responses at 24/28 weeks

Table B44 presents an overview of the relative efficacy of treatments versus abatacept + MTX for ACR70 at 24/28 weeks

Table B 44 Relative efficacy for abatacept versus alternatives for ACR70 at 24/28 weeks

Treatment effect relative to abatacept + MTX	Relative risk	2.5% CrL	97.5% CrL	Odds ratio	2.5% CrL	97.5% CrL
Placebo + MTX	3.72	1.50	10.52	4.18	1.53	15.12
Adalimumab + MTX	0.52	0.15	2.57	0.44	0.08	3.18
Certolizumab Pegol + MTX	0.43	0.11	1.75	0.32	0.05	2.05
Etanercept + MTX	0.99	0.16	3.81	0.99	0.09	4.83
Golimumab + MTX	0.90	0.19	7.48	0.88	0.10	9.65
Infliximab + MTX	1.02	0.25	9.24	1.03	0.16	11.88

Note: random effects model

5.7.6.8 Adjusted proportion for ACR70 at 24/28 weeks

Table B45 presents an overview of the adjusted proportion for ACR 70 for all treatments at 24/28 weeks.

Table B 45 Adjusted proportion for ACR70 at 24/28 weeks

Treatment	Adjusted % patients with ACR70 response	2.5%CrL	97.5%CrL
Placebo + MTX	3.8%	2.3%	5.1%
Adalimumab + MTX	27.8%	7.3%	58.6%
Certolizumab Pegol + MTX	34.1%	11.0%	69.6%
Etanercept + MTX	14.5%	5.1%	54.3%
Golimumab + MTX	16.0%	2.2%	54.6%
Infliximab + MTX	13.9%	1.7%	43.8%
Abatacept + MTX	14.4%	5.0%	33.5%

Note: random effects model

5.7.7 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

As with any meta-analysis, an MTC can be performed with a fixed effects approach or a random effects approach. Both approaches were used in this MTC.

With a fixed effects model it is assumed that differences in true relative treatment effects (whether estimated directly or indirectly) are only caused by the difference in treatment and no other factors. That is, there is no heterogeneity in the true relative treatment effects beyond those caused by differences in the interventions compared.

In contrast, with a random effects model, differences in the true study-specific treatment effects (beyond the differences attributable to the actual interventions compared) are interchangeable and the heterogeneity is constant between the different comparisons.

The choice of using a fixed or random effects model was based on the "goodness of fit" of the model to the data. The "goodness of fit" was estimated by calculating the *residual deviance,* defined as the difference between the deviance for the fitted model and the deviance for the saturated model, where the deviance measures the fit of the model to the data points using the likelihood function. Under a null hypothesis, (i.e. the model provides an adequate fit to the data), it is expected that residual deviance would have a mean equal to the number of data points (Congdon et al 2003). For each outcome measure evaluated, the model with the residual deviance closest to the number of data points was chosen.

Based on the residual difference criteria, the random effects approach was deemed more appropriate, and so was used for all base case analyses. The main rationale was to account for the heterogeneity across trials and the difference in patient characteristics described in Section 5.7.3. However, when the TEMPO trial was excluded from the MTC evidence base during scenario analyses, the heterogeneity observed in the ACR20, ACR50, and ACR70 responder analyses was considerably reduced. Therefore, based on the residual deviance, the fixed effects model was considered to be more appropriate, and produced smaller credible intervals around the point estimate.

5.7.8 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

The TEMPO trial may have included a different study population compared with the other studies, as the patient population included did not consist of inadequate responders to MTX, rather they were inadequate responders to conventional DMARDs.

In addition, the TEMPO trial evaluated etanercept in combination with MTX. Therefore, patients effectively changed their treatment from a conventional DMARD to MTX in the placebo treatment group, potentially explaining the high placebo response observed.

In particular, TEMPO reported a high HAQ CFB at 24/26 weeks in the placebo arm (-0.63). The placebo HAQ CFB from the other trials ranged from -0.13 to -0.40, while active treatment data ranged from -0.40 to -0.89 overall. This observed high placebo response could be explained by the fact that MTX is considered to have a greater efficacy than a placebo, meaning the observed impact on difference in placebo results across trials could have an impact on the relative treatment effect.

In summary, the inclusion of the TEMPO trial could raise a comparability issue and bias relative treatment effect estimates. In order to evaluate the impact of the inclusion of the TEMPO trial in the analysis a scenario analysis was performed excluding this trial from the evidence base.

As discussed in the previous section, excluding the TEMPO trial from the analyses did have some impact on the results for etanercept for the ACR50 analysis, but did not lead to a difference in the interpretation of the results.

The other differences across the trials were not expected to impact the estimation of relative effects. The random effects approach should be sufficient for handling the heterogeneity across the trials.

5.7.9 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

When comparing interventions, it is always preferable to obtain direct evidence from randomised clinical trials. For our current decision problem, no such evidence was available to compare abatacept with other biological therapies; therefore an indirect comparison was performed. To evaluate the consistency of the MTC results, the adjusted mean HAQ CFB for each therapy against placebo + MTX can be compared to the direct results found in the literature. Overall, the results from the indirect comparison are in line with the extracted change in HAQ from the clinical trials.

For example, in the case of abatacept, the pooled estimate from AIM (-0.59), Kremer Phase 2b (-0.42), and ATTEST (-0.68) was a -0.56 HAQ CFB, whilst the MTC provided a -0.57 adjusted mean HAQ CFB.

Similarly, for adalimumab, the ARMADA and DE019 trials provided a mean HAQ CFB of -0.62 and -0.56, respectively, whilst the MTC estimated a -0.60 HAQ CFB against placebo + MTX.

Finally, when comparing the relative mean difference in HAQ CFB at 24/26 weeks for abatacept obtained from the meta-analysis and MTC, the results are in line with each other (at -0.25 and -0.30 respectively).

5.8 Non-RCT evidence

The findings from the non-RCTs are in line with the RCT evidence and mixed treatment analyses described previously. Abatacept shows a positive effect against a range of accepted clinical endpoints. The results show that abatacept shows superior efficacy when compared with placebo for the efficacy measurements ACR20, 50 and 70 and DAS28 as well as; HAQ-DI, SF-36 HrQol and radiographic progression over time. The results of the non-RCT studies show that treatment effect is maintained over a period up to 7 years

5.8.1 If non-RCT evidence is considered (see section 5.2.7), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.6 and 9.7, appendices 6 and 7.

The AIM long term extension (LTE) study is reported up to 4 years beyond the end of double blind RCT trial period.

The Kremer Phase 2b LTE study is reported up to 6 years beyond the end of the double blind RCT trial period.

The ATTEST LTE study is reported up to 1 year beyond the end of the double blind RCT trial period.

For the Kremer Phase 2b trial three publications were available (Genant et al 2008; Kremer et al 2008; Westhovens et al 2009).

In addition, for LTE data of AIM, ATTEST and Kremer Phase 2b, the Clinical Study Reports (CSRs) were used.

5.8.1.1 Study methodology

The study methodology for the LTE trials is presented in Table B46 and for the integrated analyses in Table B47.

Table B 46 Study methodology for LTE trials

	Genant et al 2008 and Kremer 2008 Krermer 2009 (poster) Genant et al 2009 (poster) Kremer 2010 (ACR abstract) LTE of the AIM trial	Westhovens 2009 Westhovens 2009 (poster) LTE of the Kremer Phase 2b trial	ATTEST
	Abatacept	**Abatacept**	
Location	116 centres worldwide (USA, UK, Canada, Mexico, Poland, Belgium)	Multicentre (NR)	86 sites worldwide (US, Europe, Canada, Australia, South America and South Africa)
Design	All patients who enrolled the LTE phase, including patients originally randomised to placebo, received abatacept approximating 10mg/kg (according to weight range) in addition to MTX background	All patients who completed the 1 year DB period were eligible to enter the open-label LTE period and enrolled to abatacept approximating 10mg/kg (according to weight range) in addition to MTX background	Randomised, double-blind, double-dummy, placebo-controlled. Treatment with placebo was limited to days 1–197. On day 198, placebo treated patients were reallocated to abatacept (with blinding maintained)
Duration of study	1 year DB + 4 year LTE	1 year DB + 6 years LTE	1 year With reallocation of placebo group to abatacept at 6 months + 2 years LTE
Method of randomisation	N/A All patients allocated to abatacept. Note: results presented thereafter are only based on all patients originally randomised to abatacept who entered the LTE	N/A All patients allocated to abatacept. Note: results presented thereafter are only based on all patients originally randomised to abatacept who entered the LTE	Central randomisation system. Randomised by centre in a 3:3:2 ratio to 6 months
Intervention(s) (n =)	abatacept 10mg/kg ever 4 weeks: n=539 form the n=547 completed the DB period	abatacept 10mg/kg ever 4 weeks: n=219 form the n=235 completed the DB period	abatacept (n=156), infliximab (n=165), and placebo (n=110)
Study outcomes	• ACR20, 50 and 70, % patients MCR and maintaining response • DAS 28, DAS 28 low activity and disease remission • Radiographic assessment • HRQOL: HAQ-DI response and CFB. SF-36, VAS, SPI • Safety	• ACR20, 50 and 70 response • DAS 28, DAS 28 low activity and disease remission • Radiographic assessment • HRQOL: m-HAQ response and CFB. SF-36 • Safety	• Reduction in DAS28 (ESR) with abatacept vs. placebo at 6 months
Inclusion criteria	Patients who completed the one year DB phase. They were required to have met the inclusion criteria in the RCT.	Patients who completed the one year DB phase. They were required to have met the inclusion criteria in the RCT.	• Age ≥18 years • Patients met the ACR criteria for RA, had RA for at least 1 year, had an inadequate response to MTX by ongoing disease activity • ≥10 swollen joints, • ≥12 tender joints, • CRP levels >1 mg/dl, • Received MTX ≥15 mg/week for ≥3 months prior to randomisation and washed out all other DMARDs, No prior experience of abatacept or anti-TNF therapy
Exclusion criteria	NR	No other biologic DMARDs and if they had required treatment for Myocobacterium TBC in the past 3 years	NR
ITT	Patients who received at least 1 infusion of abatacept during the long-term portion	Patients who were originally randomised to the abatacept 10mg/kg group and who	Patients who completed the 12 month, double-blind period if they continued to meet

	Genant et al 2008 and Kremer 2008 Krermer 2009 (poster) Genant et al 2009 (poster) Kremer 2010 (ACR abstract) LTE of the AIM trial	Westhovens 2009 Westhovens 2009 (poster) LTE of the Kremer Phase 2b trial	ATTEST
	Abatacept	Abatacept	
	were included in the efficacy analyses (ITT)	received at least 1 infusion of abatacept during the long-term portion were the only patients included in the efficacy analyses (ITT)	inclusion criteria and not meet any exclusion criteria

ACR: American College of Rheumatology; DAS: disease activity score; DB: double-blind, DMARD; disease-modifying anti-rheumatic drug; ITT: intention-to-treat; LTE: long-term extension; MTX: methotrexate; N/A: not applicable; NR: not reported; RCT: randomised clinical trial

Table B 47 Study methodology for integrated analyses

	Hochberg 2010 (ACR abstract) Becker 2010 (EULAR abstract) Smitten 2010 (EULAR abstract) Integrated analyses of safety data
	Abatacept
Location	Centres worldwide
Design	All patients who enrolled in abatacept RA clinical trials in the context of the abatacept RA clinical trial programme up to December 2009
Duration of study	Short-term periods included 3173 patients and long-term periods included 3256 patients. Mean (range) of exposure was 35.6 (1.9-104.2) months (Hochberg 2010) and 34.2 (1.9-94.0) months (Becker 2010, Smitten 2010).
Method of randomisation	6 studies were DB, PC, and randomised; 1 non-randomised Phase II study; 1 non-randomised Phase III study.
Intervention(s) (n =)	Abatacept (dosage not specified; or in combination not specified) n=4149
Study outcomes	• Adverse events • Serious adverse events • Serious infections • Malignancies • Mortality • Events of clinical/special interest
Inclusion criteria	Patients receiving ≥1 dose of abatacept
Exclusion criteria	NR

5.8.1.2 Baseline population and disease characteristics

The baseline characteristics, demographics and clinical characteristics for the population entering the long-term extension trial (AIM and phase IIB), were comparable to the patients who originally entered the treatment groups at randomisation.

5.8.1.3 Patient flow

Participant flow and patient numbers are depicted in Figure B26, Figure B27, and Figure B28 for the non-RCT evidence included in this submission.

LTE of AIM trial

- 539 patients entered the open-label period, 378 in the abatacept group and 161 in the placebo group.
- 51 patients discontinued primarily due to adverse events (19), lack of efficacy (12), and withdrawal of consent (11).
- 390 patients (72.4%) were still ongoing at the end of year five of the open-label period.

LTE of Kremer Phase 2b trial

- 219 patients entered the long-term extension period.
- 89 patients discontinued primarily due to adverse events (35), lack of efficacy (24), and withdrawal of consent (15).
- 114 patients (52.1%) were still ongoing at the end of the seventh year of the long-term extension period

LTE of the ATTEST trial

- 372 patients entered the long-term extension period
- 43 patients discontinued due to withdrawal of consent (12), adverse events (10) and lack of efficacy (9).
- 76 patients (20.4%) were still ongoing at the end of the 2 year long-term extension period.

Figure B 26 Participant flow in the LTE of the AIM trial

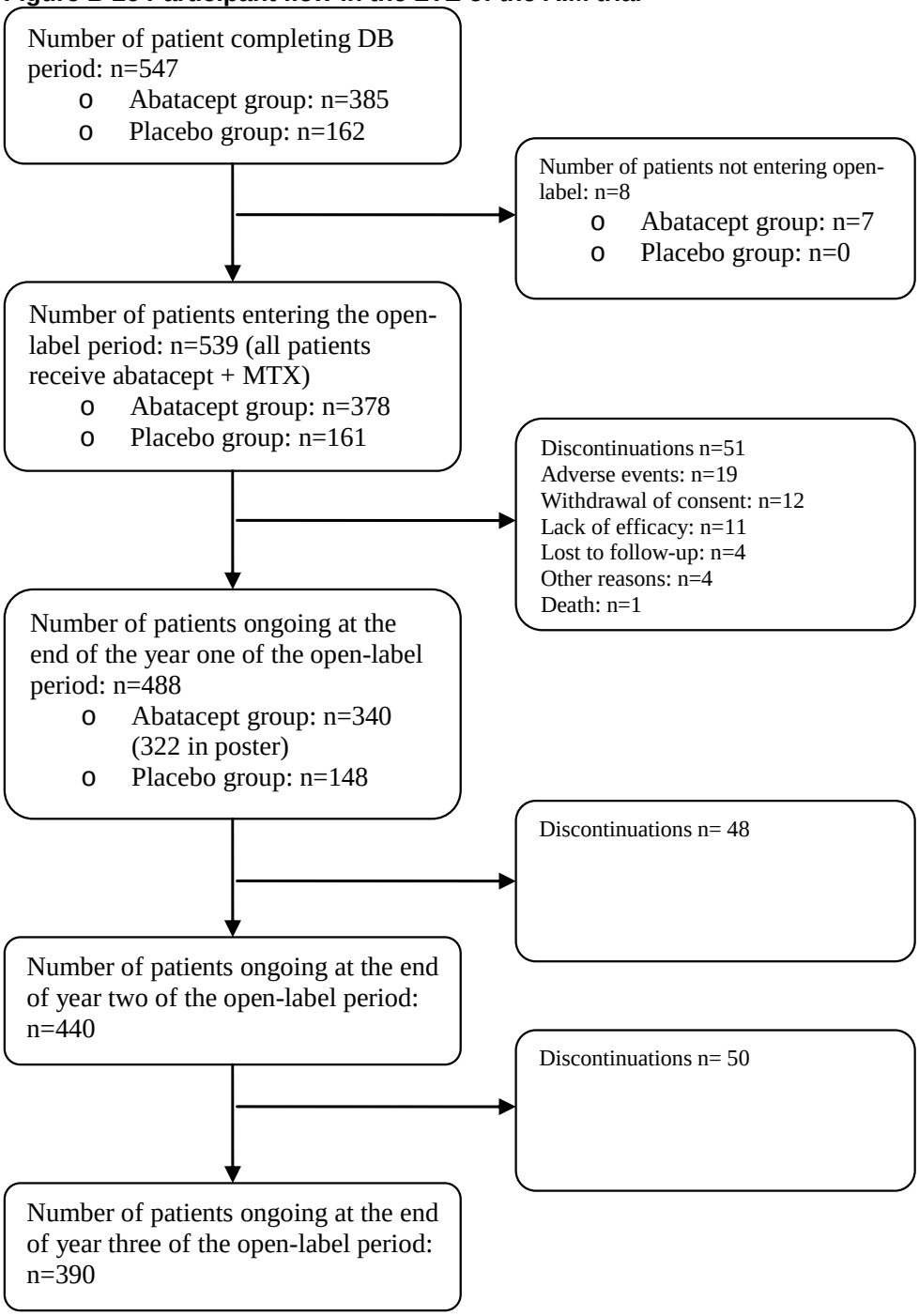


Figure B 27 Participant flow in the LTE of the Kremer Phase 2b study

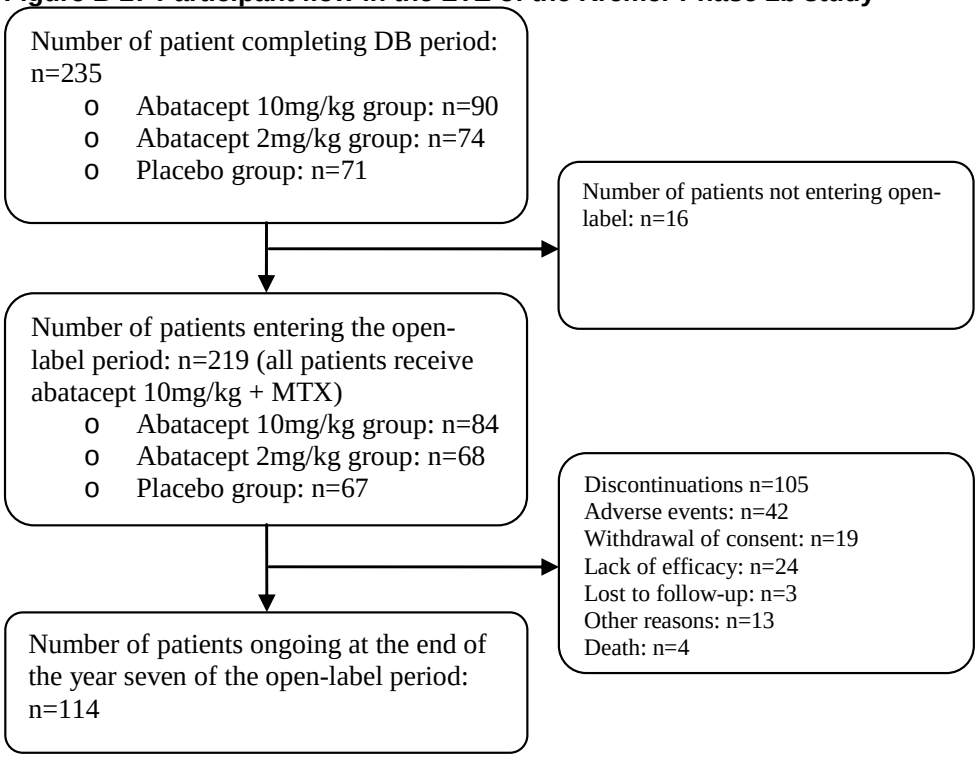
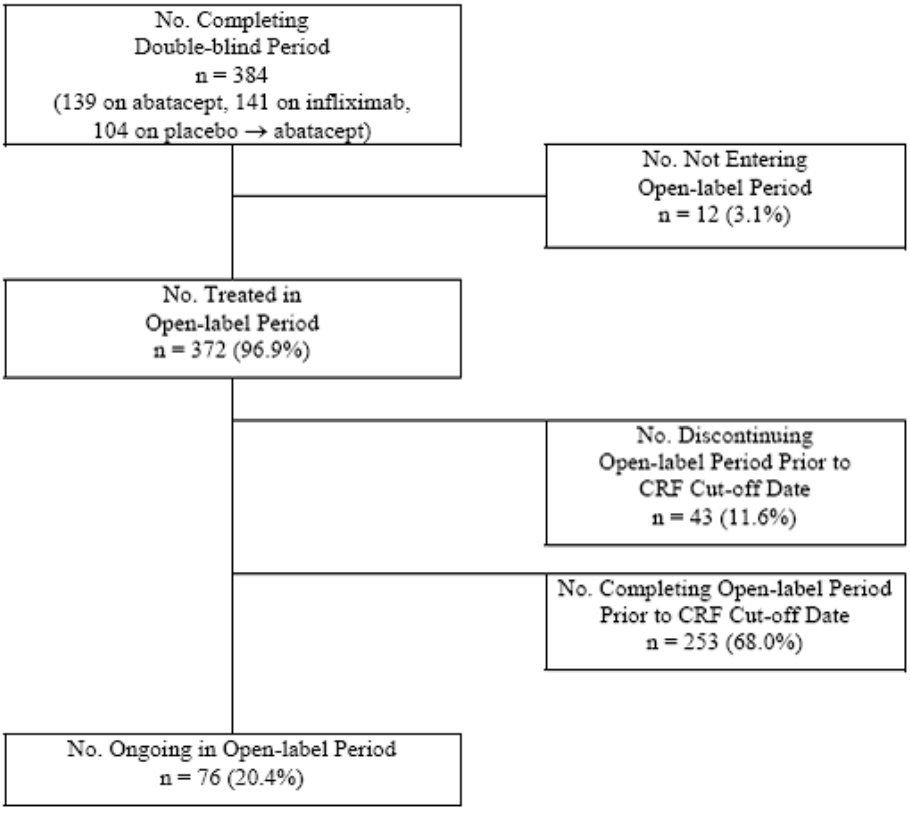


Figure B 28 Participant flow in the LTE of the ATTEST study



5.8.1.4 Results

After evaluating the clinical effectiveness data it was decided to present data from the most recent CSRs available. This was because the publications described previously were most posters (of which several iterations were available, offering different data "cuts" depending on the time of the symposium, and the audience at the symposium) or not formally published in a peer reviewed journal. Thus, the latest CSRs for the appropriate trials were felt to offer the most comprehensive and accurate data to date.

AIM 5-year data

The data presented below are the AIM data set at 5 years (1 year randomised treatment followed by 4 years' LTE data).

Approximately three quarters of patients that entered the LTE were still participating after 5 years in the AIM study, with 5% of discontinuations being due to lack of efficacy and 8.7% due to AEs. Yearly discontinuations were low.

Overall the data showed that the clinical improvements seen in the original abatacept group were maintained over the 5 year open-label extension period, while the original placebo group patients showed increases in clinical responses relative to the double blind period. Similar findings were observed in the patient reported outcomes.

Clinical endpoints

Table B 48 ACR 20/50/70 at Day 1821 (5 year data), number of subjects n/m (%)

	abatacept N=376	**placebo N = 160**
ACR20	224/268 (83.6%) (79.1, 88.0)	106/123 (86.2%) (80.1, 92.3)
ACR50	165/270 (61.1%) (55.3, 66.9)	75/123 (61.0%) (52.4, 69.6)
ACR70	107/270 (39.6%) (33.8, 45.5)	46/125 (36.8%) (28.3, 45.3)

n = Number of subjects with ACR responses, m = Number of subjects in the analysis.
Treatment groups represent treatment received in the double-blind period.

The ACR response rates (ACR20, 50, and 70) observed at the end of the double-blind period (Day 365) were maintained at the end of Year 4 (Day 1821) of the open-label period in the original abatacept group (CSR).

Increases in ACR20, 50, and 70 response rates relative to the end of the double-blind period were seen during the open-label period in the original placebo group after the start of abatacept treatment (CSR).

Table B 49 DAS 28 (CRP) at Day 1821 (5 year data) Mean Change from Baseline Over Time

	abatacept N=376	placebo N = 160
n	264	121
Baseline Mean (SD)	6.38 (0.81)	6.34 (0.76)
Post-baseline mean SD	3.24 (1.24)	3.08 (1.11)
Mean change from baseline (SE)	-3.14 (0.08)	-3.26 (0.12)
95% CI	(-3.31, -2.98)	(-3.49, -3.02)

n is the number of subjects with both baseline and post-baseline measurements.
Change from Baseline = Post-baseline - Baseline value.
Treatment groups represent treatment received in the double-blind period.

Improvements in DAS 28-CRP scores, as reflected by mean changes from baseline (Day 1), were maintained from the end of the double-blind period (Day 365) to Day 1821 (end of Year 4 of the open-label period) in the original abatacept group.

For the original placebo group (that went on to active treatment at 12 months), the mean changes from baseline in DAS 28-CRP scores increased during the open-label period to be comparable with those for the original abatacept group.

Figure B 29 Proportion of DAS28 (CRP) with low disease activity over the LTE period

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Figure 7.1.2A: Proportion of Subjects with DAS28 (CRP) Low Disease Activity Over Time: All Treated Subjects in the Open-label Period

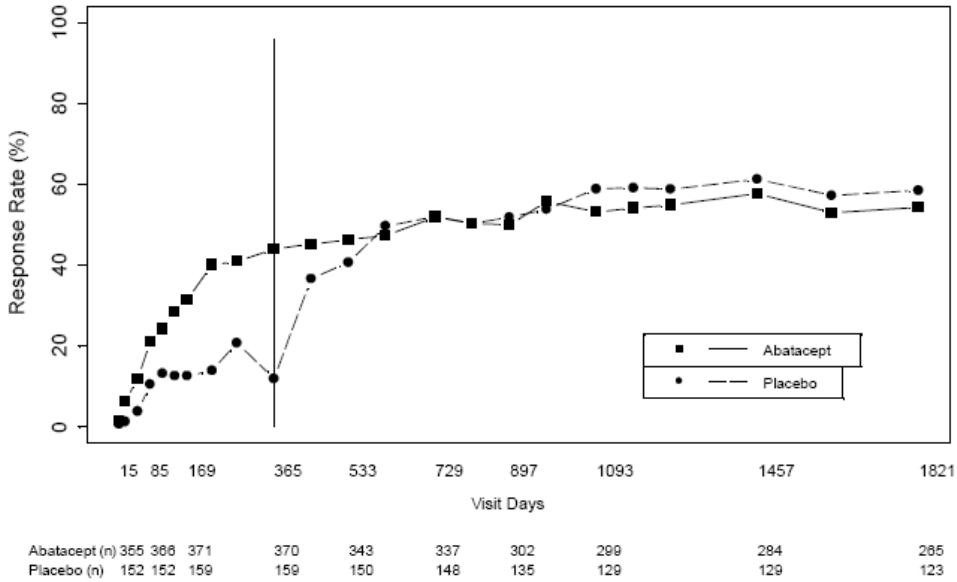
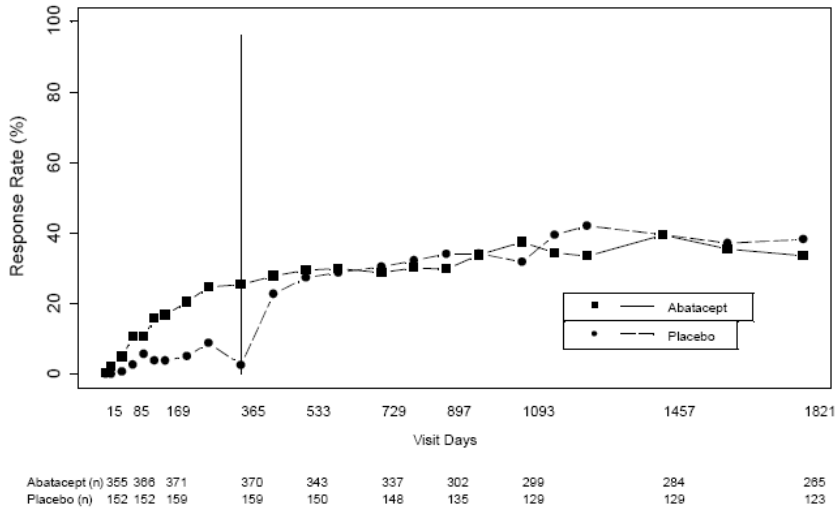


Figure B 30 Proportion of subjects with DAS28 (CRP) remission over the LTE period.

Figure 7.1.2B: Proportion of Subjects with DAS 28 (CRP) Remission Over Time: All Treated Subjects in the Open-label Period



Of the patients that were in the original abatacept group, 44.1% had achieved an LDAS and 25.4% were in remission at the end of the double blind period. At 5 years, of this group 54.7% had achieved an LDAS and 33.7% had achieved remission. These results were similar to those seen for the placebo group that was switched to active treatment at 6 months. In the original placebo group 40.7% had achieved an LDAS and 11.9% had achieved remission by the end of the double blind period. At 5 years 58.5% of subjects had achieved an LDAS and 38.2% had achieved remission.

Table B 50 DI at Day 1821 (5 year data)- Mean Change from Baseline

	abatacept N=376	**placebo N = 160**
n	271	125
Baseline Mean (SD)	1.68 (0.65)	1.69 (0.60)
Post-baseline mean SD	0.92 (0.68)	0.96 (0.66)
Mean change from baseline (SE)	-0.77 (0.04)	-0.72 (0.06)
95% CI	(-0.85, -0.68)	(-0.85, -0.60)

n is the number of subjects with both baseline and post-baseline measurements.
Change from Baseline = Post-baseline - Baseline value.
Treatment groups represent treatment received in the double-blind period.

The proportion of subjects with clinically meaningful improvements in physical function (defined as a reduction from baseline [Day 1] in HAQ score of at least 0.3 units) at Day 1821 (end of Year 4 of open-label period) was 74.2% for the original abatacept group. The HAQ responder rate for the original abatacept group at the end of the double-blind period (71.8%) was maintained during the open-label period. The proportion of subjects in the original placebo

group with clinically meaningful improvements in physical function at Day 1821 was 72.0%.

Table B 51 SF-36 at Day 1821 (5 year data)- Mean Change from Baseline

		abatacept N=376	placebo N = 160
Physical Component	n	271	124
	Baseline Mean (SD)	30.56 (6.83)	31.27 (7.42)
	Post-baseline mean SD	41.37 (9.92)	41.37 (9.70)
	Mean change from baseline (SE)	10.81 (0.63)	10.09 (0.91)
	95% CI	(9.57, 12.06)	(8.29, 11.89)
Mental Component	n	271	124
	Baseline Mean (SD)	41.41 (11.61)	40.03 (11.23)
	Post-baseline mean SD	48.17 (11.30)	47.06 (10.88)
	Mean change from baseline (SE)	6.75 (0.75)	7.03 (1.05)
	95% CI	(5.27, 8.24)	(4.95, 9.12)

n is the number of subjects with both baseline and post-baseline measurements.
Change from baseline = Post-baseline - Baseline.
Treatment groups represent treatment received in the double-blind period.

At Day 1821 (end of Year 4 of open-label period), mean improvements from baseline (Day 1) in the PCS and MCS scores, as well as for the individual SF-36 domains (8 component scores which make up the MCS and the PCS), were observed for the original abatacept and placebo groups.

AIM 5 year radiographic data

Changes from baseline in Erosion, Joint Space Narrowing (JSN), and Total scores indicated less progression of structural damage at the end of each year of the study (Year 1 to Year 5 [Year 4 of open-label period]) for the original abatacept group compared to the original placebo group.

At Day 1821 (end of Year 4 of open-label period), the mean change from baseline in the Erosion, JSN, and Total scores was 1.12, 0.90, and 2.02 units, respectively, for the original abatacept group and 2.05, 1.73, and 3.78 units, respectively, in the original placebo group.

Table B 52 Radiographic Results by Visit (Day 1821: All Treated Subjects in the Open-label Period)

		Abatacept n = 235	Placebo n = 115
Erosion Score			
	Mean Change from Baseline (SD)	1.12 (2.99)	2.05 (4.88)
Joint Space Narrowing			
	Mean Change from Baseline (SD)	0.90 (2.54)	1.73 (4.11)
Total Score			
	Mean Change from Baseline (SD)	2.02 (4.93)	3.78 (8.46)

n is the number of subjects with both baseline and post-baseline measurements.

When Erosion, JSN, and Total scores were analysed by mean change in score from the previous annual visit, there was less progression of structural damage in subjects treated with abatacept for the entire open-label treatment period relative to subjects initially treated with placebo for 1 year and then treated with abatacept.

A total of 45.1% of subjects in the original abatacept group and 39.1% of subjects in the original placebo group showed no radiographic progression (non-progression defined as change from baseline ≤ 0) based on Total score at Day 1821.

Table B 53 Proportion of Subjects without Radiographic Progression by Visit (Day 1821: All Treated Subjects in the Open-label Period)

		Abatacept N=376	Placebo N=160
ES Non-progression	Number of subjects n/m (%), 95% CI	120/235(51.1%) (44.7, 57.5)	51/115(44.3%) (35.3, 53.4)
JSNS Non-progression	Number of subjects n/m (%), 95% CI	147/235(62.6%) (56.4, 68.7)	60/115(52.2%) (43.0, 61.3)
TS Non-progression	Number of subjects n/m (%), 95% CI	106/235(45.1%) (38.7, 51.5)	45/115(39.1%) (30.2, 48.1)

n = Number of subjects without radiographic progression, m = Number of subjects in the analysis. ES=Erosion score, JSNS=Joint space narrowing score, TS=Total score

There was a greater proportion of non-progression in subjects who received abatacept during the entire treatment period relative to those who began treatment after receiving placebo for 1 year based on Erosion, JSN, and Total Scores.

Patient reported outcomes

Table B 54 Reduction of fatigue (VAS) (5 year data)

	abatacept N=376	placebo N = 160
n	261	125
Baseline Mean (SD)	62.45 (23.90)	65.00 (23.15)
Post-baseline mean SD	32.14 (26.74)	33.05 (24.49)
Mean change from baseline (SE)	-30.3 (1.83)	-32.0 (2.65)
95% CI	(-33.9, -26.7)	(-37.2, -26.7)

n is the number of subjects with both baseline and post-baseline measurements.
Change from baseline = Post-baseline - Baseline.
Treatment groups represent treatment received in the double-blind period.

The mean reduction in the fatigue VAS score observed at the end of the double-blind period for the original abatacept group (28.0) was maintained during the open-label period (mean reduction of 30.3 at Day 1821 [end of Year 4 of open-label period]). For the original placebo group, fatigue VAS scores improved during the open-label period. The mean reduction of fatigue VAS score was 22.6 at Day 365 and 32.0 at Day 1821 for the original placebo group.

Table B 55 Improvement in sleep quality (SPI) (5 year data)

	abatacept N=376	placebo N = 160
n	261	125
Baseline Mean (SD)	41.89 (20.48)	43.59 (20.00)
Post-baseline mean SD	31.24 (18.44)	34.50 (17.92)
Mean change from baseline (SE)	-10.6 (1.24)	-9.10 (1.50)
95% CI	(-13.1, -8.21)	(-12.1, -6.13)

n is the number of subjects with both baseline and post-baseline measurements.
Change from baseline = Post-baseline - Baseline.
Treatment groups represent treatment received in the double-blind period.

For the original abatacept group, the mean reduction in the SPI at the end of the double-blind period (Day 365) was 10.8, representing an improvement in sleep quality, and this improvement was maintained during the open-label period (mean reduction of 10.6 at Day 1821 [end of Year 4 of open-label period]). In the original placebo group, the reduction in the SPI at the end of the double-blind period (Day 365) was 7.97, representing less of an improvement in sleep quality than that seen for subjects initially assigned to abatacept. The improvement in sleep quality increased during the open-label period in this group after being switched to abatacept, with a mean reduction of 9.10 at Day 1821.

Kremer Phase 2b 7-year data

The data presented below are the Phase data set at 7 years (1 year randomised treatment followed by 6 years' LTE data)

Clinical endpoints

ACR 20/50/70 responses

A total of 114 (52.1%) of patients remained in the study at the end of 6 years, with only 24 (11.0%) discontinuing due to lack of efficacy. Clinically meaningful, durable and sustained ACR20, 50 and 70 responses were observed through to Day 2520 (Year 6).

Figure B 31 Proportion of patients with ACR20 response over time in the 7-year LTE

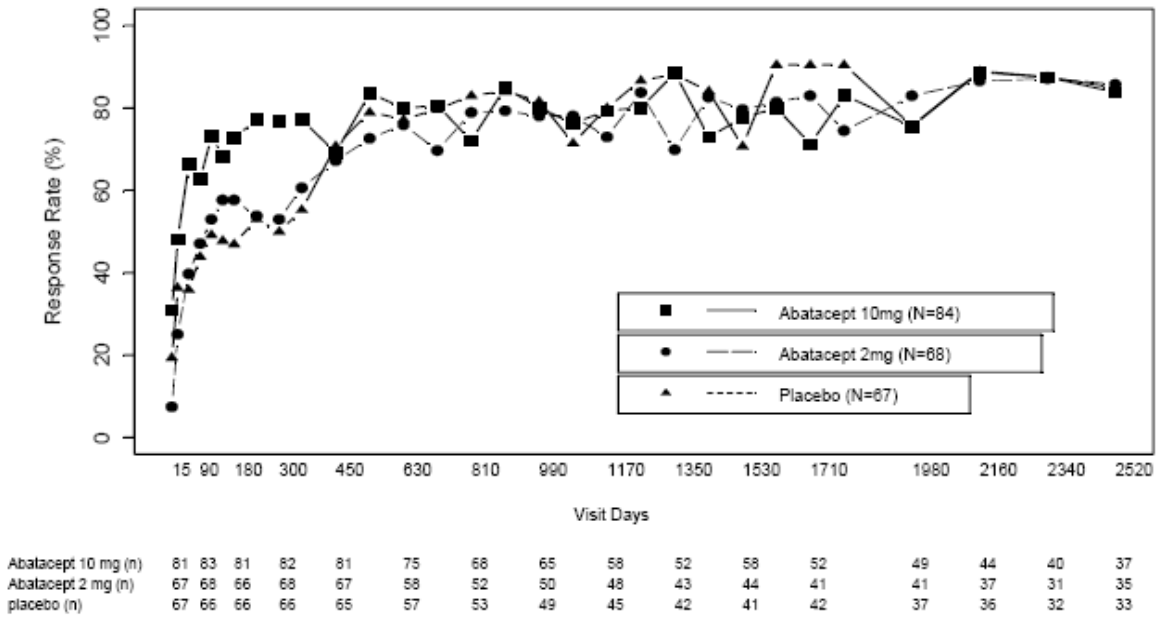


Figure B 32 Proportion of patients with ACR50 response over time in the 7-year LTE

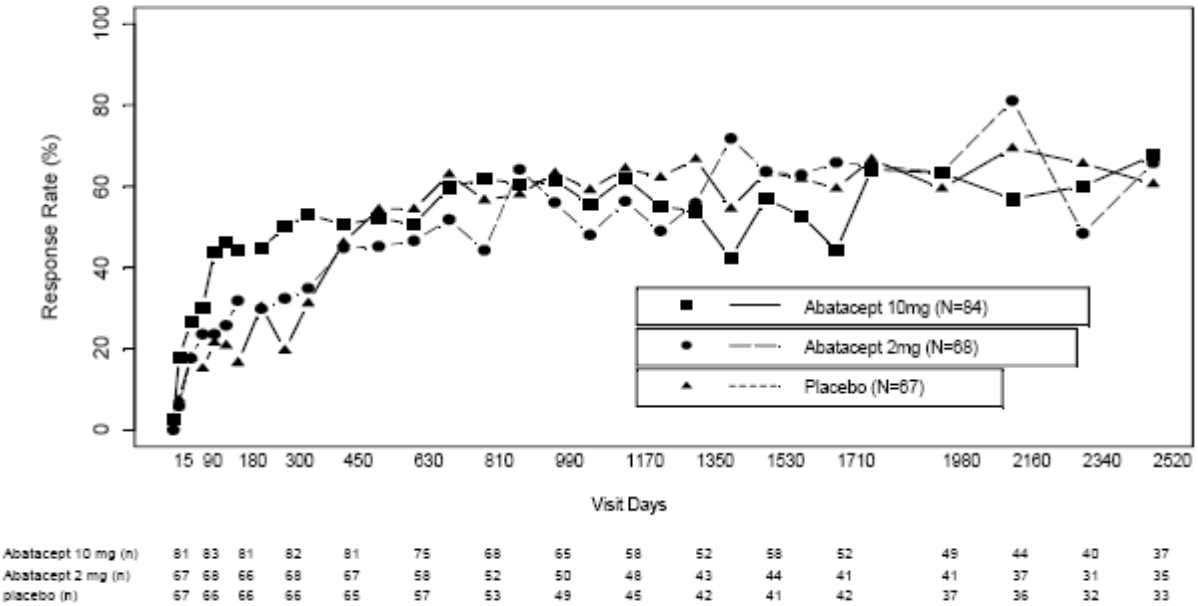
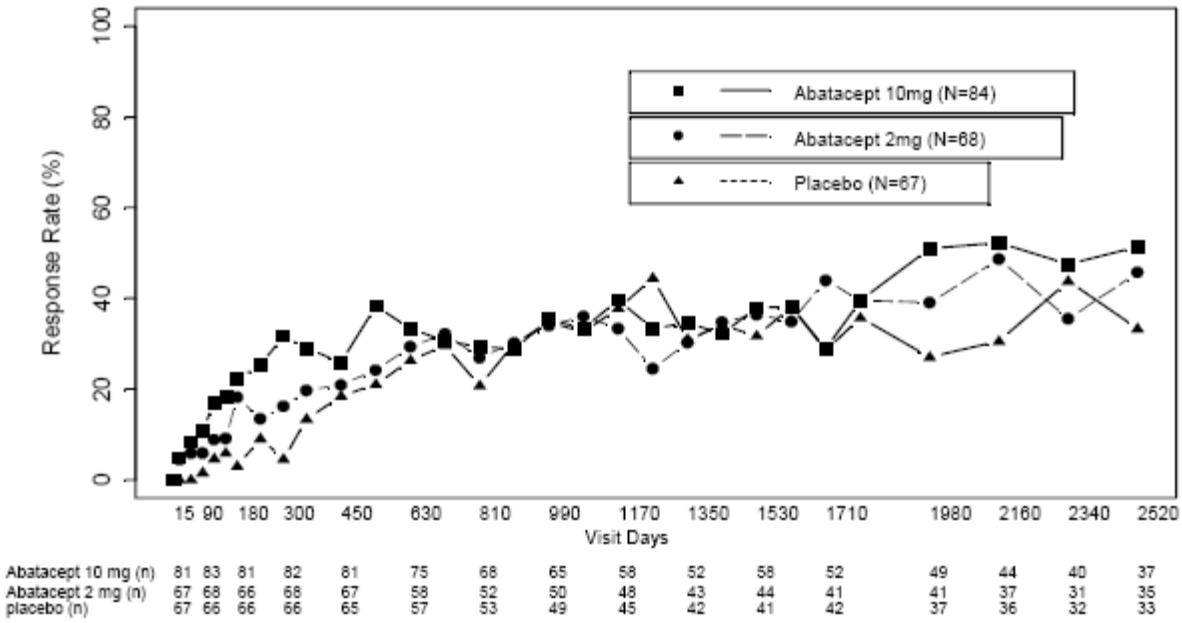


Figure B 33 Proportion of patients with ACR70 response over time in the 7-year LTE



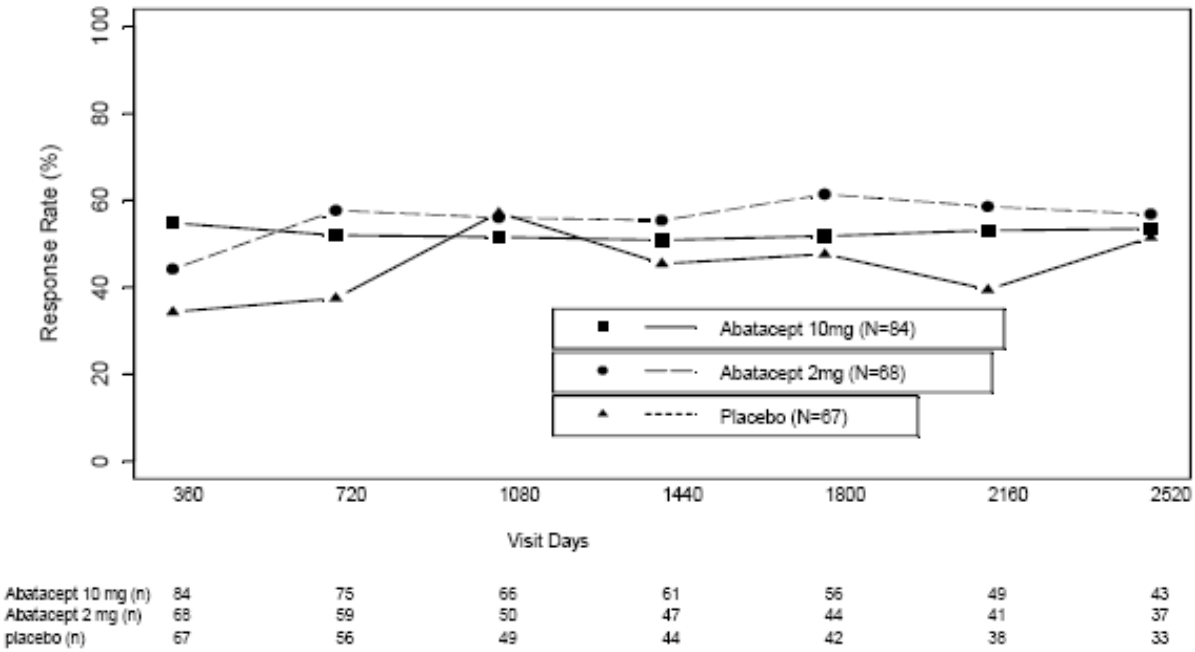
Physical function

HAQ scores

The proportion of patients with clinically meaningful improvements in physical function (defined as a reduction from baseline in mHAQ score of at least 03 units) at the end of year 6 (Day 2520) was 53.5% and 56.8% for the original 10mg/kg and 2 mg/kg abatacept groups respectively.

The mHAQ responder rate for the original abatacept groups from the double-blind period was maintained during the open-label period.

Figure B 34 Proportion of patients with HAQ response over time in the 7-year LTE



For the original placebo group the proportion of patients with clinically meaningful improvements in physical function at the end of Year 6 was 51.5%. The mHAQ responder rate for the original placebo group increased during the open-label period, and was comparable with the rate for the original abatacept group.

Health related outcomes

SF-36

At the end of Year 6 of the open label period improvements from baseline were observed in the Physical Component Summary (PCS) and Mental Component Summary (MCS), as well as in the 8 individual domains. The mean changes from baseline on Day 2520 in the PCS and MCS scores were 10.12 and 2.81 respectively for the original 10 mg/kg group and 8.26 and 7.34 respectively for the abatacept 2 mg/kg group.

Similar improvements were also observed for the original placebo group. The mean change from baseline in the PCS and MCS scores being 7.92 and 4.44, respectively.

Table B 56 SF-36 at Day 2520 (7 year data) Mean Change from Baseline

		abatacept 10mg/kg N=84	abatacept 2mg/kg N = 68	placebo N = 67
Physical Component	n	38	35	33
	Baseline Mean (SD)	31.93 (9.50)	32.75 (9.20)	32.54 (7.39)
	Post-baseline mean SD	42.04 (13.43)	41.01 (12.33)	40.46 (11.44)
	Mean change from baseline (SE)	10.12 (1.88)	8.26 (1.58)	7.92 (1.80)
	95% CI	(6.31, 13.93)	(5.04, 11.48)	(4.26, 11.58)
Mental Component	n	38	35	33
	Baseline Mean (SD)	46.35 (12.07)	42.53 (13.34)	44.51 (12.09)
	Post-baseline mean SD	49.16 (11.38)	49.87 (8.34)	48.95 (13.13)
	Mean change from baseline (SE)	2.81 (1.85)	7.34 (1.75)	4.44 (2.26)
	95% CI	(-0.94, 6.56)	(3.78, 10.91)	(-0.17, 9.05)

n is the number of subjects with both baseline and post-baseline measurements.
Change from baseline = Post-baseline - Baseline.
Treatment groups represent treatment received in the double-blind period.

ATTEST 2-year data

The data presented below are the Phase data set at 2 years (1 year randomised treatment followed by 1 years' LTE data)

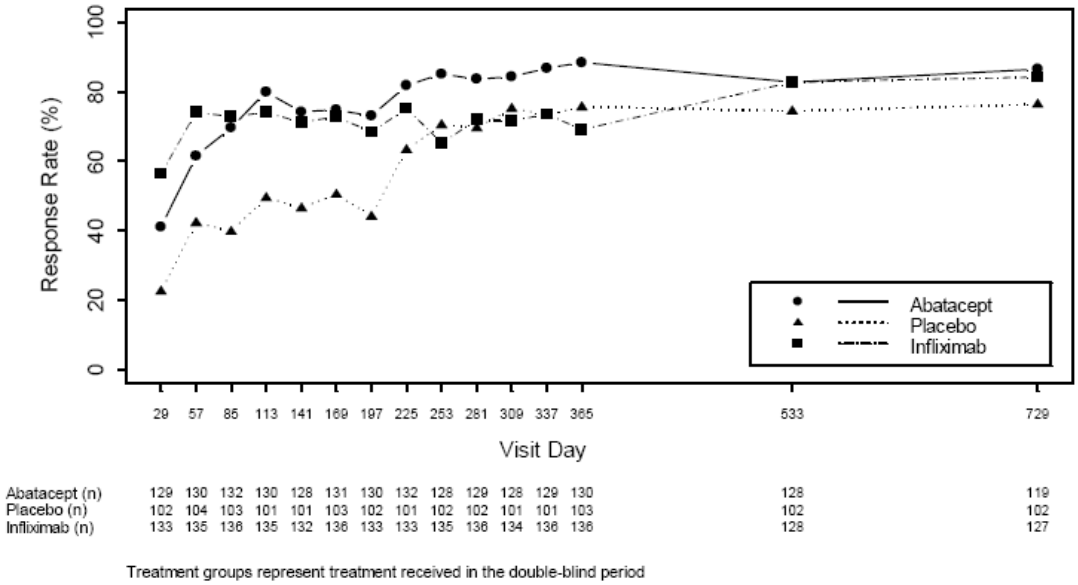
ACR20/50/70 responses

During the last 6 months of the double-blind period, patients in the placebo group were reallocated to treatment with abatacept. The ACR 20/50/70 response rates observed at the end of the double-blind period were maintained at the end of Year 2 (Day 729) of the open-label period for both the original abatacept and placebo groups.

In the infliximab group, increases in ACR20, 50 and 70 response rates, relative to the end of the double-blind period, were seen in the original infliximab group after the start of abatacept treatment.

Figure B 35 ACR20 response over time

Figure 7.1.1A: ACR 20 Response Rate Over Time for Subjects Entering Open-label Period



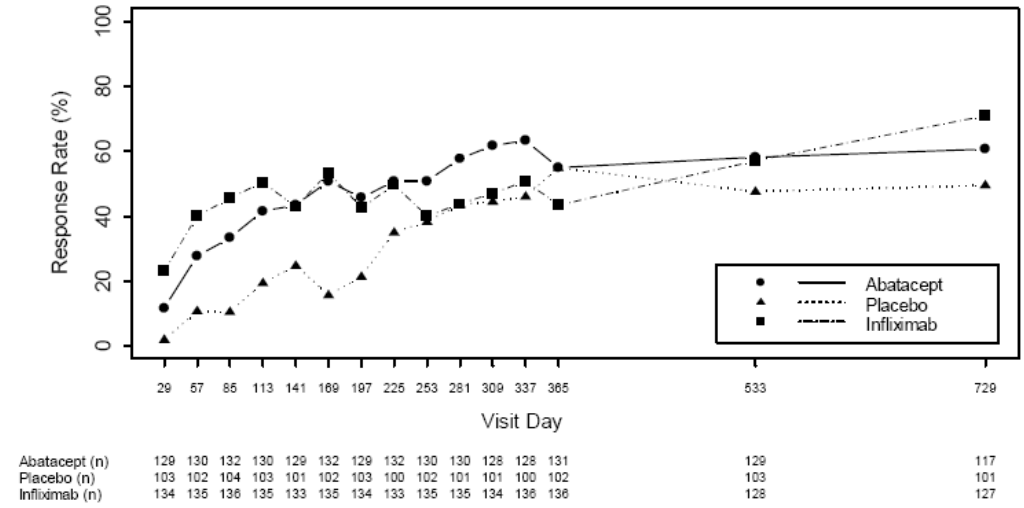
Abatacept (n)	129	130	132	130	128	131	130	132	128	129	128	129	130	128		119
Placebo (n)	102	104	103	101	101	103	102	101	102	102	101	101	103	102		102
Infliximab (n)	133	135	136	135	132	136	133	133	135	136	134	136	136	128		127

Treatment groups represent treatment received in the double-blind period

The ACR20 response rate in the original infliximab group was similar to that seen in the original abatacept group by Day 553 (Month 6 of open-label period), and this response rate was maintained through Day 729).

Figure B 36 ACR50 response over time

Figure 7.1.1B: ACR 50 Response Rate Over Time for Subjects Entering Open-label Period

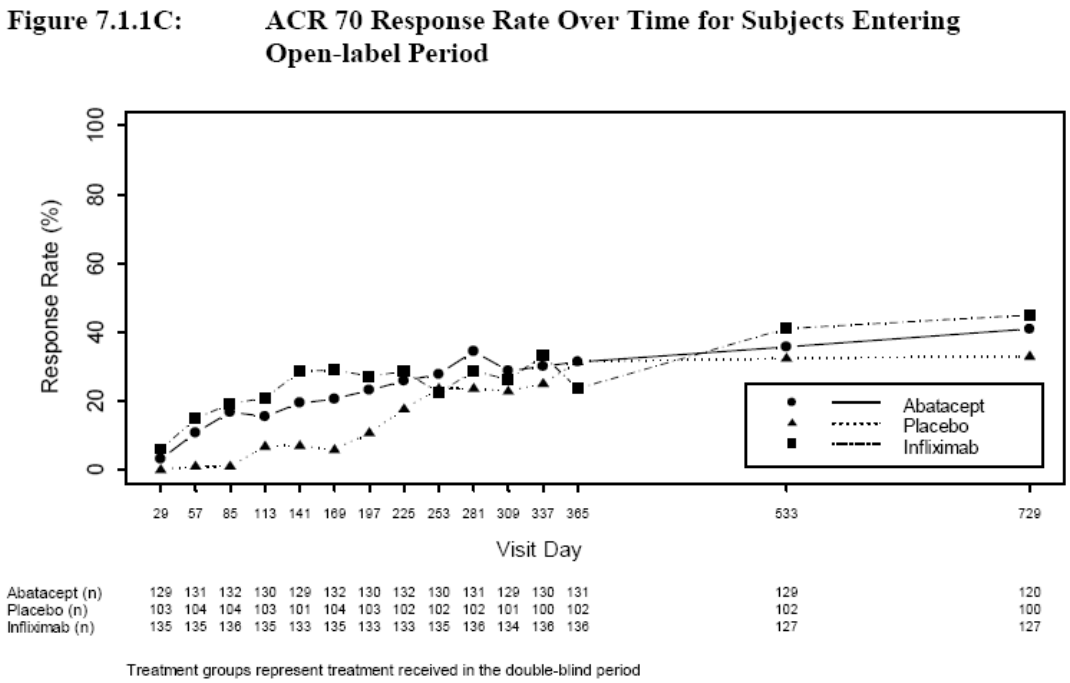


Abatacept (n)	129	130	132	130	129	132	129	132	130	130	128	128	131	129		117
Placebo (n)	103	102	104	103	101	102	103	100	102	101	101	100	102	103		101
Infliximab (n)	134	135	136	135	133	135	134	133	135	135	134	136	136	128		127

Treatment groups represent treatment received in the double-blind period

Within each of the original double-blind groups, the majority of subjects who demonstrated an ACR50 or ACR 70 response at Day 365 (end of double-blind period) continued to demonstrate the same level of ACR response at the end of the first year of the open-label period (Day 729).

Figure B 37 ACR70 response over time



Sustainability of response

Within each of the double-blind groups, the majority of subjects who demonstrated an ACR50 or ACR70 response at Day 365 (the end of the double-blind period) continued to demonstrate the same level of ACR response at the end of the first year of the open-label period (Day 729)

Table B 57 Proportion of patients with sustained ACR response at Day 729

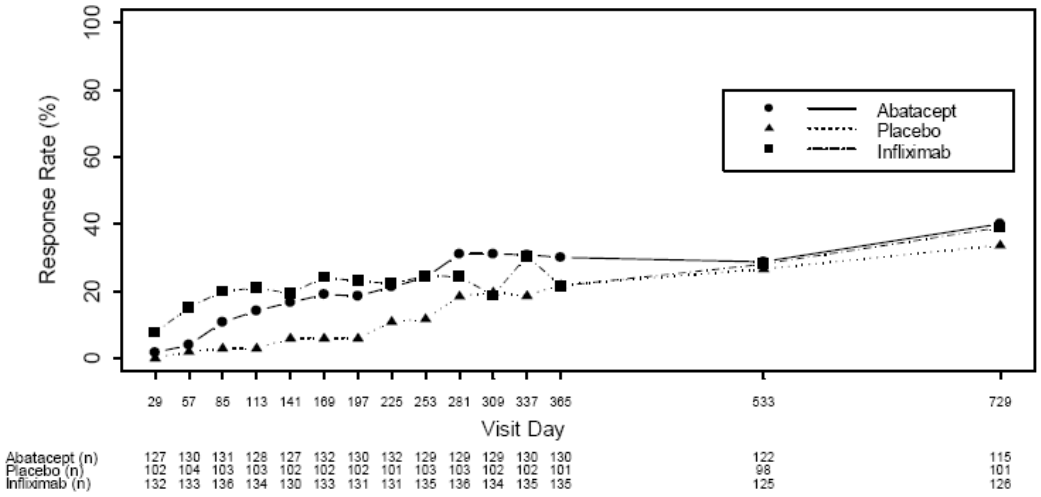
	Abatacept N=132	Infliximab N=136	Placebo N=104
Sustained ACR50 n/m (%) 95% CI	50/72(69.4%) (58.8, 80.1)	52/59 (88.1%) (79.9, 96.4)	41/56 (73.2%) (61.6, 84.8)
Sustained ACR70 n/m (%) 95% CI	32/41 (78.0%) 65.4, 90.7)	29/32 (90.6%) (80.5, 100.0)	22/32 (68.8%) (52.7, 84.8)

DAS28 responses

Improvements in DAS were consistent with the symptomatic improvements assessed by the ACR variables.

Figure B 38 DAS28 (CRP) remission over time

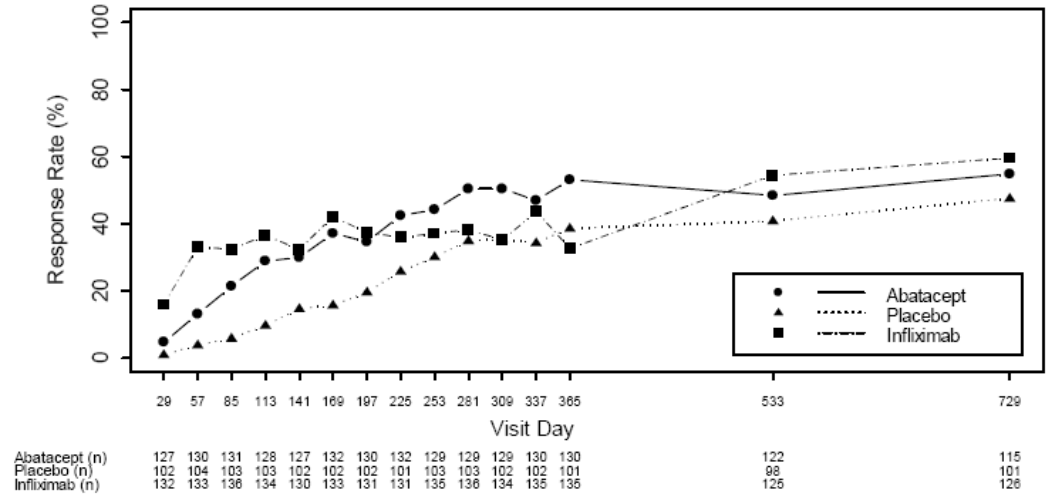
Figure S.3.5: Proportions of Subjects with DAS 28 (CRP) Remission Over Time



Treatment groups represent treatment received in the double-blind period

Figure B 39 DAS28 (CRP) low disease activity over time over time

Figure S.3.6: Proportions of Subjects with DAS 28 (CRP) Low Disease Activity Over Time



Treatment groups represent treatment received in the double-blind period

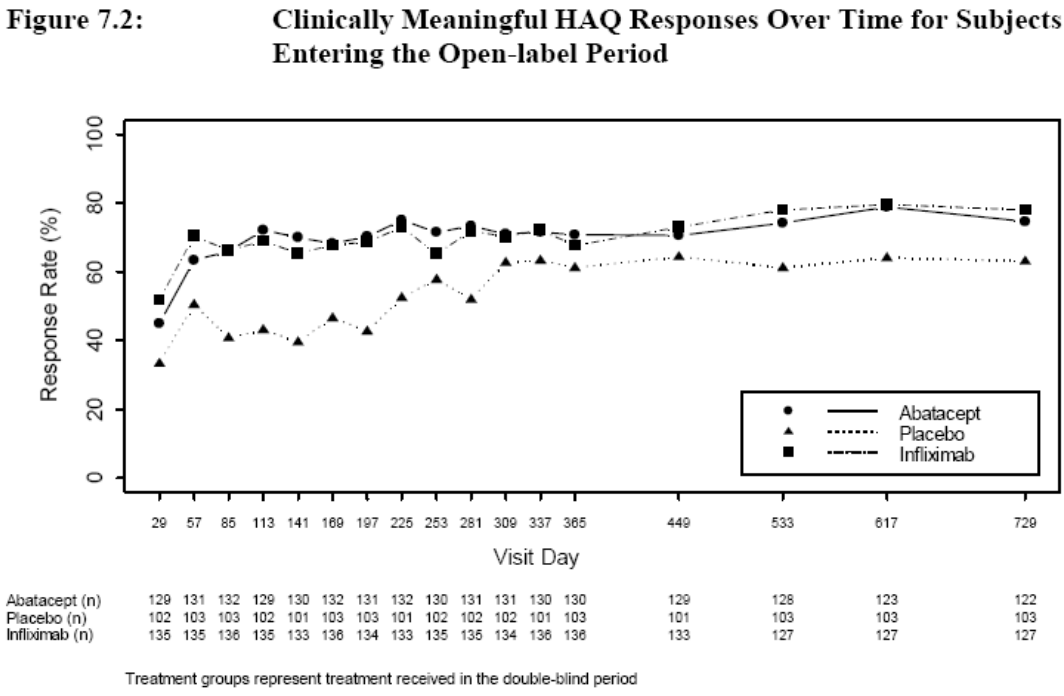
Physical Function (HAQ)

The proportion of subjects with clinically meaningful improvements in physical function at the end of Year 1 (Day 729) of the open-label period was 74.6% for the original abatacept group The HAQ responder rate for the original abatacept group from the double-blind period was maintained during the open-label period.

The proportion of subjects with clinically meaningful improvements in physical function at the end of Year 1 of the open-label period was 78.0% for the original infliximab group. The HAQ responder rate for this group was similar to the rate for the original abatacept group at the end of the double-blind period, and did not change after being switched to abatacept in the open-label period.

The placebo group maintained their clinically meaningful improvements in physical function seen at the end of the double-blind period.

Figure B 40 Clinically meaningful HAQ responses over time



5.9 Adverse events

Overall, abatacept is generally well tolerated in this patient population, with there being no unexpected or unusual events reported. Most adverse events reported were of mild to moderate in intensity, and not unusual, nor unexpected, in this patient population. Over a 1 year comparison period, a relative difference in safety was observed in the abatacept group compared with the infliximab group, with fewer SAEs, serious infections, acute infusional events and discontinuations due to AEs in the abatacept group.

5.9.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.8 and 9.9, appendices 8 and 9.

None of the RCTs identified were powered to detect significant differences between treatments with respect to the incidence of an adverse event.

5.9.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

RCT evidence

There were 4 deaths in the ATTEST trial at 1 year, 2 in the AIM trial during the 1 year double blind phase and 1 was reported in the Kremer Phase 2b trial during the one year double blind phase.

In the ATTEST study, of the 4 deaths reported in the first year double blind phase; 1 was in the abatacept arm, 2 in the infliximab arm and 1 in the placebo-abatacept arm.

Two of the above deaths were reported in the first 6 months of the study, one in the abatacept arm was due to a cerebrovascular accident and one in the infliximab arm was due to fibrosarcoma. The other infliximab-treated patient had peritoneal tuberculosis (TB) and died during the second 6 months of the trial due to septic shock following surgery. One patient who was initially randomized to the placebo group in the double blind phase died within the first year while receiving abatacept from pneumonia and sepsis. The investigator assessment deemed the death possibly related to study treatment.

In the AIM study, one death was reported during the double-blind phase from bronchopulmonary aspergillosis, the patient had underlying pulmonary disease and prior TB exposure. The other death in the placebo group was due to severe bronchopneumonia, which was deemed unrelated to the study drug.

In the Kremer Phase 2b study one patient died due to complications following coronary artery bypass graft surgery and considered unrelated to abatacept.

The total adverse events (AEs) and discontinuation rates across the three RCTs included in this submission are presented in Table B58.

At 6 months, the ATTEST trial reported that a comparable number of patients experienced AEs in the placebo (83.6%), abatacept (82.7%), and infliximab (84.8%) groups, just under half of which were related to study drug. Similarly, in the AIM trial, 84% of patients in the placebo group and 87.3% of patients in the abatacept group reported an AE; 47.5% and 49.4% were drug related, respectively.

Both the Kremer Phase 2b and ATTEST trials demonstrated a lower percentage of patients experiencing serious AEs (SAEs) in the abatacept groups compared with all other treatments. At 1 year, the proportion of patients experiencing AEs was similar to that at 6 months, although the absolute percentage of SAEs was higher (ranging from 9.6% to 18.2% across all treatments).

Slightly more AEs/SAEs were reported in the infliximab group in the ATTEST study. Over 1 year, a relative difference in safety was

observed in the abatacept group compared with the infliximab group, with fewer SAEs (9.6% vs. 18.2%), serious infections (1.9 vs. 8.5%), acute infusional events (7.1% vs. 24.8%) and discontinuations due to AEs (3.2% vs. 7.3%) in the abatacept group. In the clinical environment and real-life setting, increased AEs and SAEs may have an impact on the compliance of a patient, and thus this data should be considered when a clinician makes a choice between abatacept and infliximab.

In the AIM trial, 84% of patients in the placebo group and 87.3% of patients in the abatacept group reported an AE, 47.5% and 49.4% were drug related, respectively.

The most frequently reported AEs (>5%) at 1 year across the three RCTs included in this submission are presented in Table B59.

Kremer Phase 2b only reported four AEs: headaches, nasopharyngitis, nausea, and cough.

In the AIM and the ATTEST studies, the most frequently reported AEs were infections and infestations, experienced by up to 59.6% of patients in the ATTEST abatacept group and 68.5% in the infliximab group.

Overall, a higher percentage of patients reported AEs (>5%) in the ATTEST trial than in any of the other RCTs included in this submission.

Table B 58 Total adverse events and discontinuation rates across RCTs

Trial	AIM trial (n=656)		Kremer Phase 2b (n=339)			ATTEST (n=431)		
	Placebo + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Placebo + MTX	Abatacept 2 mg/kg every 4 weeks + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Placebo + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Infliximab 3mg/kg every 8 weeks + MTX
	(%) unless otherwise indicated	(%) unless otherwise indicated	(%) unless otherwise indicated	(%) unless otherwise indicated	(%) unless otherwise indicated	(%) unless otherwise indicated	(%) unless otherwise indicated	(%) unless otherwise indicated
6 months			n=119	n=105	n=115	n=110	n=156	n=165
Death, number of events (%)			0	0	0	0	1 (0.6%)	1 (0.6%)
Total adverse events (AEs), number of events (%)						92 (83.6%)	129 (82.7%)	140 (84.8%)
AEs related to study drug, number of events (%)						46 (41.8%)	64 (41%)	74 (44.8%)
discontinuation due to AEs, number of events (%)						1 (0.9%)	3 (1.9%)	8 (4.8%)
total SAEs, number of events (%)			12 (10.1%)	12 (11.4%)	3 (2.6%)	13 (11.8%)	8 (5.1%)	19 (11.5%)
discontinuation due to SAEs, number of events (%)			1 (0.8%)	4 (3.8%)	0	0	2 (1.3%)	4 (2.4%)
12 months	n=219	n=433	n=119	n=105	n=115	N/A	n=156	n=165
Death, number of events (%)	1 (0.5%)	1 (0.2%)					1 (0.6%)	2 (1.2%)
Total adverse events (AEs), number of events (%)	184 (84%)	378 (87.3%)					139 (89.1%)	154 (93.3%)
AEs related to study drug, number of events (%)	104 (47.5%)	214 (49.4%)					72 (46.2%)	96 (58.2%)
discontinuation due to AEs, number of events (%)	4 (1.8%)	18 (4.2%)					5 (3.2%)	12 (7.3%)
total SAEs, number of events (%)	26 (11.9%)	65 (15%)	19 (16%)	19 (18.1%)	14 (12.2%)		15 (9.6%)	30 (18.2%)
discontinuation due to SAEs, number of events (%)	3 (1.4%)	10 (2.3%)	2 (1.7%)		2 (1.7%)		4 (2.6%)	6 (3.6%)

AE: adverse events; MTX: methotrexate; N/A: not applicable

Table B 59 Most frequently reported AEs (>5%) at one year

Trial	AIM trial (n=656)		Kremer Phase 2b (n=339)			ATTEST (n=431)		
	Placebo + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Placebo + MTX	Abatacept 2 mg/kg every 4 weeks + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Placebo + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Infliximab 3mg/kg every 8 weeks + MTX
	number of events (%)	number of events (%)	number of events (%)	number of events (%)	number of events (%)	number of events (%)	number of events (%)	number of events (%)
NERVOUS SYSTEM DISORDERS	**35 (16.0%)**	**64 (14.8%)**					**46 (29.5%)**	**54 (32.7%)**
HEADACHE	26 (11.9%)	76 (17.6%)	18 (15.1%)	17 (16.2%)	17 (14.8%)		23 (14.7%)	32 (19.4%)
DIZZINESS	16 (7.3%)	40 (9.2%)					12 (7.7%)	13 (7.9%)
INFECTIONS AND INFESTATIONS	**113 (26.1%)**	**41 (18.7%)**					**93 (59.6%)**	**113 (68.5%)**
NASOPHARYNGITIS	25 (11.4%)	66 (15.2%)	11 (9.2%)	19 (18.1%)	17 (14.8%)		20 (12.8%)	26 (15.8%)
INFLUENZA	12 (5.5%)	31 (7.2%)					13 (8.3%)	11 (6.7%)
PHARYNGITIS	10 (4.6%)	26 (6.0%)					12 (7.7%)	17 (10.3%)
BRONCHITIS	12 (5.5%)	18 (4.2%)					<5%	<5%
UPPER RESPIRATORY TRACT INFECTION	**21 (9.6%)**	**47 (10.9%)**					**11 (7.1%)**	**19 (11.5%)**
SINUSITIS	15 (6.8%)	18 (4.2%)					10 (6.4%)	7 (4.2%)
URINARY TRACT INFECTION	11 (%.0%)	22 (5.1%)					8 (5.1%)	18 (10.9%)
HERPES SIMPLEX	<5%	<5%					6 (3.8%)	10 (6.1%)
GASTROENTERITIS	<5%	<5%					4 (2.6%)	13 (7.9%)
GASTROINTESTINAL DISORDERS	**32 (14.6%)**	**59 (13.6%)**					**64 (41.0%)**	**85 (51.5%)**
DIARRHOEA	21 (9.6%)	47 (10.9%)					21 (13.5%)	21 (12.7%)

Trial	AIM trial (n=656)		Kremer Phase 2b (n=339)			ATTEST (n=431)		
	Placebo + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Placebo + MTX	Abatacept 2 mg/kg every 4 weeks + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Placebo + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Infliximab 3mg/kg every 8 weeks + MTX
	number of events (%)	number of events (%)	number of events (%)	number of events (%)	number of events (%)	number of events (%)	number of events (%)	number of events (%)
DYSPEPSIA	10 (4.6%)	27 (6.2%)					19 (12.2%)	17 (10.3%)
NAUSEA	24 (11.0%)	52 (12.0%)	17 (14.3%)	12 (11.4%)	16 (13.9%)		16 (10.3%)	20 (12.1%)
GASTRITIS	<5%	<5%					6 (3.8%)	9 (5.5%)
ABDOMINAL PAIN UPPER	13 (5.9%)	19 (4.4%)					<5%	<5%
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**4 (1.8%)**	**10 (2.3%)**					**36 (23.1%)**	**42 (25.5%)**
BACK PAIN	12 (5.5%)	40 (9.2%)					12 (7.7%)	10 (6.1%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**14 (6.4%)**	**34 (7.9%)**					**28 (17.9%)**	**50 (30.3%)**
PRURITUS	<5%	<5%					5 (3.2%)	10 (6.1%)
URTICARIA	<5%	<5%					3 (1.9%)	11 (6.7%)
RASH	<5%	<5%					1 (0.6%)	9 (5.5%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**13 (5.9%)**	**23 (5.3%)**					**5 (3.2%)**	**13 (7.9%)**
COUGH	13 (5.9%)	29 (6.7%)	15 (12.6%)				<5%	<5%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**25 (11.4%)**	**43 (9.9%)**					**25 (16.0%)**	**36 (21.8%)**
OEDEMA PERIPHERAL	<5%	<5%					8 (5.1%)	6 (3.6%)
FATIGUE	15 (6.8%)	23 (5.3%)					<5%	<5%
VASCULAR DISORDERS	**4 (1.8%)**	**19 (4.4%)**					**23 (14.7%)**	**37 (22.4%)**
HYPERTENSION	3 (1.4%)	24 (5.5%)					13 (8.3%)	12 (7.3%)
HYPOTENSION	<5%	<5%					1 (0.6%)	9 (5.5%)

Trial	AIM trial (n=656)		Kremer Phase 2b (n=339)			ATTEST (n=431)		
	Placebo + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Placebo + MTX	Abatacept 2 mg/kg every 4 weeks + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Placebo + MTX	Abatacept 10 mg/kg every 4 weeks + MTX	Infliximab 3mg/kg every 8 weeks + MTX
	number of events (%)	number of events (%)	number of events (%)	number of events (%)	number of events (%)	number of events (%)	number of events (%)	number of events (%)
PSYCHIATRIC DISORDERS	**3 (1.4%)**	**8 (1.8%)**					**19 (12.2%)**	**23 (13.9%)**
INSOMNIA	<5%	<5%					5 (3.2%)	12 (7.3%)

Non-RCT evidence (LTE studies)

After evaluating the clinical data (as outlined previously) it was decided to present the safety data from the most recent CSRs available. This was because the publications described previously were mostly posters (of which several iterations were available, offering different data “cuts” depending on the time of the symposium, and the audience at the symposium) or not formally published in a peer reviewed journal. Thus, the latest CSRs for the appropriate trials were felt to offer the most comprehensive and accurate data to date.

AIM LTE Safety data

Over the 71 months of the study (double-blind and open label) abatacept, administered IV monthly, was generally well tolerated in patients with active RA.

There were 17 deaths reported in the LTE, including 15 (2.8%) within 56 days of the last infusion of abatacept and 2 that occurred more than 56 days after the last infusion. Five deaths: pneumonia, septic shock and sinusitis; septic shock and fall; lung neoplasm malignant; lobar pneumonia; acute lymphocytic leukaemia) were considered to be related to abatacept.

Table B 60 AEs with an outcome of death during the LTE

Table 8.2: AEs with an Outcome of Deaths During Open-label Period

Subject No. (Age/Sex)	Abatacept 10 mg/kg No. Infusions DB/OL	Cause of Death	Study Day	Relationship
IM101102-80-1 (60/F)	14 / 15	Pneumonia/Septic shock/ Sinusitis	776	Probable
	14 / 15	Retroperitoneal hemorrhage/ Hypovolemic shock	778	Unlikely
IM101102-81-1 (65/F)	0 / 8	Myocardial ischemia	572	Unrelated
	0 / 8	Post procedural complications	575	Unrelated
IM101102-82-5 (66/F)	14 / 50	Neuroendocrine carcinoma	1795	Unrelated
IM101102-88-24 (69/F)	14 / 43	Cerebrovascular accident	1562	Unlikely
IM101102-90-1 (63/F)	0 / 53	Septic shock/Fall	1842	Possible
IM101102-98-12 (63/M)	14 / 2	Lung neoplasm malignant	415	Possible
IM101102-98-29 (53/M)	0 / 36	Cardiogenic shock	1352	Unrelated
IM101102-99-6 (52/F)	0 / 22	Cardiac arrest	987	Unrelated
IM101102-102-3 (70/M)	14 / 7	Lobar pneumonia	585	Probable
IM101102-115-4 (64/M)	14 / 16	Cardiac arrest	809	Unlikely
IM101102-117-15 (44/M)	14 / 16	Cardiac arrest	802	Unrelated
IM101102-140-17 (56/M)	13 / 22	Metastatic malignant melanoma	967	Unrelated
		Anorexia	968	Unrelated
IM101102-142-24 (65/M)	14 / 19	Aortic aneurysm rupture	936	Unrelated
IM101102-145-17 (41/F)	0 / 37	Acute lymphocytic leukaemia	1393	Probable
IM101102-148-3 (61/F)	14 /41	Respiratory failure	622	Unrelated

Source: Table S.6.3, Appendix 4.1, and Appendix 9.1 of IM101102 Double-blind CSR.[1]

Only deaths as a result of AEs in the open-label period + 56 days post last infusion of abatacept are listed.

F = female; M = male; DB = double-blind; OL = open-label

Serious adverse events were reported by 211 (39.1%) of patients, the most frequent being RA, including worsening of RA in 36 (6.7%) and osteoarthritis in 20 (3.7%).

Table B 61 Serious adverse events reported during the open label period

System	Abatacept (N=539)
Total patients with SAE	211 (39.1%)
Musculoskeletal and connective tissue disorders	78 (14.5%)
Infections and infestations	52 (9.6%)
Neoplasms (benign, malignant and unspecified)	35 (6.5%)
Injury, poisoning and procedural complications	29 (5.4%)
Gastrointestinal disorders	26 (4.8%)
Cardiac disorders	16 (3.0%)
Nervous system disorders	14 (2.6%)
Hepatobiliary disorders	10 (1.9%)
General disorders and administration site conditions	9 (1.7%)
Renal and urinary disorders	9 (1.7%)
Respiratory, thoracic and mediastinal disorders	9 (1.7%)
Vascular disorders	8 (1.5%)
Metabolism and nutrition disorders	6 (1.1%)
Reproductive system and breast disorders	6 (1.1%)
Blood and lymphatic system disorders	5 (0.9%)
Eye disorders	5 (0.9%)
Investigations	4 (0.7%)
Psychiatric disorders	2 (0.4%)
Skin and Subcutaneous tissue disorders	2 (0.4%)

Overall, adverse events were reported for 517 patients (95.9%), although the majority were mild or moderate in intensity; 31% had at least one AE that was severe or very severe. Nasopharyngitis, urinary tract infection and upper respiratory tract infection were the most commonly reported AEs.

Fifty-four (10.0%) of patients discontinued treatment due to AEs.

The overall incidence rates for SAEs, infections and infestations SAEs and AEs, malignant neoplasms and auto-immune disorders did not increase during the open-label period relative to the double-blind period.

Phase 2b 7-year LTE safety data

Over the 6 years after the 12 months of the double-blind period abatacept, was generally well tolerated in patients with RA.

There were 6 deaths reported during the open label period. Causes of death include: lung adenocarcinoma with pleural metastasis; severe dyspnoea; cardiac failure congestive; cardiopulmonary failure; acute myocardial infarction; aortic aneurysm rupture). No death was considered to be related to abatacept.

Table B 62 AEs with an outcome of death during the LTE

Table 8.2: AEs with an Outcome of Deaths During Open-label Period

Subject No.	(Age/Sex)	Cause of Death	Study Onset Day	Relationship
IM101100-21-1	(61/Female)	Lung Adenocarcinoma with pleural metastasis	484	unlikely
IM101100-41-8	(65/Male)	Severe Dyspnea*	1051	unlikely
IM101100-51-13	(56/Male)	Cardiac Failure Congestive	2574	unlikely
IM101100-61-19	(58/Male)	Acute Myocardial Infarction	2351	unlikely
IM101100-69-1	(55/Female)	Aortic Aneurysm Rupture	2377	unrelated
IM101100-76-4	(81/Male)	Cardiopulmonary Failure	649	unrelated

Source: Table S.6.3

* Medical evaluation confirmed that the subject was suffering from MTX-induced pulmonary fibrosis and 2 pulmonary emboli.

Serious adverse events were reported by 113 (51.6%) abatacept-treated patients, the most frequent being musculoskeletal and connective tissue disorders (43, 19.6%) and infections and infestations (33, 15.1%).

Table B 63 Serious adverse events reported during the open label period

System	Abatacept (N=219)
Total patients with SAE	113 (51.6%)
Musculoskeletal and connective tissue disorders	43 (19.6%)
Infections and infestations	33 (15.1%)
Injury, poisoning and procedural complications	20 (9.1%)
Respiratory, thoracic and mediastinal disorders	19 (8.7%)
Neoplasms (benign, malignant and unspecified)	16 (7.3%)
Cardiac disorders	14 (6.4%)
Gastrointestinal disorders	13 (5.9%)
Vascular disorders	13 (5.9%)
Nervous system disorders	11 (5.0%)
Surgical and medical procedures	8 (3.7%)
General disorders and administration site conditions	7 (3.2%)
Investigations	6 (2.7%)
Metabolism and nutrition disorders	6 (2.7%)
Reproductive system and breast disorders	6 (2.7%)
Hepatobiliary disorders	5 (2.3%)
Blood and lymphatic system disorders	4 (1.8%)
Skin and Subcutaneous tissue disorders	3 (1.4%)
Renal and urinary disorders	2 (0.9%)
Ear and labyrinth disorders	1 (0.5%)
Eye disorders	1 (0.5%)
Immune system disorders	1 (0.5%)
Psychiatric disorders	1 (0.5%)

Thirty six patients (16.4%) experienced SAEs that were considered to be related to study drug; the most frequent of these were infections and infestations (19, 8.7%) and neoplasms (8, 3.7%).

Overall, adverse events were reported by 113 patients (51.6%) abatacept treated patients, although the majority were mild or moderate in intensity. RA (including worsening of RA), nasopharyngitis, upper respiratory tract infection, bronchitis, sinusitis, and urinary tract infection and were the most commonly reported AEs.

Forty two (10.0%) of patients who received abatacept during the open-label period discontinued treatment due to AEs. For 29 of these patients, discontinuation was due to an SAE.

The overall incidence rates for SAEs, infections and infestations SAEs and AEs, malignant neoplasms and auto-immune disorders for the abatacept group (2 mg/kg and 10 mg/kg combined) did not increase during the open-label period relative to the double-blind period, and no new safety signals were identified during the open-label period.

ATTEST 2-year LTE safety data

Over the 12 months long-term extension period following the 12months double blind period, abatacept, administered IV monthly, was generally well tolerated in patients with active RA.

Table B 64 Overview of AEs in the open-label period

Table 8.1: Summary of Subjects with Adverse Events Reported During the Open-label Period: All Treated Subjects in the Open-label Period

	----Number (%) of Subjects---- Abatacept (N=372)
Deaths	3 (0.8)
SAEs	82 (22.0)
Related SAEs	11 (3.0)
Discontinued due to SAEs	4 (1.1)
AEs	348 (93.5)
Related AEs	163 (43.8)
Discontinued due to AEs	9 (2.4)

Includes data up to 56 days post the last dose in the open-label period.

There were 3 deaths reported (myocardial infarction, respiratory failure, accident) and none were considered to be related to the study drug. Each of these deaths occurred inpatients who had received abatacept in the double-blind period.

Table B 65 AEs with an outcome of death during the LTE

Table 8.2: Adverse Events with an Outcome of Deaths During Open-label Period

Subject No. (Age/Sex)	Abatacept 10 mg/kg No. Infusions DB/OL	Cause of Death	Study Day	Relationship
IM101043-19-1 (60/F)	14 / 27	Myocardial infarction	1136	Not related
IM101043-68-8 (53/F)	14 / 11	Respiratory failure	673	Not related
IM101043-78-7 (52/F)	14 / 10	Accident	641	Not related

Source: Table S.6.3, Appendix 4.1, and Appendix 9.1 of IM101043 Double-blind CSR.[1]

F = female; M = male; DB = double-blind; OL = open-label

Serious adverse events were reported by 82 (22.0%) abatacept treated patients. These included 30 (22.7%) from the original abatacept group; 33 (24.2%) from the original infliximab group and19 (18.3%) from the original placebo group. The most frequent SAE reported was worsening of RA in 18 (4.8%). Serious urinary tract infection (5 [1.3%]), osteoarthritis (4 [1.1%]) and arthritis (4 [1.1%] were the only others reported in at least 1% of subjects.

Table B 66 Serious adverse events reported during the open label period

System	Abatacept (N=372)
Total patients with SAE	82 (22.0%)
Musculoskeletal and connective tissue disorders	31 (8.3%)
Infections and infestations	14 (3.8%)
Injury, poisoning and procedural complications	12 (3.2%)
Cardiac disorders	7 (1.9%)
Neoplasms (benign, malignant and unspecified)	5 (1.3%)
Reproductive system and breast disorders	5 (1.3%)
Respiratory, thoracic and mediastinal disorders	5 (1.3%)
General disorders and administration site conditions	2 (0.5%)
Hepatobiliary disorders	2 (0.5%)
Metabolism and nutrition disorders	2 (0.5%)
Vascular disorders	2 (0.5%)
Blood and lymphatic system disorders	1 (0.3%)
Endocrine disorders	1 (0.3%)
Eye disorders	1 (0.3%)
Gastrointestinal disorders	1 (0.3 %)
Investigations	1 (0.3%)
Renal and urinary disorders	1 (0.3%)
Skin and Subcutaneous tissue disorders	1 (0.3%)

Eleven (3.0%) of patients experienced a total of 12 SAEs that were considered to be related to study drug (5 from the original abatacept group, 4 from the original placebo group, 2 from the original infliximab group

Table B 67 Serious adverse events considered related to study drug

Table 8.3B: Related Serious Adverse Events During Open-label Period

Subject No. (Age/Sex)	Abatacept 10 mg/kg No. Infusions DB/OL	Related SAE	Study Day	Outcome
IM101043-11-9 (48/F)	14 / 27	Psoriasis	839	Resolved w/trt
IM101043-14-12 (63/F)	14 / 32	Anemia	882	Resolved, no trt
IM101043-22-7 (57/F)	7 / 34	Pyrexia Urinary tract infection	728 959	Resolved w/trt Resolved w/trt
IM101043-25-15 (50/F)	7 / 28	Anal fissure	674	Resolved w/trt
IM101043-29-4 (52/F)	14 / 12	Subcutaneous abscess	589, 680	Trt interruption Resolved w/trt
IM101043-51-3 (52/M)	14 / 22	Basal cell carcinoma	642	Resolved w/trt
IM101043-51-8 (63/F)	0 / 9	Cellulitis	606	Discontinuation Resolved w/trt
IM101043-79-1 (23/F)	7 / 25	Cellulitis	823	Trt interruption Resolved w/trt
IM101043-80-11 (53/F)	0 / 15	Laryngeal granuloma	815	Discontinuation Resolved w/trt
IM101043-87-5 (29/F)	14 / 26	Urinary tract infection	389	Resolved w/trt
IM101043-87-9 (73/F)	7 / 27	Urinary tract infection	1074	Resolved w/trt

Overall, adverse events were reported for 348 patients (95.5%), although the majority were mild or moderate in intensity. Nasopharyngitis, urinary tract infection and diarrhoea were the most commonly reported AEs.

Nine (2.4%) of patients discontinued treatment due to AEs.

The overall incidence rates for SAEs, infections and infestations SAEs and AEs, malignant neoplasms and auto-immune disorders did not increase during the open-label period relative to the double-blind period.

Non-RCT evidence (Integrated analyses)

The integrated safety data from 4149 patients up to 7 years (12,132 patient years of exposure) demonstrate that abatacept is generally well tolerated. Incidence rates of overall AEs and SAEs remained stable over time. Similarly, the incidence rates for infections, serious infections, and malignancies did not increase in the long-term period versus the short-term period. Results from the integrated analysis demonstrated only small variations between time intervals suggesting that the safety profile of abatacept did not change significantly with increased exposure to treatment over time. According to Smitten et al (2010) malignancies (e.g. colorectal cancer, lung cancer, lymphoma, prostate cancer, or breast cancer) in abatacept patients were not significantly increased compared to that expected based on the general population.

The results from Hochberg et al (2010) summarised in Table B68 present the safety data for the longest mean exposure (35.6 months). These results are in line with the other integrated analyses by Becker et al (2010) and Smitten et al (2010). Table B68 shows generally consistent incidence rates for all safety issues presented over time; one exception is the lower incidence of acute infusion events in the cumulative period as compared to the short-term period, 3.90/100p-y vs. 11.61/100p-y.

During the cumulative period, Hochberg et al (2010) also report that the incidence rate (95% CI) of hospitalised infection was 2.64 per 100 p–y (2.35–2.95) and there were few opportunistic infections (0.36 [0.27–0.49]), with only eight cases of tuberculosis (0.07 [0.03–0.13]) observed overall. Lastly, the incidence rates (95%CI) for the most common serious infection were pneumonia: 0.46 (0.34–0.59); urinary tract infection: 0.20 (0.13–0.30); cellulitis: 0.18 (0.11–0.28).

Table B 68 Safety events during the short-term, long-term, and cumulative periods

		ST (n=3173)	LT (n=3256)	Cumulative (n=4149)
P–y exposure		2331	9752	12,132
Deaths	Patients with event, n	12	60	73
	Incidence rate*	0.51 (0.27–0.90)	0.62 (0.47–0.79)	0.60 (0.47–0.76)
Overall SAEs	Patients with event, n	400	1086	1373
	Incidence rate*	18.15 (16.41–20.02)	14.31 (13.47–15.18)	14.61 (13.85–15.41)
Serious infections†	Patients with event, n	85	260	332
	Incidence rate*	3.68 (2.94–4.55)	2.79 (2.46–3.15)	2.87 (2.57–3.19)
Malignancies (excluding NMSC)	Patients with event, n	16	72	88
	Incidence rate*	0.69 (0.39–1.11)	0.74 (0.58–0.93)	0.73 (0.58–0.89)
Lung cancer	Patients with event, n	5	13	18
	Incidence rate*	0.21 (0.07–0.50)	0.13 (0.07–0.23)	0.15 (0.09–0.23)
Lymphoma	Patients with event, n	1	8	9
	Incidence rate*	0.04 (0.00–0.24)	0.08 (0.04–0.16)	0.07 (0.03–0.14)
Autoimmune events	Patients with event, n	48	NP	232
	Incidence rate*	2.07 (1.53–2.75)	NP	1.99 (1.74–2.26)
Acute infusional events‡	Patients with event, n	225	NP	377
	Incidence rate*	11.61 (10.14–13.22)	NP	3.90 (3.52–4.32)

**Data show incidence rates per 100 p-y (95% confidence intervals)*
‡Events occurring within one hour of the start of the infusion, only reported in 6 studies.

LT: long-term; NMSC: non-melanoma skin cancer; NP: analysis not performed; SAE: serious adverse event; ST: shot-term;

5.9.3 Give a brief overview of the safety of the technology in relation to the decision problem.

Abatacept was generally well tolerated, both in the short-term and long-term. The LTE studies and the integrated analyses for abatacept demonstrate no new clinically important safety issues were identified over time. Death rates in the DB and LTE periods were low.

Results from the ATTEST trial provide insight into the relative safety of abatacept compared to other treatments, as defined in the decision problem. From these data, abatacept demonstrates fewer SAEs, lower discontinuation rates due to AEs/SAEs, and lower serious infections and acute infusional events.

In all trials, the overall incidence of AEs was similar for both treatment groups and the majority of AEs reported were mild to moderate in severity. The proportion of patients and incidence rates of AEs, SAEs, infections, and serious infections were stable over time, and the type of events in the long-term and cumulative periods were consistent with those experienced in the trial period. This implies that the safety profile of abatacept is consistent and predictable on extended exposure to abatacept.

5.10 Interpretation of clinical evidence

The substantial body of evidence available for abatacept from the three RCTs and non-RCT included in this submission demonstrates that abatacept+MTX has a safety and tolerability profile similar to MTX for the treatment of moderate to severe RA.

The evidence also shows that abatacept is more efficacious than MTX at reducing the signs and symptoms of RA.

Abatacept also shows greater efficacy than infliximab at reducing the signs and symptoms of RA, yet with an improved tolerability profile.

The results from the clinical trials and MTC demonstrate that abatacept is a suitable therapeutic alternative for RA patients with inadequate response to MTX. As an infusion pharmacotherapy with a clinical effect that is maintained over a long period, abatacept may be preferred by certain patients for whom subcutaneous delivery is inappropriate, and may be considered by some physicians as a viable alternative to agents with a more rapid onset of effect, but with poorer level of sustainability.

Thus, abatacept will offer a degree of choice for sufferers and health carers alike in the treatment and management of this very heterogeneous disease.

5.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

Clinical data

Meta-analysis and indirect treatment comparison

The results from the meta-analysis showed abatacept + MTK to be more efficacious than placebo + MTX in:

- reducing HAQ score at 24/26 weeks and 52 weeks
- reducing the DAS28 score st 24/28 weeks and ACR 20/50/70 response criteria.

- achieving a DAS28 defined remission.

The mixed treatment comparison supports the view that abatacept is more efficacious than placebo in terms of ACR response, and that abatacept is expected to have a level of clinical efficacy that is comparable to that of other biologic DMADs.

RCTs and non-RCTs

The clinical evidence from the three RCTs and non-RCT data presented in this submission demonstrate that abatacept provides clinically meaningful and sustained benefits across multiple efficacy measures; signs and symptoms, structural damage and physical function, without dose adjustment for patients with established moderate to severe RA that have previously shown and inadequate response to MTX.

Abatacept has demonstrated statistical significance in achieving clinical efficacy outcomes compared to placebo, over a short term double blind period. However, what has also been shown by abatacept is that the efficacy improvements seen are maintained or further improve over time. Sustained long term efficacy seen over time, for example, for 7 years as shown in Kremer Phase 2b, could have an impact on long-term reduction of radiographic progression and improvement in physical function (Schiff 2010).

AIM

Data are presented from the AIM study over 5 years, (1 year DB and 4 years LTE). The data show that clinical improvements seen in the original abatacept group were maintained over 4 years open label extension period. ACR20, ACR50 and ACR70 results were maintained at 5 years as well as DAS28 results. The mean baseline DAS28 was 6.34 and at 5 years the mean DAS28 score was 3.24. This is a significant reduction in DAS28, and is clinically relevant.

Of the patients that were in the original abatacept group, 44.1% had achieved an LDAS and 25.4% were in remission at the end of the double blind period. At 5 years, 54.7% of this group had achieved an LDAS and 33.7% had achieved remission. These results were similar to those seen for the placebo group that was switched to active treatment at 6 months. In the original placebo group 40.7% had achieved an LDAS and 11.9% had achieved remission by the end of the double blind period. At 5 years 58.5% of subjects had achieved an LDAS and 38.2% had achieved remission.

To regard these results in the context of a real life rheumatology department, to have almost 40% of patients still achieving remission, 5 years into treatment, is a good clinical outcome.

The proportion of subjects with clinically meaningful improvements in physical function as measured by the HAQ response was also maintained for 5 years in the AIM study.

The AIM study was the only RCT to measure the effects of abatacept on radiographic progression. Changes from baseline in Erosion, Joint Space Narrowing (JSN), and Total scores indicated less progression of structural damage at the end of each year of the study (Year 1 to Year 5 [Year 4 of open-label period]) for the original abatacept group compared to the original placebo group. A total of 45.1% of subjects in the original abatacept group and 39.1% of subjects in the original placebo group showed no radiographic progression (non-progression defined as change from baseline ≤ 0) based on Total score at the end of the 5 years. As progressive structural damage in RA is associated with increasing functional disability over time (Scott et al 2000, Welsing et al 2001), the fact that 45% of the original abatacept group showed absolutely no structural progression over 5 years has a substantial beneficial impact of the physical function of these patients.

Kremer Phase 2b study

The results from the Kremer Phase 2b study, support those discussed above from the AIM study. Sustained improvements in efficacy are seen over 7 years in patients receiving abatacept + MTX (1 year DB + 6 years LTE). Clinically meaningful, durable and sustained ACR20, 50 and 70 responses were observed through to Year 7, while the mHAQ responder rate for the original abatacept groups from the double-blind period was maintained during the open-label period. In addition, at the end of Year 7 improvements from baseline were observed in the Physical Component Summary (PCS) and Mental Component Summary (MCS), as well as in the 8 individual domains.

Again, similar to the AIM trials results, these results show that abatacept has efficacy over a period of 7 years. In addition, responses at 1 year are maintained through to year 7.

Recent studies have shown that the efficacy of some biological therapies diminishes, or wears off, over a period of time, leading to the need for dose escalation (to maintain therapeutic effect) with subsequent increased costs of treatment (Wolbink et al 2005, Bartelds et al 2007, van der Laken et al 2007). In addition, the development of antibodies is associated with an increased risk of infusion reactions and reduced duration of response to treatment. Such phenomena may be, at least partially, due to the development of neutralising antibodies against anti-TNF inhibitors, and in particular is seen with infliximab due to the fact that the molecule is partly murine in origin. The fact that abatacept maintains response over a long time period is a benefit that this different mode of action biologic offers.

ATTEST

The results of the ATTEST trial further support the benefits of abatacept compared to placebo. The results show that over the years of the study, the efficacy benefits (as measured by assessments of signs and symptoms, physical function and disease activity) are greater in patients who are given abatacept + MTX compared with placebo + MTX. In addition, in patients who originally received infliximab in the first year, and were then switched on to abatacept, efficacy benefits increased over the second year and were similar to those seen in the abatacept group.

During the second year, patients who had initially received infliximab were switched to abatacept. In those patients who had originally received abatacept, the efficacy benefits observed in year 1 were maintained throughout the second year while, in those patients who were switched from infliximab to abatacept at the end of the first year, the efficacy benefits were seen over the second year, and were similar to the abatacept group by the end of Year 2.

Interestingly, a considerable proportion of infliximab non-responders who switched to abatacept at 1 year achieved improved clinical responses with abatacept over the second year (Schiff et al 2009a).

Within each of the double-blind groups, the majority of subjects who demonstrated an ACR50 or ACR70 response at year 1 (the end of the double-blind period) continued to demonstrate the same level of ACR response at the end of year 2 (Schiff et al2009b).

At the end of year 1 the percentage of ACR50 responders were numerically higher with abatacept versus placebo. The number of responders was also higher for abatacept than infliximab treatment (with overlapping 95% CIs for the estimate of difference for ACR50 45.5 vs 36.4%, estimate of difference [95% CI] = 9.1 [-.2, 20.5]).

At the end of year 1 the percentage of ACR70 responders were numerically higher with abatacept versus placebo, and abatacept compared to infliximab treatment (with overlapping 95% CIs for the estimate of difference for ACR70 26.3 vs 20.6%, estimate of difference [95% CI] = 5.7 [-.4.2, 15.6]).

Similar DAS28 results were observed at 6 months between abatacept and infliximab, but abatacept led to a greater reduction in mean DAS28 change from baseline at 1 year compared to infliximab; since 95% CI of difference did not overlap (–2.88 vs –2.25; estimate of difference [95% CI] = –0.62 [–0.96, –0.29]).

The results showed that at 1 year 35.3% of patients receiving abatacept achieved an LDAS (DAS28 <3.2) compared to 22.4% of patients who had received infliximab (estimate of difference [95% CI] = 12.9 [2.1,3.7]). In addition, 18.7% of patients who had

received abatacept achieved remission (DAS28 <2.6) compared to 12.2% of infliximab patients (estimate of difference [95% CI] = 18.7 [-2.2,15.2]).

These results are very important, when considering the UK clinical environment. The DAS28 is the most widely used efficacy measurement in the UK. The difference between abatacept and infliximab shown at 1 year in the ATTEST study should be a consideration when making a choice between these agents.

In the ATTEST trial, the infliximab group had a numerically lower reduction in HAQ-DI change from baseline and a numerically lower percentage of responders than the abatacept group at both 6 months and 1 year; however, 95% CIs of estimates of difference overlap.

When considered together, these efficacy results suggest that introducing abatacept early in the treatment paradigm for RA may lead to favourable benefits, and when choosing an iv biologic agent, then a more efficacious choice would be abatacept.

Safety data

The safety data from the RCTs and non-RCTs and long term integrated safety analyses show that, overall, abatacept has a favourable safety profile that is consistent with observations from short-term experience in all RA populations studied (Schiff 2010). No new clinically important safety issues have been identified from the long term data.

The increased risk of serious infections with the anti-TNF agents is well documented (Furst 2009, Listing et al 2005, Kroesen et al 2003, Salliot et al 2007, Bongartz et al 2006). The number of serious infections presented in the integrated safety summary are higher in the abatacept arm than placebo; however, this is at the lower end of the range observed in RA patients treated with other biologics (Kareskog et al 2006, Schiff et al 2006, Askling & Dixon 2008).

5.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

The main strength of the evidence base identified is the high quality data from the placebo-controlled RCTs for abatacept in the treatment of active RA for MTX inadequate responders. However, there are no trials directly comparing abatacept to alternative TNF inhibitors in a head to head manner. However, the ATTEST study was designed to compare abatacept + MTX, and infliximab + MTX,

with placebo + MTX , so it does give an opportunity to analyse the efficacy and safety of two different biologic agents under the same study conditions.

The clinical development programme for abatacept in RA included a total of 3 Phase II and 3 Phase III studies in patients ≥18 years of age with moderately to severely active RA. All trials were randomised, double-blind and placebo controlled. Each trial was followed by an open-label, uncontrolled period.

The clinical development programme evaluated the effects of abatacept on signs and symptoms of RA, physical function, progression of structural damage, and health-related quality of life. In the safety evaluation, special attention was paid to immunomodulatory activity (including infectious complications, malignancies, autoimmunity, infusion reactions, and immunogenicity).

To place the efficacy and safety data of abatacept into context relative to other therapies approved for first or second-line use, the profile of abatacept was indirectly compared with the safety and efficacy profile of anti-TNF-α agents, based on the available published literature and meta-analytical approaches. These indirect comparisons supplement the data from the ATTEST study.

Some of the limitations to the evidence base relate to the fact that a large proportion of long-term data was derived from open-label and uncontrolled clinical studies. This is a natural consequence of the study design, in that patients in the controlled arm of the double-blind studies are eventually given an opportunity to have access to the experimental therapy: this has been the case in almost all clinical programmes in RA. Because they are from open-label uncontrolled studies, these data may not allow for the same rigorous assessments as provided by the original controlled and short term studies. Nevertheless, the data accumulated during this period are informative regarding the LT efficacy, in light of the high retention rates, particularly in the MTX-IR population.

The efficacy endpoints to assess the efficacy of abatacept for the RA treatment were selected as they reflect various aspects of the RA disease burden and include Signs and Symptoms, Structural Damage, Physical Function, and Health-related Outcomes.

A recently extended marketing authorisation for abatacept use in RA patients who have had an inadequate response to MTX is supported by the following additional information:

- Efficacy and safety data from 4,632 subjects that have accumulated through the LTE periods of the pivotal Phase 2/3 studies in the MTX-IR and TNF-IR. These provide safety

data from 4,149 subjects for up to 8 years (11,658 person years [p-y] of clinical study exposure).

- Data from the post-marketing experience (~32,187 p-y experience), the majority of which was from regions where abatacept was approved for use without the restriction of prior failure to other therapies.

5.10.3 Please 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.

There are a limited number of abatacept head-to-head trials, so the evidence-base is also limited for the decision problem at hand. There is an ongoing head-to-head trial comparing the efficacy and safety of subcutaneous abatacept (not currently licensed) to subcutaneous adalimumab, both with background MTX in biologic-naïve patients with moderate to severe RA who had inadequately responded to MTX (IM 101-235). This is due to complete in 2013 (www.clinicaltrials.gov).

However, a MTC was conducted. Outcomes reflecting clinical benefit for patients with active moderate to severe RA measured in the evidence reviewed include ACR20, ACR50, and ACR70, HAQ CFB, and DAS 28. Overall, the outcomes assessed were considered clinically relevant and comparable across trials and interventions, and these endpoints have been used in this submission.

In addition recent EULAR guidelines recommend that treatment of RA should target remission or low disease activity. It states that “valid measures for this purpose have been recently reviewed and include the Disease Activity Score (DAS), 28-joint count DAS (DAS28), Simplified Disease Activity Index and Clinical Disease Activity Index.” (EULAR recommendations, Ann Rheum Dis May 2010).

Because RA is the rheumatic disease with the best methodologically characterised instruments, there are, consequently, many measures for use in patients who have RA. Currently, these measures are the ACR response criteria; the DAS and DAS28; the SDAI and CDAI; the Larsen and Sharp scores (or their modifications); the HAQ-DI; and often the SF-36 (Aletaha and Smolen 2006). Thus the endpoints used in this submission are compatible to those used in a wider arena.

As for the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice, currently no

available therapy cures RA, and whilst the ultimate treatment objective is to reach remission, this is rarely achieved in the established phase of RA. Current therapies, therefore, aim to attain a low level of disease activity in order to slow down the progression of the disease, to limit structural damage and to maintain the functional capacity and quality of life (ACR 2002).

Consequently, it is a sustained low level or absence of inflammation that represents the best prognosis value concerning irreversible joint damage (Welsing et al 2004; Boers et al 2001). Hence, there is a general consensus that disease activity and the level of inflammation must be controlled as early, completely and continuously as possible, and for the longest period of time based on patients' tolerance (Fransen et al 2004; Wolfe et al 2001; Balsa et al 2004; Welsing et al 2004). Therefore the outcomes presented in this submission are of great relevance to the endpoints which are of importance in clinical practice.

Comparison with conventional DMARDs

The efficacy and safety of abatacept as compared to MTX (and placebo) has been demonstrated in the three RCTs, 2 phase III and 1 phase II, included in this submission: AIM, Kremer Phase 2b, and ATTEST. These three trials considered several outcomes reflecting clinical benefit for patients with active moderate to severe RA following an inadequate response to MTX including ACR20, 50, and 70, HAQ CFB, and DAS 28. The AIM and the Kremer Phase 2b trials were also extended into LTE studies to focus on long-term outcomes including all ACR responses, HAQ-DI, DAS 28, SF-36, and radiographic progression, for up to 7 years.

Overall, all outcomes assessed were considered clinically relevant and comparable across trials. No data were available to compare abatacept to other conventional DMARDs, i.e. other than MTX.

Comparison to biological DMARDs/therapies

The evidence base is limited and no direct evidence from RCTs comparing abatacept to other biologicals was available for review except for the three-arm ATTEST study.

On the other hand, results from the MTC demonstrate that the difference between mean HAQ CFB for abatacept + MTX is comparable to that of alternative biologic agents.

Patient and clinician choice

There is no doubt from the evidence presented that abatacept is an effective and well-tolerated pharmacotherapeutic agent for the treatment of moderate to severe RA, and is a viable treatment option for RA patients with inadequate response to MTX.

Rheumatoid arthritis is a chronic, life-long disease which has a devastating effect on patients and their carers and family, especially those unfortunate enough to be suffering from moderate or severe disease. No therapy can cure RA; all that can be offered is an appropriate spectrum of viable, alternative therapies, which can be chosen (and modified as appropriate) to give the best outcomes for a particular patient, depending upon his or her personal circumstances.

Given the wide heterogeneity of the disease, no single therapy option is going to meet the needs of all patients. Current practice is shifting towards a more proactive, aggressive approach which recommends early use of biologics in patients with severe, active, and progressive disease. The aim is to avert or delay progression of irreversible structural damage, before it is too late.

Thus, RA patients will be treated with biologic therapies sooner, and for a longer period of time, than was previously the case. So the availability of a range of treatment options can only be of benefit. As abatacept shows a prolonged maintenance of effect, with a favourable long-term effectiveness and safety profile, its profile as an agent suitable for such extended use (as the profession anticipate) will give patients and physicians a viable choice versus other alternative agents.

Choice is also important in other respects:

- The patient who cannot self-administer subcutaneous drugs deserves a choice.
- The physician who considers a slower onset of action, with long-term sustainability, deserves a choice.
- The nurse who wishes to see their patient at regular intervals, but who prefers a shorter infusion time due to time demands, deserves a choice.
- The health care professional who is concerned about the compliance of their patient to regimens which may not be appropriate for them, deserves a choice.

Abatacept will offer all these stakeholders a biologic agent with a favourable risk/benefit profile.

5.10.4 Identify any factors that may influence the external validity 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 patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

- Patients enrolled and randomised in the three RCTs included in this submission broadly reflect those treated in routine clinical practice, namely, adult patients with active RA, moderate to severe, with inadequate response to MTX.
- Patients included in the all of the RCT trials closely reflect those treated in routine clinical practice, namely, adult patients with active RA, moderate to severe, with inadequate response to MTX.
- The dosing and formulation of the product were in line with that intended for general use post-licensing and the SmPC.
- The demographics of study populations were comparable to that of the RA population in the UK in terms of age, gender, as well as baseline HAQ scores. However, patients in the clinical trials may have had more severe RA, and be further along their disease progression pathway, than usually considered acceptable in clinical practice in order to receive a first biologic. For example, in the AIM study the average baseline DAS 28 score was 6.4, and between 6.8-6.9 in ATTEST. However, the BSR (define) and BHPR (define) recommend biological treatment for patients with a DAS 28 > 3.2 (2010 ref). In this respect, the Kremer Phase 2b trial population appears to be a better reflection of practice in the UK with an average baseline DAS 28 score of 5.5 for randomised patients.
- RCTs included in this submission were global, multicentre trials with study populations from Europe and the US. However, UK sites were used in both trials.
- The current NICE clinical guideline 79, Management of RA in adults (TA guidance 141, 2009) states abatacept is not recommended by NICE (within its marketing authorisation) for the treatment of people with RA. However, in June 2010 NICE issued a FAD on the use of adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor. The FAD has been sent to the formal consultees. Subject to any appeal by consultees, the FAD may be used as the basis for the Institute's final guidance. The FAD stated:

'Adalimumab, etanercept, infliximab and abatacept are recommended as treatment options only for adults with severe active rheumatoid arthritis who have had an inadequate response to, or have an intolerance of, other DMARDs, including at least one TNF inhibitor, and who have a contraindication to rituximab, methotrexate, or when rituximab or methotrexate is withdrawn because of an adverse event.

A team experienced in the diagnosis and treatment of rheumatoid arthritis and working under the supervision of a rheumatologist should initiate, supervise and assess response to treatment with rituximab, adalimumab, etanercept, infliximab or abatacept'.

- EULAR recommendations for the management of early arthritis state that regular monitoring of disease activity and adverse effects should guide decisions on choice and changes in treatment strategies (DMARDs including biological agents) (EULAR 2007).

- EULAR recommendations for the management of RA with synthetic and biological disease-modifying antirheumatic drugs provides 15 recommendations for clinical practice (EULAR 2010); 4 are relevant to abatacept:

- In patients responding insufficiently to MTX and/or other synthetic DMARDs with or without glucocorticoids, biological DMARDs should be started; current practice would be to start a TNF inhibitor (adalimumab, certolizumab, etanercept, golimumab, infliximab) which should be combined with MTX.

- In patients with insufficient response to MTX or other synthetic DMARDs, a biological DMARD should be started; current practice is to start a TNF inhibitor plus MTX (Smolen et al 2010). In Europe, TNF inhibitors and tociluzumab are the only biologics licensed as first-line, while in the US abatacept is licensed as well.

- Patients with RA for whom a first TNF inhibitor has failed, should receive another TNF inhibitor, abatacept, rituximab or tocilizumab.

- DMARD naïve patients with poor prognostic markers might be considered for combination therapy of MTX plus a biological agent.

- When adjusting treatment, factors apart from disease activity, such as progression of structural damage, comorbidities and safety concerns should be taken into account.

These EULAR recommendations reflected expert opinion at the time, which may change, especially with the recent approval of other biological agents as potential first biological agent for DMARD inadequate responders.

- The BMS FDA briefing document provides the rationale behind abatacept development for unmet medical needs and its proposed use in clinical practice:

  'Many patients do not achieve an adequate response to RA therapy. Less than 50% of patients treated with methotrexate respond. Of patients who do not achieve an adequate response to methotrexate, less than 50% achieve an adequate response to TNF-blocking agents. Thus, a substantial number of RA patients lack adequate clinical improvement with current therapies'.

- In AIM, one of the principal abatacept efficacy studies, the ACR20 response rates in major demographic and clinical subgroups were greater for abatacept than for placebo in all subgroups analysed, including age, gender, body weight, duration of arthritis, and rheumatoid factor status. This supports the fact that there is no need to select abatacept patients for treatment by subgroup.

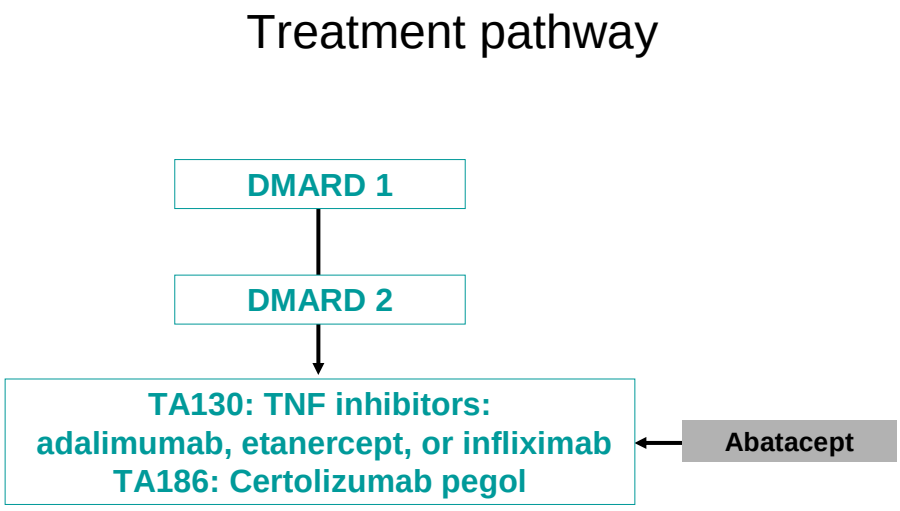
UK clinical and therapeutic landscape for treating RA

BMS consider it appropriate at this stage to attempt to put the abatacept clinical and safety data presented above into the broader context of the UK therapeutic landscape for RA, and to discuss the wider clinical issues pertinent to these data, and this submission. The relevant data for abatacept have already been discussed in some detail in Section 2 (Context); however, BMS feel that juxtapositioning a brief overview of these issues adjacent to the clinical efficacy and safety data may help in terms of clarification.

Treatment pathway for RA

The current treatment pathway for RA is to initiate treatment with conventional DMARDs (methotrexate [MTX] for example) as first-line therapy (alone or in combination). Patients failing to respond to at least two conventional DMARDs (one of which should be MTX), and have active disease, can progress to treatment with anti-TNF agents.

Figure B 41 Treatment pathway for RA



However, nearly 30% of patients have an insufficient response or intolerance to a first anti-TNF agent plus MTX, meaning that they need to move onto another biologic. This means that the most effective choice of first-line therapy is not always being chosen, or is not always available, for managing this heterogeneous disease – so there remains an unmet medical need.

Currently, when choosing a first-line biologic agent, the choice lies with the formulations delivered subcutaneously and those delivered intravenously (infliximab). Abatacept, as an infusion agent, would offer clinicians a direct choice opposite infliximab.

Therapeutic landscape

At present, in England and Wales, patients with moderate to severe active RA and an inadequate response to MTX have access to several anti-TNF agents as their first line biologic agent. While all have demonstrated a consistent and favourable benefit/risk, in certain situations, an anti-TNF agent may not be the optimal treatment choice in these patients. The armamentarium of biologic agents available to rheumatology clinicians therefore needs to offer as wide a choice as possible, so that they can match the most suitable pharmacotherapy to the needs of the individual patient.

In practice, what this means is that when a physician chooses a first-line biologic agent, he or she really does have to put the needs and requirements of the individual patient at the centre of their decision making process, and consider every parameter that may influence the efficacy, safety and appropriateness of their chosen biologic intervention.

Such parameters may include:

- mode of delivery (sc versus iv)
- compliance
- injection site reactions
- frequency of administration
- onset of action

Choice of intravenous agent

Once a patient for whom iv administration is most appropriate has been identified, the choice of agent lies between infliximab and abatacept.

However, there are some other important efficacy and safety considerations related to infliximab infusion, which make having abatacept as an alternative infusion of choice more critical than purely personal preference. Specifically, the issues relate to, the efficacy and safety data from the ATTEST study, the immunology of infliximab versus that of abatacept and the increased risk of TB reactivation by anti-TNF agents.

Efficacy and safety

BMS consider the data from the abatacept ATTEST study to be the most relevant in this contextualsied discussion, as the ATTEST study was designed: (a) to obtain data on the magnitude of the treatment effect in RA of infliximab versus placebo and (b) to obtain relative efficacy and safety data between abatacept and infliximab.

As discussed previously, the data from the ATTEST trial would suggest that abatacept offers a different clinical and safety profile to infliximab, such that its risk/benefit effects as an iv agent may be better suited to some patients who (currently) can only receive infliximab.

Immunology

Infliximab is a chimeric monoclonal antibody to TNF that contains human constant and murine variable regions of IgG1. Because infliximab contains murine sequences (i.e. non-human sections), its administration is associated with formation of anti-chimeric antibodies (HACA) (Haraoui et al 2004).

Recent studies have shown that the efficacy of some biological therapies diminishes, or wears off, over a period of time, leading to

the need for dose escalation (to maintain therapeutic effect) with subsequent increased costs of treatment (Wolbink et al 2005, Bartelds et al 2007, van der Laken et al 2007). In addition, the development of antibodies is associated with an increased risk of infusion reactions and reduced duration of response to treatment. Such phenomena may be, at least partially, due to the development of neutralising antibodies against infliximab.

In contrast, because of its biologic structure (i.e. a fusion protein composed of an immunoglobulin G FC portion fused to the extracellular domain of CTLA-4, that acts by inhibiting the co-stimulation of T-cells) abatacept does not appear to be highly immunogenic (Sibilia and Westhovens 2007, Haggerty et al 2007).

Thus, the available data suggest there are differences between abatacept and infliximab in terms of their immunology, ones which may have significant consequences with regard their relative clinical effectiveness and safety in different patient populations.

Infliximab: loss of clinical effectiveness leading to dose escalation

As the clinical data from the RCT and non-RCT LTEs in this submission show, abatacept maintains its clinical effect over several years, without the need for dose escalation. In contrast, infliximab treatment is associated with loss of response, requiring dose increases in 31% of patients within the first year of treatment (Blom et al 2010).

Infliximab dose escalation is often used as part of everyday clinical practice, (van Vollenhoven 2004, Blom et al 2010). This implies that the availability of abatacept as an alternative to infliximab could have significant implications, not only with regard to physician confidence in the therapeutic effectiveness/value of the agent, but also with regard to the “hidden costs” of dose escalation with infliximab (or rather the lack of such dose escalation costs with abatacept).

TB reactivation by infiximab

It has been estimated that *Mycobacterium tuberculosis* infects about a third of the world’s population (i.e. close to 2 billion people) (Dye et al 1999). Treatment of RA, and other autoimmune disorders, with anti-tumor necrosis factor (anti-TNF) agents is associated with an increased risk of reactivation of latent *Mycobacterium tuberculosis*. Consequently, progression of recently acquired tuberculosis infection, or reactivation of remotely acquired infection, should be expected with anti-TNF agents (Gardam et al 2003).

While the clinical data for abatacept are not as mature as those for infliximab, there are indications that because of its different mode-

of-action – thought to primarily affect adaptive immunity or antigen-specific immunity, with less effect on innate immunity (the primary defense against pathogens) (Ndejembi et al 2005, Tay L, et al 2007, Khraishi 2009) – abatacept could have a lower propensity to reactivate latent *M tuberculosis*. Clinical data by Smitten et al (2008), Schiff et al (2009) and the Orencia Summary of Product Characteristics (2010) for abatacept support this viewpont.

Thus, based on their different modes-of action, abatacept may offer the physician a viable therapeutic option opposite infliximab with regard to their propensity for TB reactivation.

6 Cost effectiveness

The cost-effectiveness of abatacept in the treatment of moderate to severe active RA and an insuffienct response or intolerance to cDMARDs including methotrexate or a TNFa agent, was compared to cDMARDs and infliximab. The analyses were conducted in accordance with the NICE reference case for economic evaluation. The perspective is restricted to the UK NHS and PSS and the cost-base year is 2009.

A patient-level simulation model was developed to estimate costs and outcomes (QALYs) of RA patients with an insufficient response or intolerance to prior cDMARDs, from the beginning of their treatment to death. The model uses mean change in HAQ score over time as effectiveness outcome. Costs were taken from UK sources and publications identified in the systematic review. Utilities were determined using a UK study. The model was constructed in conjunction with clinical, health economic and modelling experts and has been reviewed by independent modellers.

The model uses similar assumptions to previous models in RA, deriving utility from HAQ with the same caveats that this probably underestimates the impact of RA and the cost-effectiveness. The model adopts a life-time time horizon with 20-year data reported in the sensitivity analysis. Assumptions used in the model were informed by evidence obtained from the systematic review of published economic evaluations of biologic treatments for RA. When a range of values was available, its impact was tested in sensitivity analysis.

The results of the cost-effectiveness analysis suggest that in RA patients with moderate to severe active RA who have an insufficient response or intolerance to cDMARDs including methotrexate or an anti-TNFα agent, treatment with abatacept is cost effective compared with both cDMARDs and infliximab with cost per QALYs of £29,916 and £25,711, respectively. Probabilistic sensitivity analyses (PSA) confirm these findings.

6.1 Published cost-effectiveness evaluations

Identification of studies

6.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 9.10, appendix 10.

The objective for this submission is to assess the cost-effectiveness of abatacept in combination therapy with MTX among adult patients with moderate to severe active RA with an inadequate response to, or intolerance to, MTX monotherapy. Relevant comparators, as listed in the NICE scope for this appraisal, are the conventional DMARDs (cDMARDs) and biologic DMARDs; adalimumab, certolizumab pegol, etanercept, golimumab and. infliximab.

A systematic literature review was performed to identify the relevant economic evidence base for this submission. Published economic models as well as information on costs and cost-effectiveness including biologic DMARDs were identified. The search was an update of a recently published review presented within a NICE appraisal (Roche Tocilizumab 2009).

The following electronic databases were searched, no time restrictions were applied:

- Health Economic Evaluations Database (HEED) on February 24, 2010 via Dialog Datastar and updated on October 15, 2010.
- Medline (1980 to date (MEYY) and Medline-In-Process (MEIP) on March, 3 2010 via Dialog Datastar and updated on October 19,2010 via OVID.
- Embase March, 3 2010 via Dialog Datastar and updated on October 19, 2010 via OVID
- EconLit March, 4 2010 via Dialog Datastar and updated on October 18, 2010 via OVID
- NHS Economic Evaluation Database (NHS EED) and Health Technology Assessment (HTA) via the Cochrane Library,

accessed via Wiley Interscience, http://www.mrw.interscience.wiley.com/, were searched on March 3, 2010 and on October 15, 2010.

The NICE website was also searched in March 2010 and on October 15, 2010 for additional references.

Following removal of duplicates, HEED, Medline, Embase, and EconLit references were cross-checked with the findings of the Cochrane Library. Only English language publications/abstracts were considered. The search was further restricted manually according to inclusion/exclusion criteria listed below in Table B69.

The complete search strategy and search histories are provided in Appendix 10 (see section 9.10)

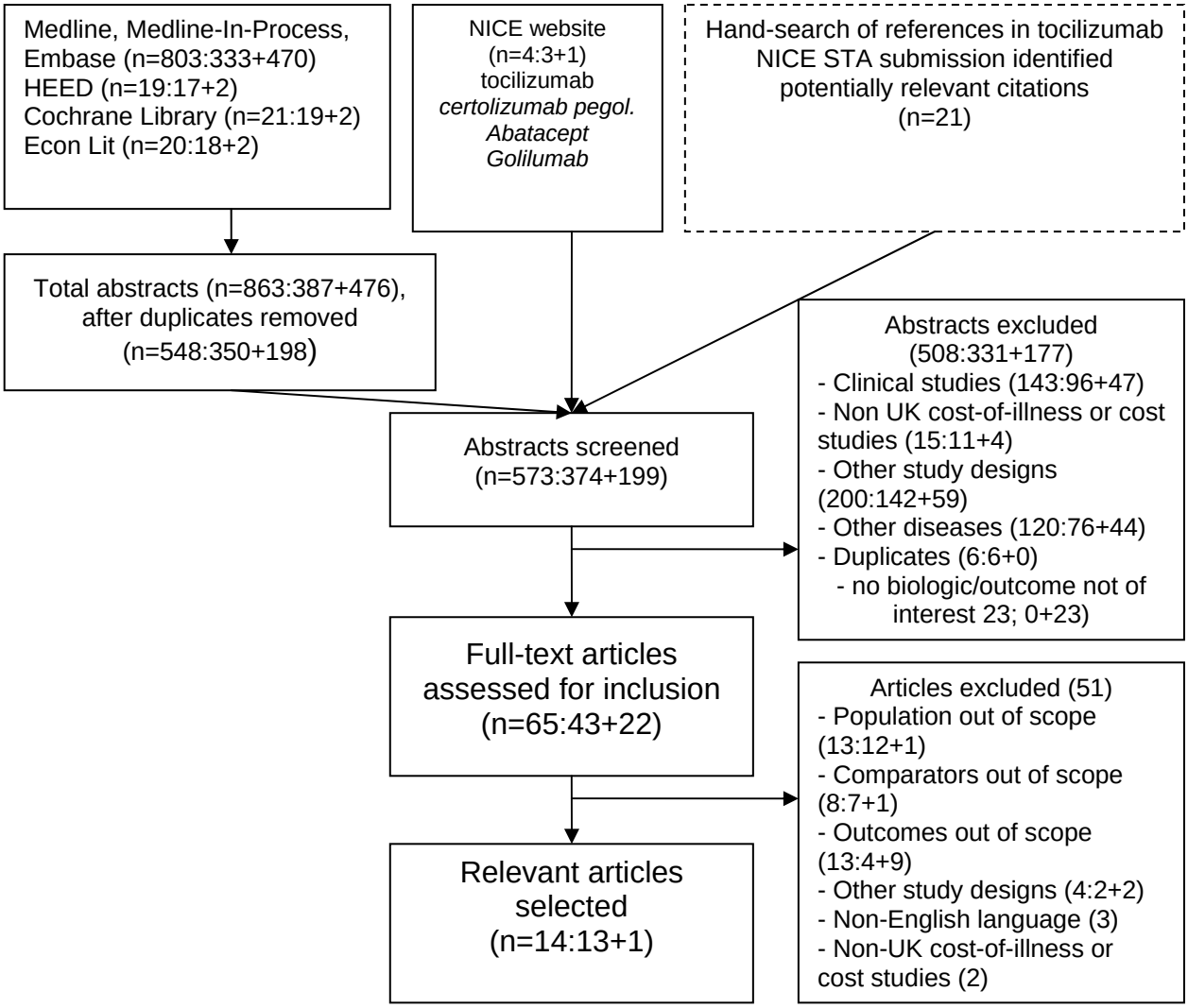
Table B 69 Study inclusion criteria used

Inclusion criteria	Population: adult patients suffering from moderate to severe RA with an inadequate response to, or intolerance to, MTX monotherapy. Interventions: abatacept in the proposed indication in combination with background MTX treatment; or /and biologic DMARDS + MTX (i.e. etanercept, adalimumab, infliximab, rituximab, tocilizumab, certolizumab pegol and golimumab). Comparators: biologic DMARDs as listed under interventions in combination with background MTX treatment, cDMARDs, or placebo (including 'do nothing' option and treatment with MTX alone). Outcomes: economic evaluations, costs, QALYs, ICERs and utilities Study design: cost-consequence/benefit analyses; cost-effectiveness/utility analyses; and UK-based cost studies and cost-of-illness studies. .

RA: Rheumatoid Arthritis, MTX: Methotrexate, QALY: Quality Adjusted Life Year, ICER: Incremental Cost Effectiveness Ratio

The flow diagram describing the economic evaluation search results and study selection process is illustrated in Figure B42. Please note that the number after the "+" represent the results from the updated search.

Figure B 42 Economic evaluation search flow diagram



Fourteen economic evaluations meeting the selection criteria for the indicated patient population and comparing abatacept with other therapies (or placebo) were included in this submission.

Description of identified studies

6.1.2 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. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

A summary of the economic evaluations included in this submission is presented in Table B2. A list of the studies excluded and reasons for their exclusion is provided in Table B3.

Table B70 Summary list of other cost-effectiveness evaluations

Study	Year	Country	Summary of model	Patient population (average age in years)	Comparator(s)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Bansback et al 2005	2005	Sweden	Cost-utility analysis with patient level simulation model with a life time horizon. Evaluation of treatment sequence after failure proceed to next regimen (DMARD)	cDMARD failure ≥ 2 drugs in pts with ACR50/DAS good or ACR20/DAS 28 moderate age base case 50 years	ACR50/DAS good			
					Adalimumab+MTX	Adalimumab + MTX: 2.1045	€ 102,610	€ 34,922
					Etanercept+MTX	Etanercept + MTX: 2.0974	€ 103,129	€ 35,760
					Infliximab+MTX	Infliximab+ MTX: 1.8379	€ 102,099	€ 48,333
					cDMARDs	cDMARDs: 1.1818	€ 70,387	-
					ACR50/DAS28 moderate		-	
					Adalimumab+MTX	Adalimumab + MTX: 2.7424	€ 114,462	€ 44,018
					Etanercept +MTX	Etanercept + MTX: 2.9515	€ 133,590	€ 51,976
					Infliximab +MTX	Infliximab + MTX: 2.4121	€ 114,732	€ 64,935
					cDMARDs	cDMARDs: 1.7041	€ 68,757	-
Barbieri et al 2005	2000	UK	Cost-utility analysis with Markov model with a time	cDMARD failure	Infliximab + MTX	Only incremental	£ 13,881 (1st year)	£33,618

Study	Year	Country	Summary of model	Patient population (average age in years)	Comparator(s)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
			horizon of 1 year expanded to lifetime Evaluation of treatment sequence after failure proceed to next regimen	(including MTX) age 57 years	MTX	QALYs given (0.26 for 1 year	UK £4,981	
Brennan et al 2007	2004	UK	Cost-utility analysis with patient level simulation model with a life time horizon. Treatment sequence when relapse	cDMARD failure ≥ 2 drugs age 54.9 years	Anti-TNF: Infliximab, Etanercept, Adalimumab cDMARD	5.1514 3.5931	£ 57,919 £ 20,706	£23,882
Certolizumab pegol STA submission	2009	UK	Cost-utility analysis with Markov model with a 45 year time horizon (to capture patients till 100 y)	cDMARD failure (age 52.2 years)	Adalimumab + MTX Infliximab + MTX Etanercept + MTX Rituximab + MTX vs. Certolizumab Pegol + MTX	2.801 2.692 2.908 2.77 2.903	£ 96,428 £104.460 £97,317 £92,936 £96,417	CZP dominates CZP dominates £ 197,037 (this Eta vs. CZP, in contrast to others) £26,157

Study	Year	Country	Summary of model	Patient population (average age in years)	Comparator(s)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Chen et al 2006	2004	UK	Cost utility analysis with patient level simulation with a life time horizon, with a partial treatment sequence	NA	Anti-TNF in sequence, 3rd place after failure of cDMARDs, 1st place or last in sequence	Adalimumab + MTX: 5.9053 Etanercept + MTX: 6.2974 Infliximab + MTX: 5.638 cDMARDs: 5.4169	£ 47,96 £ 60,329 £ 47,278 £ 16,509	£ 64,400 £ 49,800 £139,000
Golimumab STA submission	2010	UK	Cost-utility analysis with Markov model with a 45 year time horizon (to capture patients till 100 y)	cDMARD failure or TNF inhibitor failure	Methotrexate Adalimumab + MTX Certolizumab pegol + MTX Etanercept + MTX Infliximab + MTX Golilumab + MTX	4.569 5.792 5.768 6.133 5.651 5.827	£ 35,869 £ 66,875 £ 73,571 £ 17,208 £ 69,899 £ 66,875	-reference £ 25,353 £ 31,144 £ 25,514 £ 31,464 £ 25,346
Kobelt et al 2003	Not clearly stated presumably 2002	UK & Sweden	Cost-utility analysis with Markov model with a time horizon of 10 years	cDMARD failure (including MTX) (age 53.5 years, median)	Infliximab + MTX MTX	Eta + MTX: 6.2974 Infl + MTX: 5.638	£48,799 £36,859	1 year €34,800 per QALY 2 years €48,200 per QALY
Kobelt et al 2005	2004	Sweden	Cost-utility analysis with Markov model with a time horizon of 10 years	cDMARD failure (not including MTX) (age 53 years)	Etanercept + MTX MTX	cDMARDs: 5.4169 3.08	€176,915 €162,695	€37,331

Study	Year	Country	Summary of model	Patient population (average age in years)	Comparator(s)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Lekander et al 2010	2007	Sweden	Cost-utility analysis with Markov model with a time horizon of 20 years	Oral DMARD as background therapy (age 54 years)	Infliximab+ oral DMARDs Oral DMARDs	5.798 4.779	€190,089 € 66.825	€ 22,830
Russell et al 2009	2006	Canada	Cost-effectiveness analysis with a patient level decision model tree with a time horizon of 2 years Different treatment sequences	cDMARD failure or anti-TNF failure (45-60 years, average NR)	Abatacept, Etanercept-Inliximab_DMARDs (1) or etanercept, abatacept, infliximab-DMARDs (2) vs. etanercept-inflximab-adalimumab-DMARDs (3) with remission (A) and low disease activity state (B)	NA, only treatment success	CAN $39,759 (1B) CAN $40,952 (2B) CAN $40,489 (3B) CAN $38,061 (1A) CAN $39,154 (2A) CAN $38,565 (3B)	NA
Sany et al 2009	2001-2003	France	No model. Cost-effectiveness based on a RA patient cohort with cost year before and two years on treatment	RA patients with 98.7% on MTX (53.4±11.8 years)	Infliximab plus MTX in year 1 &2 vs. only MTX in previous year	NA, only per HAQ	Year before initiation of infliximab €6,633 vs. €27,650 year 1 infliximab	NA
Tocilizumab STA	2008	UK	Cost-utility analysis with Markov model with a life	Failure on cDMARDS	Sequence: Tocilizumab +MTX	8.946	£100,485	£19,870

Study	Year	Country	Summary of model	Patient population (average age in years)	Comparator(s)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
submission			time horizon Treatment sequence	or Failure on anti-TNF (age 52.5 years)	followed by etanercept, rituximab, leflunomide, gold, ciclosporin palliative care sequence without tocilizumab	7.775	£77.231	
Vera-Llonch et al 2008	2006	US	Cost-utility analysis with patient level simulation model with a life time horizon (and 10 year)	MTX IR patients (age 55-60 year, average NR)	Abatacept + MTX MTX	4.1 3.0	US $147,853 US $ 80,096	US $43,041 (95% CI 39,070-46,725)
Virkki et al 2008	Not specified	Finland	No model: Cost-utility and cost effectiveness model based on RA cohort with mean follow up of 21 months (range 1.5-78 months)	DMARD IR patients with infliximab as first biologic (mean age 51years ± 11 (SD))	Infliximab vs. continuation of cDMARD	0.179	NR	Median € 51,884 (IQR €36,193-€112,404) Mean €153.121
Wong et al 2002	1998	US	Cost-utility analysis with Markov model with a life time horizon based on cohort	MTX IR patients age in model 20 or 70 years cohort age (NR)	Infliximab + MTX MTX	13.33 12.99	US $ 93,000 US $ 84,100	US $30,500 per QALY (text), US $30,690 per QALY (table 4)

cDAMRD: conventional DMARD, MTX: Methotrexate, MTX-IR: Methotrexate-Inadequate Responder, HAQ: Health Assessment Questionnaire, NR: Not Reported, QALY: Quality Adjusted Life Year

\Table B 71 List of excluded studies and reasons for exclusion

Study	Reason for exclusion
Allaart et al 2007	Population : recent onset of RA
Bagust et al 2009	Study design: ERG review, not economic evaluation
Barra et al 2009	Comparator: mixed bag of anti-TNF treatments used (no distinction between interventions)
Brennan et al 2004	Intervention: monotherapy with biologic DMARD
Burton et al 2008	Outcomes: only indirect cost included as study focused on work productivity loss in the US
Chiou et al 2004	Population: not after MTX (or DMARD) failure/inadequate response
Choi et al 2002	Population: MTX naive patients Intervention: monotherapy with biologic DMARD
Cole et al 2008	Study design: quality-of-life study
Davies et al 2009	Population: not after MTX (or DMARD) failure/inadequate response
Farahani et al 2006	Intervention: no biologics
Fautrel 2005	Study design: not a cost-effectiveness analysis; non-UK based cost study.
Finckh et al 2009	Population : recent onset of RA
Globe et al 2010	Outcomes: only indirect cost included as study focused on work productivity loss
HTA 2009/2010	Population : failure on TNF
Instituto de efectivida Clinic y Sanataria	Study design: review of the literature
Jobanputra et al 2002	Study design: model updated and improved by Chen et al 2006
Karaca et al 2010	Study design: not a cost-effectiveness analysis; non-UK based cost study.
Kielhorn et al 2008	Population: after TNF inhibitor failure/inadequate response
Kobelt et al 2004	Comparator: mixed bag of anti-TNF treatments used (no distinction between interventions)
Kobelt et al 2009	Population: not clear definition of patient population at baseline, unknown whether after MTX (or DMARD) failure/inadequate response Comparator: mixed bag of treatments used (no distinction between interventions)
Lacroix et al 2009	Study design: not a cost-effectiveness analysis
Lindgren et al 2009	Population: after TNF inhibitor failure/inadequate response
Mittendorf et al 2008	Study design: quality-of-life study
Puolakka et al 2009	Outcomes: only indirect cost included as study focused on work productivity loss
Prokes et al 2009	Non-English publication
Pugner et al 2000	Study design: not a cost-effectiveness analysis
Schulze-Koops et al 2009	Non-English publication
Spalding & Hay 2006	Population: not after MTX (or DMARD) failure/inadequate response
Tanno et al 2006	Population: not after MTX (or DMARD) failure/inadequate response Intervention: monotherapy with biologic DMARD
Van den Hout et al 2010	Study design: discusses deficiencies in current evaluations of the cost-effectiveness
Vera-Llonch et al 2008	Population: after TNF inhibitor failure/inadequate response
Wailoo et al 2008	Population: not after MTX (or DMARD) failure/inadequate response Intervention: monotherapy with biologic DMARD
Ward et al 2010	Study design: not a cost-effectiveness analysis
Welsing et al 2004	Intervention: monotherapy with conventional DMARD
Welsing et al 2006	Intervention: no biologics

Westhof et al 2009	Study design, not a cost-effectiveness analysis, German study
Wolfe et al 2010	Study design, not a cost-effectiveness analysis, US study
Yuan et al 2010	Population: after TNF inhibitor failure/inadequate response

6.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[4] or Philips et al (2004)[5]. For a suggested format based on Drummond and Jefferson (1996), please see section 9.11, appendix 11.

A quality assessment for each cost-effectiveness study included in this submission is provided in Appendix 11, see section 9.11.

6.2 De novo analysis

Patients

6.2.1 What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.4 and 5.3.3, respectively? 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? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

The economic model is developed to assess the cost-effectiveness of abatacept in combination therapy with MTX among adult patients with moderate to severe active RA with an inadequate response to, or intolerance to, MTX monotherapy.

The base case for the cost-effectiveness analysis presented in this submission compares abatacept + MTX and all other biologic DMARDs + MTX (adalimumab, certolizumab pegol, etanercept,

[4] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.

[5] Philips Z, Ginnelly L, Sculpher M, et al (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

golimumab, inflximab all in combination with MTX) to a cDMARD. This approach is appropriate based on the current treatment pathway in the UK. The comparison against cDMARDs in the base case is a well recognised approach that has been utilised in previous NICE appraisals

In addition as described above in more detail (Section 2) for some patients a sc administered agent provides an adequate choice of therapeutic medicine, however there are patients who would benefit more from an IV administered drug. An IV administered agent would be more appropriate for patients who; cannot self inject, have compliance issues, are needle-phobic, suffer from memory issues or have special needs (see Section 2). With infliximab being the only biologic DMARD comparator administered by IV infusion it is appropriate that abatacept is compared directly to it, this analysis is also presented below.

The patient group included in this economic evaluation reflects the study populations from the trials described in sections 1.4 and 5.3.3 and the decision problem, as well as the indicated population for abatacept in the European Public Assessment Report (EPAR) published by the EMA in 2010.

The modelled population equates to the eligible population in clinical practice in the UK according to the BSR guidelines. The average age, the average HAQ score at baseline, and the proportion of females in the included patient group were taken from the abatacept arm of the AIM trial and are presented in Table B72 below. The baseline patient characteristics are consistent across abatacept and comparator trials and with the British Society for Rheumatology Biologics Register (BSRBR) patient registry data, in particular for age and gender distributions (Watson 2005).

The BSRBR mean HAQ score for the anti-TNF cohort is higher than for the AIM trial population, 2.1 and 1.7, respectively. This discrepancy is largely due to clinical trials recruiting patients with lower baseline HAQ, and the BSRBR being a rather ‘historical’ cohort when compared with those patients included in the abatacept clinical trials for this indication. Adopting the BSRBR characteristics would require some adjustments to the HAQ CFB results and no correlation between baseline HAQ, absolute and relative response would need to be assumed. For these reasons, the patient characteristics from the pivotal AIM trial are used in the model.

Since data from the UK were available from the General Practice Research Database (GPRD) for weight distribution of RA patients, these data were used, leading to an average weight of 71.6kg, which is in line with the AIM trial. The gender-related patient weight distribution for modelled patients is presented in Table B73.

Table B 72 Age, gender, HAQ value according to AIM trial

Patient characteristic	Mean	SD
Age	51.50	12.90
Female	77.80%	-
Baseline HAQ score	1.70	0.70

HAQ: Health Assessment Questionnaire
Source: BMS AIM trial data abatacept arm, Clinical Study Report

Table B 73 Gender-related patient weight distribution for RA patients

Weight (kg)	Male distribution	Female distribution
Below 50	2%	10%
51-55	2%	10%
56-60	5%	13%
61-65	6%	13%
66-70	9%	13%
71-75	11%	10%
76-80	13%	9%
81-85	13%	7%
86-90	11%	5%
91-95	9%	3%
96-100	6%	3%
100+	13%	6%
Total	100%	100%

Source: GPRD 2000-2008, BMS, data on file

Model structure

6.2.2 Please provide a diagrammatical representation of the model you have chosen.

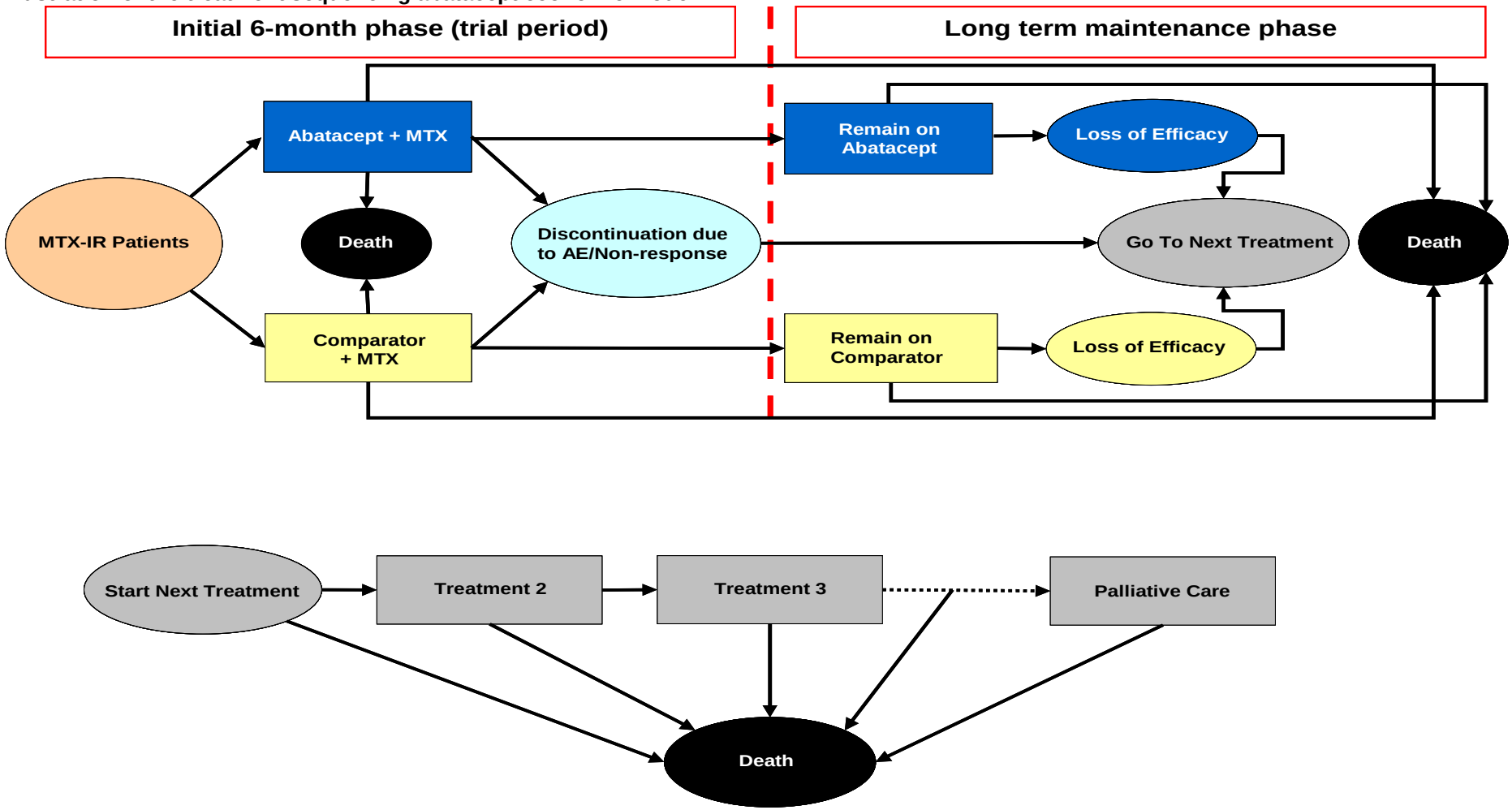
The model structure is illustrated in Figure B2.

The model is a patient-level simulation model which follows patients who are MTX-inadequate responders (MTX-IR) through different treatments until death. The treatment-sequence includes six treatments and palliative care as last line. The model has three arms representing three alternative treatment sequences; only one comparator arm is presented in Figure B2 for illustrative purposes.

The model can be explained using three phases: 1) the first 6 months of treatment; 2) the time on treatment following a treatment response; and 3) switching to another treatment option.

When entering the model, an individual MTX-IR patient is sampled and assigned baseline characteristics (i.e. age, gender, weight, HAQ score). This patient is cloned three times and three identical patients are allocated to first-line treatment with abatacept + MTX or to two possible comparators, also in combination with MTX. These 'clones' follow the treatment arms under equal conditions.

Figure B 43 Illustration of the treatment sequencing abatacept economic model



MTX: Methotrexate, MTX-IR: Methotrexate-Inadequate Responder, AE: Adverse Event

6.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.4.

The model is based on the Birmingham Rheumatoid Arthritis Model (BRAM) (Barton et al 2004, Chen et al 2006), which has previously been used as the basis for several economic models and as part of NICE single and multiple technology appraisal submissions for RA treatments (Brennan et al 2007/2004, Barton et al 2004, Chen et al 2006).

In a patient-level simulation model, individual patients are sampled and assigned different baseline characteristics. This patient is cloned three times and three identical patients are allocated to first line treatment with abatacept plus MTX, i.e. a cDMARD and infliximab plus MTX. These 'clones' follow the treatment arms under equal conditions.

Barton et al (2004) describe the intention behind this type of model as the creation of "a realistic set of virtual patient histories". In contrast to a cohort-model, a patient-level simulation presents the variability in outcomes across individuals, rather than a single average outcome. Therefore, the model structure was considered most appropriate as it allowed for a realistic representation of the complex nature of RA as a disease, and the heterogeneity of causal factors, without relying on over simplistic assumptions or jeopardising transparency.

Similar models have also been used within other NICE appraisals of the biologics for RA.

The base case for the cost-effectiveness analysis presented in this submission compares abatacept + MTX and all other biologic DMARDs + MTX (adalimumab, inflximab, etanercept, certolizumab pegol, golimumab all in combination with MTX) to a cDMARD. This approach is in line with previous NICE appraisals in RA such asTA130 and TA195.

In addition there is a subgroup of patients for who sc administration may not preferable, and for whom an IV infusion would be more appropriate. As described above, IV administration would be more appropriate for patients who; cannot self inject, have compliance issues, are needle-phobic, suffer from memory issues or have special needs (see Section 2).. Therefore abatacept plus MTX is also directly compared to infliximab plus MTX, since infliximab is the only biologic DMARD comparator also administered by IV infusion.

6.2.4 Please define what the health states in the model are meant to capture.

Health states were not used in the model. However, different costs and utilities were assigned to patients according to HAQ score at various time points in the model. Therefore, HAQ score intervals for disease-related costs and utilities were used as proxy health states to estimate results.

6.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

The analysis explicitly models the nature of RA by using changes in HAQ score over time. The worsening of HAQ score is due both to treatment discontinuation and to the underlying disease progression modelled as a latent yearly HAQ progression and treatment-specific annual HAQ progression. The model considers the decreased HRQL experienced by RA patients by mapping utility values according to HAQ score intervals (Bansback et al 2005).

The model compares the lifetime benefits and costs with abatacept plus MTX vs. comparators by taking into account efficacy, safety, HRQL, mortality, medical resource use and costs over a patient's lifetime.

The chronic and progressive nature of the disorder is captured in the treatment-sequence modelling over a lifetime time horizon. A patient can receive up to eight lines of therapy, including first-line active treatment with abatacept or the comparator, and always palliative care as the last stage before death.

Finally, as described in section 2.1 patients with RA are subject to a higher risk of death than those without RA; therefore an elevated mortality risk is used in the model to reflect the reduced life expectancy experienced by RA patients (Wolfe et al 1994). The adjustment consists of an RA risk multiplier related to each individual's HAQ score. The formula for the mortality risk adjustment is HAQ RR=1.33/unit (95% CI=1.10-1.61) and derived from Wolfe and colleagues 1994. This adjustment method was recommended by the NICE evidence review group following the review of the previous abatacept submission (Wolfe et al 1994).

6.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Key features of the model are presented in Table B74.

Table B74 Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	Life time	Chronic, progressive disease: health and economic outcomes accumulating over a long time period.	N/A
Cycle length	N/A	Patient simulation model	
Half-cycle correction	N/A	Patient simulation model	
Were health effects measured in QALYs; if not, what was used?	Yes	Reference case NICE scope	NHS GMTA June 2008
Discount of 3.5% for utilities and costs	Yes	Reference case NICE scope	NHS GMTA June 2008
Perspective (NHS/PSS)	NHS and PSS	Reference case NICE scope	NHS GMTA June 2008

Comment: NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years

Technology

6.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

The decision problem states that the relevant comparators for abatacept are biologic DMARDs and a cDMARD. Therefore, the comparators included in the model are biologic DMARDs licensed

and recommended in the UK for RA MTX-IR patients: adalimumab (SPC), certolizumab pegol (TA186, 2010), etanercept (SPC), golimumab (Appraisal consultation document October 2010), infliximab (SPC), and a cDMARD.

Please note that details on the dosing and frequency of biologic DMARDs are reported in section 6.5.5.

The model is a treatment sequence model and patients switch to cDMARDs after failure of first line biologic DMARD. Patients followed the following treatment sequence of cDMARDs; leflunomide, gold, azathioprine, ciclosporin, penicillamine, palliative care.

6.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, 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.

Throughout the model, treatment switch and treatment continuation are defined. During the first active 6 months of treatment, a patient can discontinue treatment for three reasons:

lack of response in terms of HAQ CFB <0.3

serious adverse events (SAEs);

all cause mortality and HAQ related mortality.

A responding patient (HAQ CFB >0.3) will remain on active treatment until he/she does not respond anymore (this could be after several years) or when the patient dies.

A patient may switch/discontinue treatment due to a lack of a clinically relevant HAQ response or due to SAEs. A clinically relevant HAQ response is defined as a change from baseline (CFB) in HAQ of > 0.3, in accordance with the endpoints defined in the different clinical trials (AIM, ATTEST).

Although the DAS28 score is commonly used for decisions relating to decisions in the clinical settings, as recommended in NICE guidance, few studies have linked it to utilities and resource use. As NICE prefers QALYs as an outcome measure, the CFB HAQ was used as the key clinical parameter in the model over any other measure of health effects described in Section 5, such as ACR responses and DAS28, The reason for this approach is that HAQ scores can be linked to utility values and has been widely referenced in the literature as a meaningful outcome in both clinical trials and practice. This approach is in line with several cost-effectiveness analyses, including the BRAM model (Barton et al 2004, Chen et al 2006, Malottki 2009).

The proportion of patients with SAEs that lead to discontinuation is assessed for a period of 6 months from the start of a treatment.

Patients not responding to or discontinuing treatment will move on to the next treatment according to a predetermined treatment sequence (see section 6.2.7). The same treatment sequence is used in each treatment arm. Just before a treatment switch, the patient is assumed to have a flare of RA and the HAQ score increases sharply, resulting in a decrease in utility during this time.

Once the next treatment is initiated, the cycle begins again (i.e. response assessed after 6 months, proportion of patients experiencing SAEs after 6 months, non-responders switch to next treatment in the sequence, responders continue on treatment for the treatment-specific fixed duration). This process continues until the patient dies; the last treatment line in the sequence is palliative care. Patients can die at any time in the model; the risk of death for modelled RA patients depends on age, sex, and HAQ score.

6.3 Clinical parameters and variables

6.3.1 Please demonstrate how the clinical data were implemented into the model.

HAQ CFB was used in the model as the primary outcome measure of efficacy for the cost-effectiveness analysis. HAQ scores were mapped against utility values to obtain QALYs for the cost-utility analysis (see section 6.4.7). The HAQ CFB for biologic DMARDs was taken from the MTC results presented in section 5. HAQ CFB for cDMARDs was sourced from the literature (Poor & Strand 2004, Fumagalli et al 2002 and Chen et al 2006). No HAQ CFB was assumed for palliative care.

6.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

Not applicable to a patient-level simulation model.

6.3.3 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.

Not applicable to a patient-level simulation model.

6.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

In the model HAQ values were linked to utilities. This is detailed further in section 6.4.7 and 6.4.9.

6.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[6]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

The systematic review for the MTC, the MTC results and the structure of the economic model were validated by the following individuals:

[redacted]

[6] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

[redacted]

The economic model was validated by the following individuals:

- Four expert academic health economists:

[redacted]

[redacted]

[redacted]

[redacted]

Summary of selected values

6.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

A list of all the variables included in the model is presented in Table B57.

Table B75 Summary of model input variables included in cost-effectiveness analysis

Population characteristics	Mean	SD		In PSA	Source/ comment
Age	51.50	12.90		-	AIM trial
Female	77.80%	-		-	
HAQ baseline	1.70	0.70		-	
	Weight (kg)	**Male Dist.**	**Female Dist.**	**In PSA**	**Source/ comment**
Weight distribution	Below 50	2.0%	10.0%	-	GPRD (BMS, data on file)
	51-55	2.1%	9.6%	-	
	56-60	4.5%	12.9%	-	
	61-65	6.1%	12.6%	-	
	66-70	9.4%	13.3%	-	
	71-75	11.3%	10.1%	-	
	76-80	13.3%	8.7%	-	
	81-85	12.6%	6.5%	-	
	86-90	11.3%	4.6%	-	
	91-95	9.0%	3.5%	-	
	96-100	5.8%	2.6%	-	
	100+	12.6%	5.6%	-	
	Total	100%	100%	-	
Treatment efficacy: HAQ CFB at 6 months					
Mean HAQ CFB of 1st line treatment: patients inadequately responding to MTX					
Treatment	**Expected mean HAQ CFB**	**Low (2.5%CrL)**	**High (97.5%CrL)**	**In PSA**	**Source/ comment**
Placebo + MTX	-0.27	-0.30	-0.24	Yes	
Relative efficacy versus placebo + MTX					See section 5 and Appendix 9.14
MTX + Abatacept	-0.30	-0.42	-0.16	Yes	
MTX + Etanercept	-0.28	-0.48	-0.08	Yes	
MTX + Adalimumab	-0.33	-0.51	-0.16	Yes	
MTX + Infliximab	-0.19	-0.35	-0.03	Yes	
MTX + Certolizumab pegol	-0.39	-0.54	-0.23	Yes	
MTX + Golimumab	-0.34	-0.58	-0.09	Yes	

Mean HAQ CFB for 6 months for patients failed on biologics					
Treatment	**Mean HAQ CFB**	**Low (- 20%)**	**High (+ 20%)**	**In PSA**	**Source/ comment**
Leflunomide	-0.37	-0.44	-0.30	-	Poor&Strand 2004 Fumagalli et al 2002 Chen et al 2006 Chen et al 2006 Chen et al 2006 Assumed no HAQ CFB for palliative care Assumed +/- 20% for the 95% CI.
Gold	-0.30	-0.36	-0.24	-	
Azathioprine	-0.20	-0.24	-0.16	-	
Ciclosporin	-0.33	-0.40	-0.26	-	
Penicillamine	-0.20	-0.24	-0.16	-	
Palliative care	0.00	0.00	0.00	-	
HAQ related input variables	**Mean**	**Low**	**High**	**In PSA**	**Source/ comment**
HAQ response rate	0.30	-	-	-	AIM and ATTEST trial.
Treatment Initiation	3 months	-	-	-	Assumption
Time with rapid increase before treatment discontinuation	3 months	-	-	-	Assumption
HAQ related mortality (hazard ratio)	1.33	1.10	1.61	Yes	Wolfe et al 1994
Time on treatment for responding patients					
Treatment duration for patients on biologics	**Median (Mean) in years**	**Shape**	**Scale**	**In PSA**	**Source/ comment**
First-line biologic treatment + MTX	4.21 (8.82)	0.71	7.06	Yes	NHS assessment report TNF failure 24/11/2009 Chapter 10.12 UK BSRBR 1st line data Figure 155 (Malottki et al 2009)
Treatment duration for patients on cDMARDs	**Median (Mean) y**	**Shape**	**Scale**	**In PSA**	**Source/ comment**
Leflunomide	1.79 (4.09)	0.67	3.09	Yes	Abatacept TNF-IR submission referring to BRAM model (Barton et al 2004). Assumed Palliative care to be similar to
Gold	1.84 (3.85)	0.71	3.08	Yes	
Azathioprine	0.97 (1.95)	0.73	1.60	Yes	

Ciclosporin	1.18 (1.70)	1.00	1.70	Yes	ciclosporin These treatments follow after failure on biologic DMARD treatment.
Penicillamine	1.03 (2.69)	0.62	1.86	Yes	
Palliative care	1.18 (1.70)	1.00	1.70	Yes	
Treatment discontinuation due to Serious Adverse Events (SAEs)					
Treatment	**Mean % of patients discontinuing treatment**	**Low**	**High**	**In PSA**	**Source/ comment**
MTX + Abatacept	3.00%	2.40%	3.60%	Yes	Comment: Fixed effect model was used, he low and high values were based on + and – 20% due to the large CrL presented by the MTC (Appendix 9.14).
MTX + Etanercept	4.76%	3.81%	5.71%	Yes	
MTX + Adalimumab	0.50%	0.40%	0.60%	Yes	
MTX + Infliximab	10.74%	8.59%	12.89%	Yes	
MTX + Certolizumab pegol	12.84%	10.27%	15.41%	Yes	
MTX + Golimumab	2.63%	2.11%	3.16%	Yes	
Leflunomide	20.00%	16.00%	24.00%	Yes	Chen et al 2006
Gold	18.00%	14.40%	21.60%	Yes	Chen et al 2006
Azathioprine	16.00%	12.80%	19.20%	Yes	Kruger et al 1994
Ciclosporin	12.00%	9.60%	14.40%	Yes	Chen et al 2006
Penicillamine	13.00%	10.40%	15.60%	Yes	van Rijthoven et al 1991
Palliative care	0.00%	0.00%	0.00%	Yes	Assumption
Long term HAQ progression					
Treatment	**Mean**			**In PSA**	**Source/ comment**
Biologic interventions	0			Yes	NHS assessment report TNF failure (Malottki et al 2009)
cDMARDs	0.045			Yes	
Palliative care	0.06			Yes	
Utilities					
	Coefficient			**In PSA**	**Source/ comment**
Intercept	0.804			Yes	NHS assessment report

Slope	-0.203			Yes	(Malottki et al 2009), referring to Hurst et al 1997.
Coefficient HAQ^2	-0.045			Yes	
Cost input data					
Biologic DMARDs	**Cost (2010 £)**	**Dose per unit**	**Cost per administration for IV administered agents; One-off costs for sc administered agents**	**In PSA**	**Source/ comment**
Abatacept	£242	250 mg	£158	-	Note: All drug cost were obtained from the BNF 60. Administration cost: previous TNF-IR submission abatacept, inflated to 2010
Etanercept	£89	25 mg	£30	-	One time training from nurse specialist (community), thereafter self administration: PSSRU Curtis 2009 p.116. Inflated to 2010
Adalimumab	£358	40 mg	£30	-	One time training from nurse specialist (community), thereafter self administration: PSSRU Curtis 2009 p.116. Inflated to 2010
Infliximab	£420	100 mg	£310	-	Administration cost: previous TNF-IR submission abatacept, inflated to 2010
Certolizumab pegol	£358	200 mg	£30		One time training from nurse specialist (community), thereafter self administration: PSSRU Curtis 2009 p.116. Inflated to 2010

Golimumab	£775	50 mg	£30	-	Drug cost; appraisal consultation document, October 2010. Administration cost; one time training from nurse specialist (community), thereafter self administration: PSSRU Curtis 2009 p.116. Inflated to 2010
Vial wastage	**Included in analysis?**			**In PSA**	**Source/ comment**
Infliximab	Yes			-	
Dose escalation	**Etanercept**	**Adalimumab**	**Infliximab**	**In PSA**	**Source/ comment**
% patients	1%	8%	29%	Yes	DART study (Moots 2009)
Mean dose	37.5	80.6	5.0	Yes	
Mean time to escalation in weeks	52	52	52	Yes	
Disease related cost (HAQ related)					
HAQ score interval	**Direct costs (2010 £)**			**In PSA**	
< 0.6	£2,733			Yes	Kobelt et al 2002. Table 5, Cost include: hospitalisations, surgical, interventions, ambulatory and community care, and RA cDMARD medication
0.6 < 1.1	£3,668			Yes	
1.1 < 1.6	£4,127			Yes	
1.6 < 2.1	£4,767			Yes	
2.1 < 2.6	£5,522			Yes	
>= 2.6	£5,991			Yes	

Comment: cDMARD: conventional DMARD; HAQ: health assessment questionnaire; MTX: methrotrexate; NSAID: non-steroidal anti-inflammatory drugs; PSA: probabilistic sensitivity analysis.

6.3.7 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 intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan-Meier plots.

The assessment of response at 6 months for all treatments is based on the MTC results and the clinical data extracted during the trial period. Long-term relative effectiveness is based on time on treatment for each comparator modelled from the Kaplan-Meier plots for survival in treatment provided by the BSRBR data as cited in Malottki et al 2009 (NICE Assessment report for the treatment of RA after the failure of a TNF-inhibitor, Malottki et al 2009).

6.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

By necessity, models predicting future events based on short-term trials require assumptions to be made. The key assumptions of the model are presented in Table B76.

Table B 76 Model assumptions

Assumptions
All patients who are treated with biologic agents will use MTX as background therapy.
Baseline HAQ is assumed to follow a Beta distribution in order to restrict sampling to allowable ranges.
Changes in HAQ occur over a 3-month period. HAQ scores do not change quickly, but change gradually over time with a maximum HAQ value of 3.
Response to therapy is defined as a 0.3 improvement in HAQ score in all comparisons, since this is in accordance with the endpoint in the different clinical trials.
Average duration of therapy was equal to 4.21 years for all biologic treatments in first-line therapy. No patients discontinue due to lack of efficacy until 6 months when response is measured.
During the first 6 months patients discontinue due to serious adverse events (SAEs); no cost included.
From 6 months to end of model, effectiveness has been modelled as time on treatment, taking into account efficacy and safety.
After discontinuation, patient HAQ score will rebound back to their baseline HAQ plus the progression rate of treatment.
The treatment sequence after an insufficient response to the previous therapy is the same regardless of the comparator.
The reduction in HAQ score is assumed to lower the risk of mortality.
Health-related quality of life is assumed to decrease as HAQ scores increase. Relationship is assumed to be non-linear (based on Hurst quadratic approach).
Vial wastage was taken into account for infliximab
Dose increase was taken into account for infliximab, etanercept and adalimumab

HAQ: Health Assessment Questionnaire

6.4 Measurement and valuation of health effects

Patient experience

6.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

RA is a degenerative disease of the joints rendering it a chronic condition for patients diagnosed at any stage of the disease. RA places a substantial burden on patients' quality of life by limiting the functioning and daily activities of individuals and causing substantial pain and discomfort. As described in section 2.1, this disorder is characterised by inflammation and swelling of synovial joints leading to joint deformity, functional impairment, pain, fatigue, and ultimately, disability. Pain, fatigue and loss of motion in joints make it harder for a patient with RA to remain in employment or live normally (i.e. activities in daily living).

Other aspects affecting patients' quality of life are; the high rate of morbidity in RA, as well as many common RA co morbidities such as hypertension, depression, gastroenterological diseases, and respiratory diseases (Brouwer et al 2004). Details of the disease and its impact on quality of life are described in section 2.1 and examples of the decreased HRQL measures are described in Section 5.

6.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

As the disease progresses, a patient's HRQL will worsen over time. Medications such as conventional and biologic DMARDs seek to halt the progression of the disease and thus curb the deterioration in RA patients' quality of life.

HRQL data derived from clinical trials

6.4.3 If HRQL data were collected in the clinical trials identified in section 5 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.

- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

The SF-36 physical functioning and mental components were collected at 6 months and one year for the abatacept trials (AIM, ATTEST, and Kremer 2003/2003) as detailed in Section 5.5.3.7. However, this HRQL measure was not consistently used across trials and was thus not available for all comparator treatments relevant to the decision problem as described in Section 6.2.7.

Therefore HAQ was used to link to utilities and described further in Section 6.4.7 and 6.4.9.

Mapping

6.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

How HAQ was used to link to utilities is described further in Section 6.4.7 and 6.4.9.

HRQL studies

6.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 9.12, appendix 12.

A search was performed on the HTA reports Barton et al (2004), Chen et al (2006), and previous recently published NICE appraisals in RA (Abatacept TNF-IR submission, Tocilizumab submission and Malottoki 2009). An overview of the different utility algorithms identified is presented in Table B9.

Based on our search results, it has been decided that the NHS assessment report was used as a primary guidance for utilities, whereas the comments from the ERG study group on the TNF-IR abatacept submission were also considered in a scenario analysis (ERG study group on TNF-IR abatacept submission).

6.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.
- Appropriateness of the study for cost-effectiveness analysis.

An overview of the different utility algorithms identified is presented in Table B9, section 6.4.7 and 6.4.9.

6.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

Table B77 presents an overview of the different mapping methods used in key cost-effectiveness analyses and previous NICE appraisals/guidance in RA.

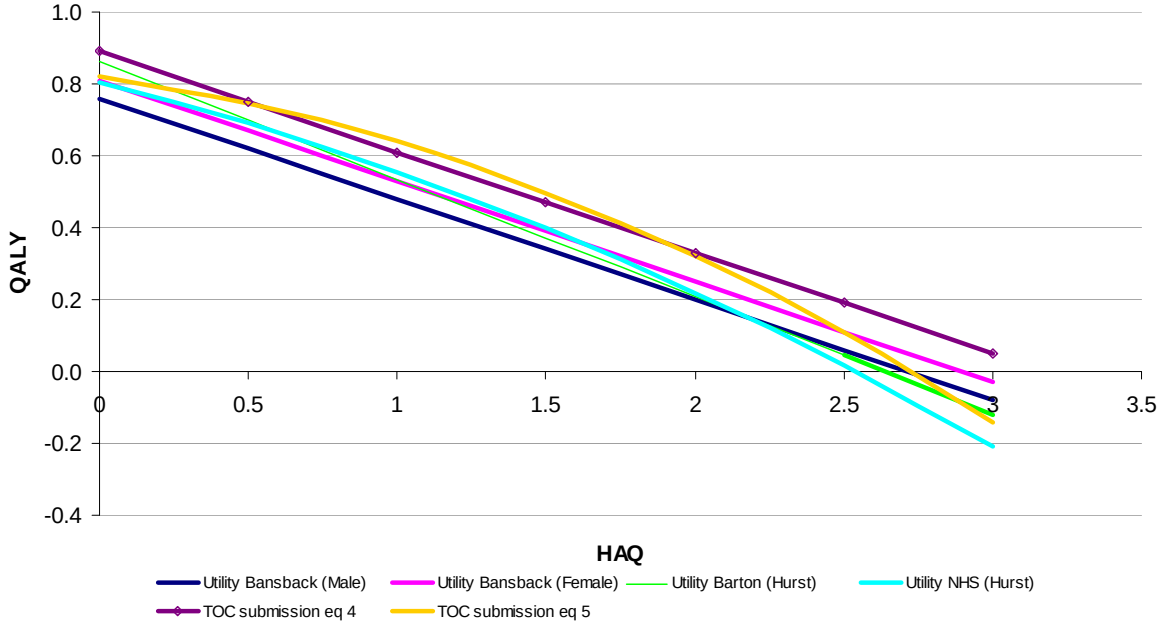
Table B 77 Utility mapping methods used in cost-effectiveness analyses and previous NICE submissions/guidance

Source	Method used
Abatacept TNF-IR STA submission 2007/2009	Bansback methodology as cited in Boggs et al 2002 HUI3: formula = 0.76 + (HAQ * -0.28) + 0.05 * (male 0 / female 1)
Barton et al 2004	Using EQ-5D social tariff for QoL variable as cited by Hurst et al 1997 0.862-0.327*HAQ
Chen et al 2006	As cited by Hurst et al 1997 *a*-*b*1HAQ-*b*2HAQ 0.804-0.203HAQ-0.045HAQ
Malottoki 2009 (NHS assessment report 2009)	As cited by Hurst et al 1997 *a*-*b*1HAQ-*b*2HAQ 0.804-0.203HAQ-0.045HAQ
Tocilizumab DMARD-IR STA submission	Hurst methodology (1997): QoL=0.862-0.327*HAQ Bansback methodology (2005): HUI3: formula = 0.76 + (HAQ * -0.28) + 0.05 * (male 0 / female 1) Eq 4: EQ-5D=0.89-0.28*HAQ Eq5: 0.82-0.11*HAQ-0.07*HAQ2

TNF-IR: Tumor Necrosis Factor-Inadequate Responder, HAQ: Health Assessment Questionnaire

Despite differences in the approach taken in the cost-effectiveness studies and past NICE appraisals, Figure B3 shows that for all methods used a HAQ change of 1 point is approximately equivalent to a change in utility of 0.3.

Figure B 44 Utility mapping methods (as described in Table 9)



HAQ: Health Assessment Questionnaire

Adverse events

6.4.8 Please describe how adverse events have an impact on HRQL.

Since the safety profile of abatacept is comparable to that of alternative biologics and cDMARDs in terms of proportion of patients experiencing AEs, the number, type, and severity of events, the AEs were not included in the model.

If a patient experienced (a) serious adverse event(s) during the first 6 months of treatment, treatment would be discontinued, however no utility decrements were applied (see Section 6.2.2).

Quality-of-life data used in cost-effectiveness analysis

6.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 6.4.3 to 6.4.8. Justify the choice of utility values, giving consideration to the reference case.

Health utilities were derived from HAQ scores. The model uses a commonly adopted approach of mapping the HAQ scores into health utilities. In the model, EQ-5D utilities were calculated from the HAQ based on the Hurst quadratic equation reported in Malottki 2009 (Malottki et al 2009).

The HAQ score is converted to an EQ-5D, which can then be used with survival outcomes to estimate the quality adjusted life years (QALYs).

(1) $$EQ\text{-}5D = 0.804 - 0.203*HAQ - 0.045*HAQ$$

As the Hurst algorithm has been accepted by NICE, the EQ-5D approach is used as the base case (Malottki 2009). In addition the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) guidelines report that HUI and EQ-5D are both deemed acceptable indirect methods to derive utility values for RA. As the HUI3 approach by Boggs et al (2002) has been accepted in previous appraisals (ERG report abatacept TNF-IR submission, 2007) a scenario analysis is performed.

Table B78 presents the utility values related to HAQ used in the base case in the model from Hurst, as cited in the NHS assessment report (Malottki 2009). The Hurst algorithm is illustrated in Figure B45.

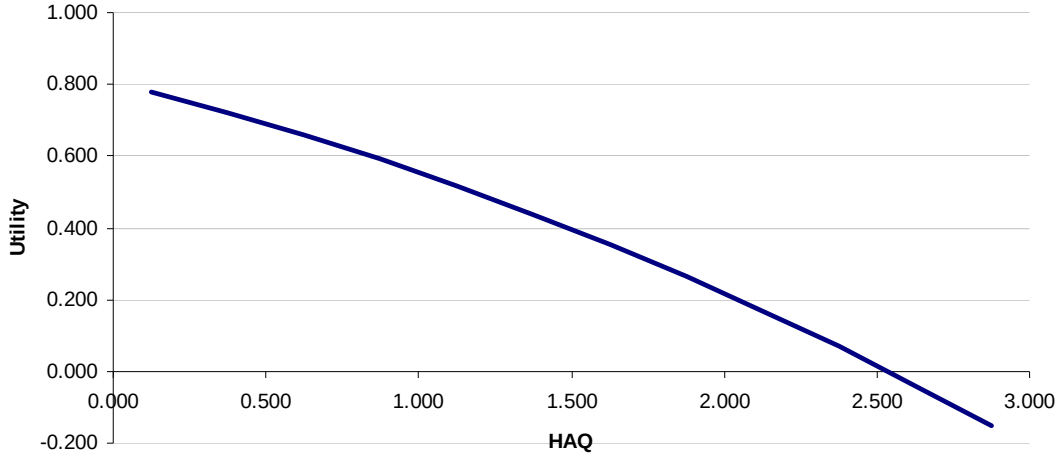
The limitation of using HAQ to derive utilities is that this method may not capture all dimensions of HRQL such as pain for example. As a result using HAQ to estimate utilities may underestimate the detrimental impact of RA on the patient as well as underestimating the impact of improvements that treatments may provide.

Table B78 Summary of quality-of-life values for cost-effectiveness analysis

HAQ score interval	Mid point HAQ score	Mid point utility
0-<=0.25	0.125	0.778
0.25-<=0.50	0.375	0.722
0.50-<=0.75	0.625	0.660
0.75-<=1.00	0.875	0.592
1.00-<=1.25	1.125	0.519
1.25-<=1.50	1.375	0.440
1.50-<=1.75	1.625	0.355
1.75-<=2.00	1.875	0.265
2.00-<=2.25	2.125	0.169
2.25-<=2.50	2.375	0.068
2.50-<=2.75	2.625	-0.039
2.75-<=3.00	2.875	-0.152

HAQ: Health Assessment Questionnaire

Figure B 45 HAQ related utility values



HAQ: Health Assessment Questionnaire

6.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[7]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Not applicable.

6.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

Health states were not used in the model. Patient costs and utilities were associated with different HAQ score intervals which covered potential variances in HRQL.

6.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

The CFB HAQ was used as the key clinical parameter in the model over any other measure of health effects described in Section 5, such as ACR responses. The reason for this is that HAQ scores can be linked to utility values and has been widely referenced in the literature as a meaningful outcome in both clinical trials and in practice. This approach is in line with several cost-effectiveness

[7] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

analyses including the BRAM model (Barton et al 2004, Chen et al 2006) and has previously been used in NICE appraisals and in the NICE 2009 assessment report of biologics for the treatment of RA (Malottki 2009).

Since adverse events were not included in the model, for the exception of the discontinuation rule due to SAEs, utility decrements for experiencing an AE were also excluded from the analysis.

6.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

The baseline HAQ score for modelled patients was 1.70 (see Section 6.2.1). Using the EQ-5D methodology to derive a utility as described in section 6.4.9, the baseline utility value is 0.33.

6.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

HRQL was not assumed to be constant over time throughout the model. Although HAQ progression was assumed to be constant over time for biologic DMARDs, an annual HAQ progression rate of 0.045 was applied to patients on cDMARDs and of 0.06 for palliative care. These rates are similar to those used in the NICE assessment report (Malottki 2009).

The annual HAQ progression rates used in published cost-effectiveness analyses and in past NICE submissions, including that in the NICE assessment report (Malottki 2009), are presented for comparison in Table B79.

Table B 79 Annual HAQ progression rates from cost-effectiveness analyses and previous NICE submissions/guidance

Source	Biologics	Conventional DMARDS (Non-biologics)	Palliative care
Abatacept TNF-IR STA submission 2007/2009	Abatacept: 0.012	0.012	0.012
Chen et al 2006	Adalimumab infliximab and etanercept 0.03	0.045	0.06
ERG report on abatacept submission 2007	Abatacept: 0.009	0.012	Unclear
Tocilizumab DMARD-IR STA submission	No progression (0)	0.0225	0.03
NHS assessment report 2009	No progression (0)	0.045	0.06

TNF-IR: Tumor Necrosis Factor-Inadequate Responder

6.4.15 Have the values in sections 6.4.3 to 6.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

Not applicable.

6.5 Resource identification, measurement and valuation

NHS costs

6.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

The clinical management of RA requires patients to have regular outpatient clinic visits, face-to-face consultations with a consultant or non-consultant physician in a rheumatology department, and regular laboratory testing. Occasionally patients may also be hospitalised. There is little documented evidence detailing resource use and costs relating to RA within the UK. For the current economic evaluation costs were obtained from the UK Kobelt et al 2002 publication (more details in Section 6.5.3 and 6.5.6).

6.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

Not deemed relevant for this submission, detailed resource use and cost were not collected for the current economic evaluation since cost data was obtained from Kobelt et al 2002.

Resource identification, measurement and valuation studies

6.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 9.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- country of study
- date of study
- applicability to UK clinical practice
- cost valuations used in study
- costs for use in economic analysis

- technology costs.

Since the economic model uses changes in functional status, as measured by the HAQ over time, treatment efficacy is also captured by improvement in HAQ score. A search was conducted in relation to UK cost data linked to HAQ scores. Several cost-effectiveness analyses provided an annual breakdown of costs in relation to HAQ ranges (Kobelt 2002 and 2005).

Kobelt 2002 estimated the 10 year cost of RA in the UK associated with HAQ levels. The estimate was based on data from cohort studies and cross-sectional surveys. The direct cost included hospitalisations, surgical, interventions, ambulatory and community care, and cDMARD medication. As no breakdown of the cost data was provided, an annual lump sum cost was used in the model and linked to 6 HAQ categories (see Section 6.5.6 for more details). Costs were corrected for inflation and discount rate.

6.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[8]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Not applicable.

[8] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Intervention and comparators' costs

6.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.

Drug acquisition costs were taken from the British National Formulary (BNF) 60 in line with section 1.10 and are presented in 2010 GBP (£) in Table B80 for biologic DMARDs. Abatacept is available in 250-mg vials at a list price of £302.40. However, based on an agreement between with the Department of Health, the net cost to the NHS is £242.17 per vial. Since Kobelt 2002 included the costs of cDMARDs within their cost estimates, these were excluded from the model. An overview of the drug cost is presented in Table B80.

Table B80 Drug unit costs for biologic DMARDs

Treatment	Unit Cost (2010 £)	Dose per unit	Dose description (SmPc)
Abatacept	£242.17	250 mg	500-1000mg (10mg/kg) week 0,2,4 thereafter every 4 wks
Rituximab	£175	100 mg	1000 mg wk 0 and 2, thereafter not more frequent then every 6 months
Etanercept	£89	25 mg	25mg twice weekly
Adalimumab	£358	40 mg	40 mg every other week
Infliximab	£420	100 mg	3mg/kg week 0, 2 and 6 thereafter every 8 weeks
Tocilizumab	£102	80 mg	8 mg/kg but no lower than 480 mg EO4W
Certolizumab pegol	£358	200 mg	400 mg week 0, 2 and 4 followed by 200 mg every 2 weeks
Golimumab	£775	50 mg	50 mg every 4 weeks

The administration cost for the IV biologic DMARDs were sourced from TA195 (TA195 Section 4.2.21), and for sc injections from the PSSRU. All costs were price indexed to 2010 values. The administration costs for biologic DMARDs are presented in Table B81.

Table B 81 Administration costs for biologic DMARDs

Biologic DMARDs	Route	Cost per Administration (2010 £)	Source
Abatacept	IV (30 min)	£158	Abatacept TNF-IR submission, also referred to in TA195 section 4.2.21;price indexed from 2008 to 2010
Etanercept	sc	£30	One time training from nurse specialist (community), thereafter self administration: PSSRU Curtis 2009 p.116. Inflated to 2010
Adalimumab	sc	£30	One time training from nurse specialist (community), thereafter self administration: PSSRU Curtis 2009 p.116 Inflated to 2010
Infliximab	IV (2-3hour)	£310	Abatacept TNF-IR submission;price indexed from 2008 to 2010
Certolizumab pegol	sc	£30	One time training from nurse specialist (community), thereafter self administration: PSSRU Curtis 2009 p.116 Inflated to 2010
Golimumab	sc	£30	One time training from nurse specialist (community), thereafter self administration: PSSRU Curtis 2009 p.116 Inflated to 2010

TNF-IR: Tumor Necrosis Factor-Inadequate Responders

Health-state costs

6.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 6.2.4.

Since evidence suggests that cost differs substantially according to functional status (Kobelt 1999, 2002 and 2005), direct medical costs included in the model were obtained from Kobelt et al (2002) for the UK setting. One publication was identified for the UK describing the direct medical costs associated with biologic treatment for MTX-IR RA patients. These costs are all provided in terms of functional capacity (i.e. linked to HAQ score). Direct costs include;

hospitalisations, surgical, interventions, ambulatory and community care, and cDMARDs (Kobelt 2002).

Table B82 Mean annual costs (£) per HAQ score

HAQ score interval	Direct costs (2010 £)
< 0.6	£2,733
0.6 < 1.1	£3,668
1.1 < 1.6	£4,127
1.6 < 2.1	£4,767
2.1 < 2.6	£5,522
>= 2.6	£5,991

HAQ: Health Assessment Questionnaire

Adverse-event costs

6.5.7 Please summarise the costs for each adverse event listed in section 5.9 (Adverse events). These should include the costs of therapies identified in section 2.7. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.

Since the safety profile of abatacept is comparable to that of alternative biologic DMARDs and cDMARDs in terms of proportion of patients experiencing AEs, the number, type, and severity of events, the costs of AEs and SAEs were excluded from the model.

Miscellaneous costs

6.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

Not applicable.

6.6 Sensitivity analysis

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

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

The uncertainty around structural assumptions has been investigated. The following assumptions were tested in scenario analysis.

Scenario analysis was performed to test the relation of HAQ with utility values. In the base case analysis the EQ-5D equation from Hurst et al 1997 was used whereas in a scenario analysis the HUI3 equation by Bansback et al 2005 was used.

$$HUI3 = 0.76 - 0.28\ HAQ + 0.05\ Female$$

6.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 6.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

First and second order Monte Carlo simulations were used to estimate the costs and benefits of the treatment under evaluation. First order uncertainty is described below for the deterministic sensitivity analysis and second order uncertainty is described in Section 6.6.3 for the probabilistic sensitivity analysis.

Since the model is a patient-simulation model, the following patient characteristics and source data are sampled.

- Age, gender, weight and baseline HAQ and time of death;
- Occurrence of discontinuation during the first 6 months of treatment due to adverse events (AEs); if discontinuation occurs, time point of discontinuation;
- Change from baseline to 24 weeks in HAQ and time point of discontinuation for responders;
- Dose increase of infliximab, adalimumab and etanercept
- By sampling many times, costs, life years gained (LYG), and QALYs gained for individual patients are accumulated and a deterministic average across patients is calculated. A single deterministic run of the model simulates the treatment of many hundreds or thousands of individual patients (O'Hagan et al 2007). Explorative analyses showed that a deterministic analysis with 8,000 simulated patients resulted in stable and robust analyses.

One way sensitivity/scenario analysis is conducted on the following key parameters in the model (Table B83).

Table B 83 Scenario and sensitivity analyses performed for cost-effectiveness analysis

Base case	Scenario
Discount rate 3.5%	Both 0%
Discount rate 3.5%	Benefits 1.5% and 6% costs
Discount rate 3.5%	Both 6%
Life time horizon	5 years
Utilities	Bansback
HAQ response rate	0.22
Vial wastage infliximab	No
Dose increase infliximab	No

HAQ: Health Assessment Questionnaire

6.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 6.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

A PSA is conducted on the following key parameters in the model (see Table B16). Flat priors have been assumed.

- HAQ change from baseline to 6 months due to average treatment effects;
- Treatment duration of MTX-IR population and population on cDMARDS;
- Long term HAQ progression;
- Occurrence of discontinuation during the first 6 months of treatment due to adverse events (AEs);
- Hazard ratio HAQ related mortality;
- Utility values
- Dose escalation
- Mean annual disease costs

The parameters used for the PSA are presented in Table B84. The PSA was conducted only for the base case analysis. For the source data see Section 6.3.6.

Table B 84 Parameters for the PSA

Relative efficacy versus placebo + MTX	**Expected mean HAQ CFB**	**Low (2.5%CrL)**	**High (97.5%CrL)**	**Distribution**
MTX + Abatacept	-0.30	-0.42	-0.16	Normal
MTX + Etanercept	-0.28	-0.48	-0.08	Normal
MTX + Adalimumab	-0.33	-0.51	-0.16	Normal
MTX + Infliximab	-0.19	-0.35	-0.03	Normal
MTX + Certolizumab pegol	-0.39	-0.54	-0.23	Normal
MTX + Golimumab	-0.34	-0.58	-0.09	Normal
Placebo + MTX	-0.27	-0.30	-0.24	Normal
HAQ CFB for 6 months for patients failed on biologics	**Lower**	**Upper**		
cDMARDs	Assumed 20% CrL	Assumed 20% CrL		Normal
Treatment duration	**Shape**	**Scale**		
Biologic DMARDs	Assumed +/- 20%	Assumed +/- 20%		Normal
cDMARDs	Assumed +/- 10%	Assumed +/- 10%		Normal
Long-term annual HAQ progression	**Lower**	**Upper**		
HAQ progression	Not distribution included			
Discontinuation first 6 months due to SAE	**Lower**	**Upper**		**Distribution**
Biologic DMARDs	Assumed 20%	Assumed 20%		Beta
cDMARDS	Assumed 20%	Assumed 20%		Beta
Utilities	**Mean**	**se**		
Intercept	0.804	0.047449		Normal
Slope	-0.203	0.075765		Normal
Coefficient HAQ^2	-0.045	0.026276		Normal
Dose increase	**Mean**	**Lower**	**Upper**	
Etanercept		Assumed	Assumed	

% patients	1%	1%	1%	Beta
Mean dose	37.5	30.0	45.0	Normal
Mean time to escalation in weeks	52.0	41.6	62.4	Normal
Adalimumab				
% patients	8%	5%	11%	Beta
Mean dose	80.6	64.48	96.72	Normal
Mean time to escalation in weeks	52.0	41.60	62.40	Normal
Infliximab				
% patients	29%	23%	35%	Beta
Mean dose	5.0	4.0	6.0	Normal
Mean time to escalation in weeks	52.0	41.6	62.4	Normal
HAQ related disease cost	**se**			
Annual HAQ related disease cost	Assumed 20%			Normal
Other				
HAQ related mortality	1.33	1.10	1.61	Normal

MTX: Mixed Treatment Comparison, HAQ: Health Assessment Questionnaire, CFB: Change from Baseline, CrL: Credibility Limit, cDMARD: conventional DMARD

6.7 Results

This economic analysis demonstrates that abatacept in combination with MTX is a cost-effective treatment option in comparison with cDMARDS for patients with moderate to severe RA who have had an inadequate response to MTX. In addition when abatacept is compared directly with infliximab, the only other biologic delivered by IV administration, abatacept is shown to be a cost-effective strategy. The PSA confirm these findings.

Clinical outcomes from the model

6.7.1 For the outcomes highlighted in the decision problem (see section 4), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Table B85 Summary of model results compared to QALY Adjusted mean HAQ change from baseline at 24/26 weeks

Treatment	Adjusted mean HAQ CFB at 24/26 weeks	Relative efficacy versus abatacept +MTX at 24/26 weeks	
Placebo + MTX	-0.27 (-0.30; -0.24)	-0.30 (-0.42; -0.16)	The QALYs gained for abatacept are higher compared with these for cDMARD and infliximab. This is in line with the findings from the MTC, as abatacept is found the be more efficacious compared to cDMARD and most likely slightly better compared to infliximab
Infliximab + MTX	-0.46 (-0.62; -0.30)	-0.11 (-0.30; 0.10)	
Abatacept + MTX	-0.57 (-0.69; -0.43)		

HAQ: Health Assessment Questionnaire, CFB: Change from Baseline, MTX: methotrexate, QALY: Quality Adjusted Life Year, MTC: Mixed Treatment Comparison, cDMARD: conventional DMARD

6.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Not applicable.

6.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

Not applicable.

6.7.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

Not applicable.

6.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

The model does not provide the disaggregated incremental QALYs and costs per health state.

Table B86 presents the resource use predicted by category of cost for each comparator.

Table B86 Summary Summary of predicted resource use by category of cost (results base case analysis)

Breakdown of Costs	cDMARD	Certolizumab pegol	Etanercept	Infliximab	Adalimumab	Abatacept	Golimumab
Drug costs (£)	NA	£32,150	£35,649	£29,645	£40,505	£34,742	£43,844
Admin costs (£)	NA	£28	£30	£7,303	£30	£8,052	£30
Direct costs (£) *	£76,276	£71,798	£71,974	£72,475	£71,386	£71,754	£71,498

cDMARD: conventional DMARD
* Direct costs include the drug cost of cDMARD

Base-case analysis

6.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

Table B87 Base case results (each biologic DMARD vs. cDMARD)

	Total QALY	Total LY	Total cost	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus cDMARD (QALYs)
cDMARD	4.88	27.39	£76,276				
Certolizumab pegol	6.16	27.61	£103,976	£27,700	0.22	1.28	£21,592
Etanercept	6.12	27.60	£107,653	£31,377	0.22	1.24	£25,361
Infliximab	5.96	27.57	£109,419	£33,143	0.19	1.08	£30,693
Adalimumab	6.29	27.64	£111,922	£35,645	0.25	1.41	£25,359
Abatacept	6.16	27.60	£114,548	£38,272	0.21	1.28	£29,916
Golimumab	6.25	27.63	£115,372	£39,096	0.24	1.37	£28,592

cDMARD: conventional DMARD, QALY: Quality Adjusted Life Year, ICER: Incremental Cost Effectiveness Ratio, LY: Life Years, LYG: Life Years Gained

Table B 88 Base case results (abatacept vs. cDMARD and vs. infliximab)

	Total QALY	Total LY	Total cost	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus abatacept (QALYs)
cDMARD	4.880	27.386	£76,276	£38,272	0.21	1.28	£29,916
Infliximab	5.959	27.572	£109,419	£5,129	0.02	0.20	£25,711

cDMARD: conventional DMARD, QALY: Quality Adjusted Life Year, ICER: Incremental Cost Effectiveness Ratio

The base case for the cost-effectiveness analysis presented in this submission compares abatacept plus MTX and all other biologic DMARDs (adalimumab, certolizumab pegol, etanercept, golimumab, inflximab, all in combination with MTX) to a cDMARD. In addition, abatacept plus MTX has been separately compared to infliximab plus MTX, as described in Sections 2 and 6.2 there is a group of patient for whom sc administration may not be appropriate, with infliximab being the only biologic DMARD comparator administered by IV infusion.

Our analysis shows that abatacept in combination with MTX is a cost-effective treatment option in comparison to cDMARDS for patients with RA who have had an inadequate response to MTX. The ICER for abatacept against cDMARDs is comparable to those ICERs for biologic DMARDs which have been previously been recommended by NICE. In addition when abatacept is compared with the only available other biologic delivered by IV, abatacept is demonstrated to be a cost-effective strategy compared to inflximab. Abatacept is expected to accrue more benefits with slightly higher costs, which is in line with the findings from the MTC. The PSA confirm these findings.

Sensitivity analyses

6.7.7 Please present results of deterministic sensitivity analysis.

Consider the use of tornado diagrams.

Deterministic sensitivity analyses were not performed, since we have tested the robustness of the model with scenario analyses and a PSA. For scenario analyses (i.e. discount rate, time horizon, HAQ response rate, dose increase, and vial wastage) and structural deterministic analyses (i.e. utility approach) see Section 6.7.9.

6.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

Table B 89 PSA results base case (each biologic DMARD vs. cDMARD)

	Total QALY			Total cost			Incremental costs (£)			Incremental QALYs			ICER (£) versus cDMARD (QALYs)		
	Mean	**2.5%**	**97.5%**	**Mean**	**2.5%**	**97.5%**	**Mean**	**2.5%**	**97.5%**	**Mean**	**2.5%**	**97.5%**	**Mean**	**2.5%**	**97.5%**
cDMARD	4.75	4.65	4.86	75,095	73,754	76,472									
Certolizumab pegol	6.05	5.88	6.22	103,385	100,721	106,119	28,290	25,388	30,794	1.30	1.12	1.49	21,833	17,056	27,531
Etanercept	6.02	5.84	6.20	107,067	104,267	109,844	31,973	29,615	34,380	1.27	1.14	1.39	25,232	21,339	30,043
Infliximab	5.84	5.68	6.02	108,456	105,453	111,643	33,362	30,282	36,364	1.09	0.92	1.26	30,565	24,084	39,535
Adalimumab	6.15	5.98	6.34	111,436	108,594	114,601	36,342	33,483	39,392	1.40	1.22	1.58	25,963	21,256	32,207
Abatacept	6.07	5.91	6.24	114,596	111,278	117,673	39,502	36,738	42,422	1.32	1.20	1.44	29,888	25,538	35,341
Golimumab	6.13	5.97	6.30	114,105	110,812	117,436	39,010	36,044	42,014	1.38	1.21	1.57	28,332	22,915	34,855

cDMARD: conventional DMARD, QALY: Quality Adjusted Life Year, ICER: Incremental Cost Effectiveness Ratio

Table B 90 PSA results base case (abatacept vs. cDMARD and vs. infliximab)

	Incremental costs (£) Mean and 95% CI			Incremental QALYs Mean and 95% CI			ICER (£) versus cDMARD (QALYs) Mean and 95% CI			% of abatacept being CE at WTP £30,000
	Mean	**2.5%**	**97.5%**	**Mean**	**2.5%**	**97.5%**	**Mean**	**2.5%**	**97.5%**	
cDMARD	39,502	36,738	42,422	1.32	1.20	1.44	29,888	25,538	35,341	55%
Infliximab	6,140	3,568	8,889	0.23	0.05	0.42	26,680	8,547	163,810	61%

cDMARD: conventional DMARD, QALY: Quality Adjusted Life Year, ICER: Incremental Cost Effectiveness Ratio

Figure B 46 Scatter plot all treatments vs. cDMARD

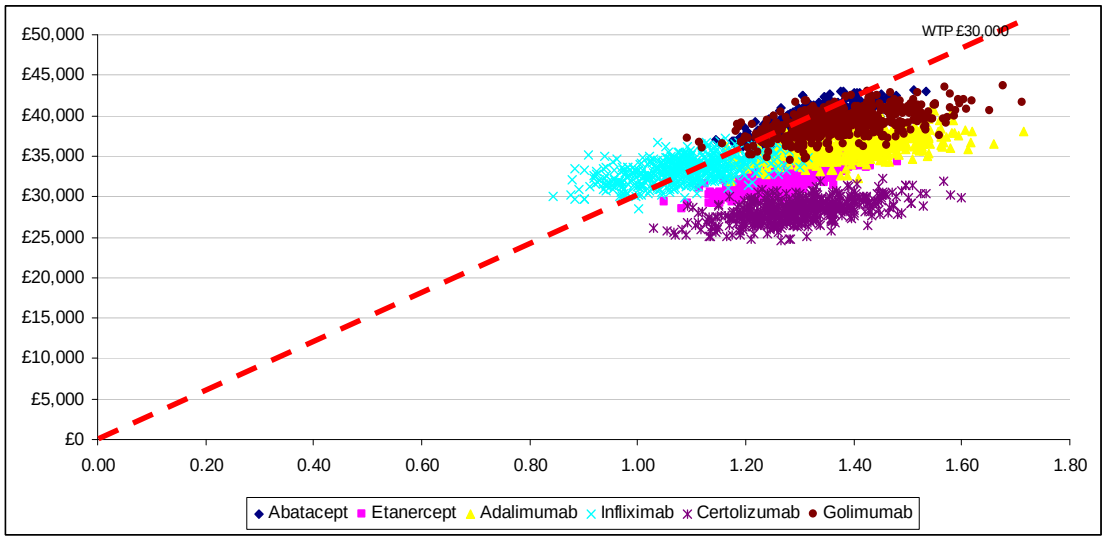


Figure B 47 Scatterplot abatacept vs. cDMARD

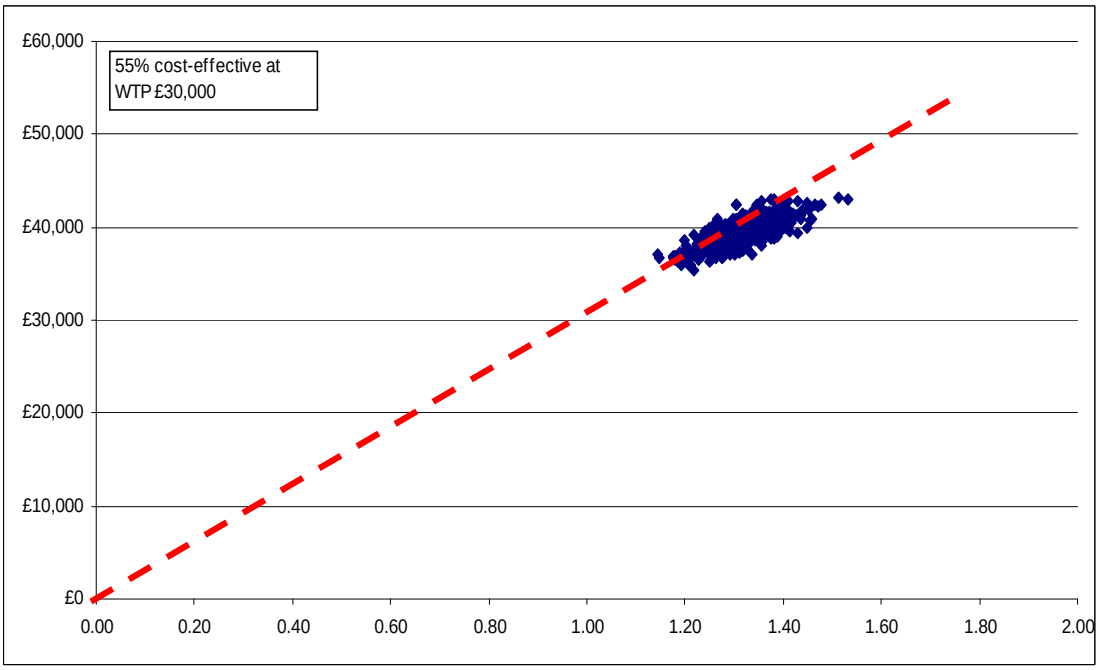


Figure B 48 Scatterplot abatacept vs. infliximab

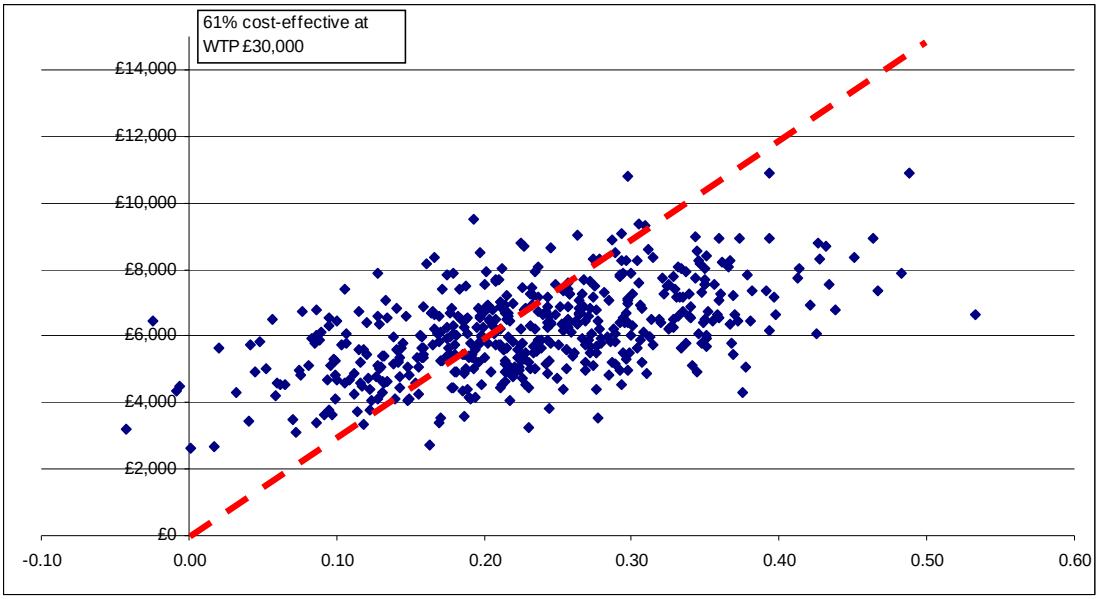
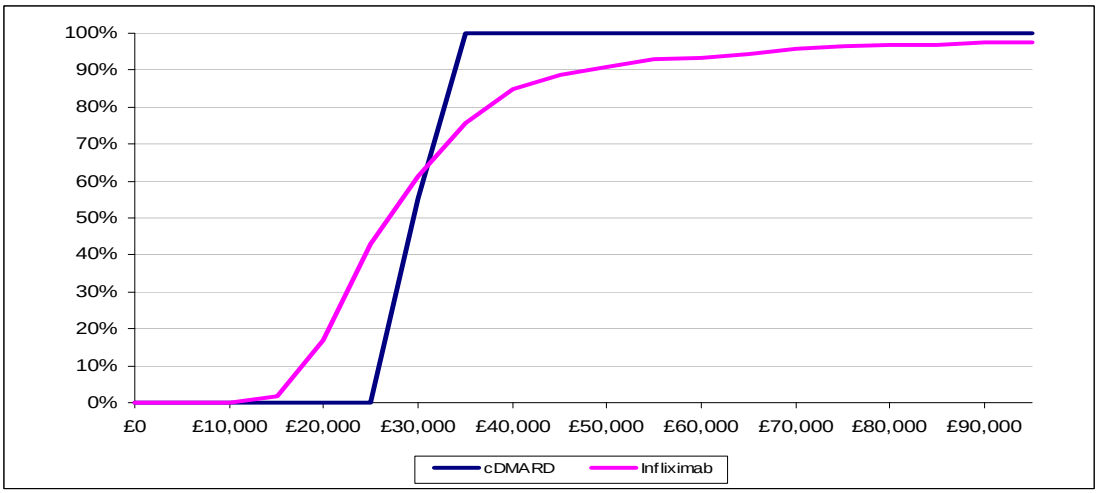


Figure B 49 CEA curve abatacept vs. cDMARD and vs. infliximab



cDMARD: conventional DMARD

6.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

The results of the different scenario analyses and the structural sensitivity analysis performed are presented in Table B50 and Table B51 for each comparator. The incremental values of the parameter in both the base case scenario and in the scenario analyses are provided. Base-case results are presented in the first row of each Table.

Table B 91 Abatacept vs. cDMARD scenario analyses results

Alternative analyses			Impact on incremental results			
			cDMARD			
Parameters	**Base-case**	**Variation**	**Costs £**	**QALYs**	**ICER (£/QALY)**	**% change**
Base-case	-	-	38,528	1.30	29,646	-
Discount rate effects and costs	3.5%	0% both	48,554	2.09	23,212	21.70%
		1.5% effects and 6% for costs	43,066	0.98	43,853	47.92%
		6% both	34,152	1.00	34,105	15.04%
Analysis time frame	Life time	5 years	23,386	0.28	84,390	184.66%
Utilities	Hurst	Bansback	39,212	1.22	32,047	8.09%
HAQ response rate	0.3	0.22	40,403	1.34	30,095	1.51%

HAQ: Health Assessment Questionnaire, ICER: Incremental Cost Effectiveness Ratio, QALY: Quality Adjusted Life Year, cDMARD: conventional DMARD

Table B 92 Abatacept vs. Inflximab scenario analyses results

Alternative analyses			Impact on incremental results			
			Infliximab			
Parameters	**Base-case**	**Variation**	**Costs £**	**QALYs**	**ICER (£/QALY)**	**% change**
Base-case	-	-	5,434	0.21	25,355	-
Discount rate effects and costs	3.5%	0% both	8,532	0.33	25,674	1.26%
		1.5% effects and 6% for costs	5,731	0.16	36,065	42.24%
		6% both	4,792	0.18	27,014	6.54%
Analysis time frame	Life time	5 years	3,044	0.06	49,012	93.30%
Utilities	Hurst	Bansback	6,051	0.25	24,390	3.80%
HAQ response rate	0.3	0.22	5,675	0.21	26,884	6.03%
Vial wastage infliximab	Yes	No	10,078	0.17	57,843	128.13%
Dose increase infliximab	Yes	No	9,642	0.26	37,025	46.02%

HAQ: Health Assessment Questionnaire, ICER: Incremental Cost Effectiveness Ratio, QALY: Quality Adjusted Life Year

6.7.10 What were the main findings of each of the sensitivity analyses?

The scenario analysis showed that reducing the time horizon had a big impact on the results. Whereas changing the HAQ response rate hardly showed any different.

The structural sensitivity analysis showed that the utility approach did not have an impact on the results.

6.7.11 What are the key drivers of the cost-effectiveness results?

The key drivers of the cost-effectiveness results are drug acquisition costs and drug administration costs.

6.8 Validation

6.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

The systematic review for the MTC, the MTC results and the structure of the economic model was validated by the following Key Opinion Leader board:

[redacted]

The economic model was validated by the following Key Opinion Leader board:

[redacted]

[redacted]

[redacted]

Validation of the core model included three major steps

- Structural review, of formulas, cell references and clinical validity
- Validation by extreme values
- Review and validation of macros

For validation of the results, please see Section 6.10.1

6.9 Subgroup analysis

Although subgroups were identified a paucity of data made it not possible to conduct de novo analysis, therefore no subgroup analyses were performed.

6.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness due to known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 5.3.7.

Moderate and moderate to severe RA subgroups were identified. However lack of data made de novo analysis difficult. A publication by the BSRBR demonstrates same effectiveness of the biologics in both the moderate and severe RA patient groups.

6.9.2 Please clearly define the characteristics of patients in the subgroup.

Not applicable.

6.9.3 Please describe how the statistical analysis was undertaken.

Not applicable.

6.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 6.7.6 (Base-case analysis).

Not applicable.

6.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 4.

Not applicable.

6.10 Interpretation of economic evidence

The results obtained from the de-novo model estimate that abatacept is cost effective in comparison to cDMARDs and infliximab in the target population. The ICERs presented are consistent with those presented in previous NICE appraisals for RA.

With the considerable clinical and economic burden of RA this evidence supports that abatacept be recommended for use for patients who have experienced an insufficient response or intolerance to cDMARDs, based on its favourable clinical efficacy, safety and cost-effectiveness profile.

6.10.1 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?

The results obtained from the de-novo model estimate that abatacept is cost-effective in comparison to cDMARDs and infliximab in the target population. The ICER for abatacept against cDMARDs is comparable to those ICERs for biologic DMARDs which have been previously been recommended by NICE. In addition ICERs presented are consistent with the results presented in previous and ongoing NICE appraisals in RA (TA185 and golimumab NICE ACD).

6.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 4?

The modelled population is reflective of the decision problem identified in Section 4 and equals patients eligible for biologics in England and Wales according to the abatacept licence and BSR guidelines.

6.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The strengths of the abatacept cost-utility can be characterised as follows:

- The individual micro simulations methodology allows for realistic representation of the complex RA treatment pathway, remaining transparent

- The decision analytic modeling approach used in the analysis is consistent with the previous published economic models of RA treatment and aligned with NICE reference case.

- The sequences of treatments used in this evaluation reflect real UK clinical practice and weighted against UK market share data to reflect real life setting.

- Assumptions used in the model were informed by evidence obtained from the systematic review of published economic evaluations of biologic treatments for RA and clinical studies. When a range of values was available, its impact was tested in sensitivity analysis.

- Robustness of model and results under extensive probabilistic sensitivity analyses

The key challenge of modelling a treatment sequence is the appropriate use of source data. The source data summarised below are limited and therefore assumptions are necessary for support:

- Long term time on treatment for biologic and cDMARDs was not available;

- Relative efficacy data as measured by the HAQ CFB in a mixed treatment comparison is not estimated for patients who switched to subsequent treatment lines. In general, for many agents data is lacking after failure of first line biologics.

- Long term relative HAQ progression data for responding patients was not available. Therefore, the HAQ progression was assumed to be similar for all biologic treatments and set to zero. This is in line with the Malottki 2009.

After first line biologic treatments, the treatment sequence is assumed to be identical in both arms, and differences between the arms are most pronounced on the short term. Therefore the results obtained are most likely driven by the first treatment line. Also, a short time horizon (i.e. 5 years) has been used, which eliminates the use of the assumptions described above.

6.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

The economic model is considered to be robust. Availability of more consistent long-term data on biologic DMARDS would be of interest for the analysis.

Section C – Implementation

7 Assessment of factors relevant to the NHS and other parties

It is estimated that, in terms of drug and administration cost, in the first year following positive NICE guidance for abatacept, there would be low net cost to the NHS in England and Wales. There would be a net cost of £380,000 in the population of RA patients with severe RA and £1.13million in moderate and severe patients respectively. This is based on the assumption that abatacept takes over market share from infliximab, the only other recommended biologic agent administered intravenously.

With an estimated 34,636 patients suffering with severe RA, or 103,907 patients suffering with moderate to severe RA, in England and Wales who experience an insufficient response or intolerance to DMARDs, approximately 173 (if severe disease) to 520 (if moderate to severe RA) patients would be treated with abatacept in within the first year of a positive recommendation.

Given the considerable clinical and economic burden of RA, as well as this low net cost we ask the Appraisal Committee to recommend abatacept as a treatment option for RA.

7.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

Abatacept in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who responded inadequately to previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) including methotrexate (MTX) or an anti-TNFα. It is estimated in Table C1 that in England and Wales that 34,636 patients with severe RA (DAS28 greater than 5.1) are eligible for a first biologic therapy or 103,907 patients with moderate and severe disease (DAS28 greater than 3.2) eligible for a first biologic. These figures were calculated based on the population of England and Wales and

the estimated proportion of patients who have received DMARDs and experience failure an insufficient response or adverse event.

As summarised in Table C1, the model presents two scenarios; one scenario encompassing patients with severe RA only (in line with TA130) and a second scenario encompassing patients with moderate and severe RA in line with the abatacept licence. In order to perform this scenario calculations a series of assumptions are made to estimate the around the RA patient population eligible for treatment with abatacept:

- The model assumes a prevalence of RA of 0.86% (Symmons 2002) in England and Wales, and estimates that there are 346,357 cases of RA in total.
- It is estimated that 10% of the total number of patients have severe RA and are eligible for a first biologic therapy (TA195 costing template)
- It is estimated that 30% of the total patients have moderate and severe RA (assumption based on clinical opinion)
- It is assumed that 100% of eligible patients will actually go onto receive a biologic therapy.

Using these assumptions it is estimated 173 patients with severe RA are eligible for abatacept treatment, or that there are 520 patients with moderate and severe disease who are eligible to receive for abatacept therapy.

Table C 1 Estimated number of patients with an insufficient response or intolerance to DMARDs and eligible for abatacept in England and Wales

		Source
Total population England and Wales	51,220,237	The Information Centre for Health and Social Care
Estimated prevalence of rheumatoid arthritis	0.86%	Symmons 2002
Total cases of rheumatoid arthritis	346,357	Calculation
Percentage of severe patients eligible to receive a first biologic treatment	10%	TA195 costing template
Total severe patients eligible to receive a first biologic treatment	34,636	Calculation
Percentage of moderate to severe patients eligible to receive a first biologic treatment	30%	Correspondence with clinician
Total moderate to severe patients eligible to receive a first biologic treatment	103,907	Calculation
Estimated percentage of patients who would receive abatacept	0.5%	Data on file
Estimated total number of severe patients to receive abatacept	**173**	Calculation
Estimated total number of moderate to severe patients to receive abatacept	**520**	Calculation

7.2 What assumption(s) were made about current treatment options and uptake of technologies?

In addition to assuming that abatacept will receive positive NICE guidance as per the expected indication, the following assumptions have been made in this budget impact analysis:

- Uptake was not phased on the assumption that NICE Guidance would be implemented quickly.
- Patients prescribed certolizumab would be in their first year of therapy; this is reflected in the cost accordingly.
- All patients on abatacept would be in their first year of therapy and would receive 14 infusions over 12 months.
- Doses were based on the standard doses described in the relevant Summaries of Product Characteristics.
- Dose escalation or increased dosing frequency for infliximab is not included although well reported in the literature.
- It is assumed that sc administration would not incur any costs although these injections may be preformed by a nurse for those who are unable to self administer.
- It is assumed that there is no vial sharing.
- It is assumed that no new therapies become available.
- Golimumab was not included as final guidance was not issue at the time of this submission.
- Cost of co-therapy with non- biologic DMARD is excluded as this is standard to most patients and to all biologic therapies.

The assumptions within the budget impact model are alighned with those of patient simulation model described in Section 6. The points where it differs are; in relation to the dose escalation of infliximab and to the sc administration cost. The reasoning behind this is that the patient simulation is able to incorporate complex criteria that are not possible to capture in a simpler budget impact model.

7.3 What assumption(s) were made about market share (when relevant)?

UK market shares for the each of anti-TNFα agents as first biologic agents, presented Table C2, were estimated from market research (BMS market research data on file). Assumptions were made in

relation to abatacept market share with an estimated 0.5% of the total patients offsetting the infliximab share in the first year.

Table C3 shows the estimated numbers of patients on each therapy for currently and under each scenario. This table shows that in the first year; 173 severe patients are estimated to receive abatacept in the first scenario, or 520 moderate and severe patients are estimated to receive abatacept in the second scenario.

Table C 2 Market shares for the anti-TNFα agents for England & Wales (BMS market research data on file)

Drug	Current market share after an insufficient response or intolerance to DMARDs	Market share after insufficient response or intolerance to DMARDs including abatacept
Adalimumab	42.5%	42.5%
Certolizumab	5%	5%
Etanercept	42.5%	42.5%
Infliximab	10%	9.5%
Abatacept	-	0.5%

Table C 3 Estimated number of patients starting on a first biologic in England & Wales

	Current practice: No Abatacept Severe patients	Scenario 1: With Abatacept Severe patients	Current practice: No Abatacept Moderate and severe patients	Scenario 2: With Abatacept Moderate and severe patients
Adalimumab	14,720	14,720	44,160	44,160
Certolizumab	1,732	1,732	5,195	5,195
Etanercept	14,720	14,720	44,160	44,160
Infliximab	3,464	3,290	9,871	9,871
Abatacept	-	**173**	-	**520**

7.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

Abatacept is administered as a 30-minute IV-infusion (outpatient visit). Following the initial administration abatacept should be given 2 and 4 weeks after the first infusion then every 4 weeks thereafter (SPC). This results in 14 infusions in the first year and 13 infusions per year thereafter. Abatacept is administered in combination with methotrexate and based on safety data, no adverse events are expected that would be additional to those observed with other biologic treatments for RA (see the Safety Section 5.9 for a review

of safety data). Given its favourable tolerability profile, no pre-medication are required prior to abatacept infusion.

7.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

Drug costs for the anti-TNFα therapies were obtained from MIMS, July 2010 (MIMS, 2010). The list price for abatacept is £302.40 per 250mg vial, however based on the agreement with the Department of Health the net cost to the NHS per vial is £272.17 which is utilised within this impact analysis.

The intravenous infusion cost per administration was assumed to be £158 for abatacept, based on data used in the anti-TNFα Assessment Report (Chen et al 2005) and inflated from the 2004 value to 2010 prices (Curtis 2008). An intravenous infusion administration cost of £310 was assumed for infliximab based on data from the technology assessment report from the anti-TNFα appraisal (Chen et al 2005) and inflated from 2005. These administration costs are assumed to include pre-medication and monitoring where appropriate.

Table C 4 Estimated drug and administration costs

Drug	Unit cost (£, 2009)	Annual treatment cost including administration (£, 2009)	Comments
Adalimumab	£357.50/40mg	£9,295	40mgx26/year; Self-administered
Certolizumab	£357.50/200mg	£7,150	200mgx26/year;Self-administered (12 weeks free drug in first year)
Etanercept	£89.38/25mg	£9,296	25mgx104/year; Self-administered
Infliximab	£419.62/100mg	£10,244	3 vials per patient per infusion; 6.5 infusions per year
Abatacept	£242.17/250mg	£10,171	3 vials per patient per infusion; based on 14 infusions in year 1 (note 13 infusions in each subsequent year)
Drug	**Administration route**	**Cost per administration**	**Cost of administration per year**
Adalimumab	Subcutaneous	£0	£0
Certolizumab	Subcutaneous	£0	£0
Etanercept	Subcutaneous	£0	£0
Infliximab	Intravenous	£310 (Chen et al 2005)	£2,015
Abatacept	Intravenous	£158 (Chen et al 2005)	£2,212

7.6 Were there any estimates of resource savings? If so, what were they?

Analysis was conducted in relation to drug budget. Direct savings were identified in the cost-effectiveness section in terms of AEs costs and non-drug medical resource costs. There is a potential for reduced hospitalisation, outpatient visits and joint replacement with abatacept treatment based on a sustained/improved efficacy over time and favourable safety and tolerability profile.

7.7 What is the estimated annual budget impact for the NHS in England and Wales?

The purpose of this analysis is to estimate the budgetary impact of reimbursing abatacept on the NHS drug budget. Costs are offset by current estimated expenditure on patients who would otherwise have continued on infliximab therapy.

The calculation assumes that abatacept is recommended by NICE as per indication (i.e. abatacept in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid

arthritis in adult patients who responded inadequately to previous therapy with one or more DMARDs including methotrexate (MTX) or a TNF-alpha inhibitor). It is assumes that 0.5% of eligible patients would be initiated onto abatacept in the first year of positive NICE guidance. As infliximab is the only recommended anti-TNFα administered IV this analysis assumes that abatacept offsets market share from infliximab only. It is also therefore assumed that patients who would have been prescribed an anti-TNFα administered sc would continue to do so.

A summary of the estimated budget impact is shown in Table C5 with consideration of the offset of current expenditures in patients who would have been prescribed infliximab. The net budget impact in the severe population only is estimated to be £378,398 in the first year. If a wider population of both moderate and severe patients is considered the net budget impact is estimated to be £1,13million.

This impact appears to be minimal, considering there is an estimated total of £321 million in severe to £965 million in moderate to severe patients which would be spent on anti-TNFα therapies as first biologic therapy.

Table C 5 Summary of budget impact of NICE guidance for abatacept in England and Wales in the first year

	Total costs* current practice: No Abatacept Severe patients	**Total costs* current practice: With Abatacept Severe patients (Scenario 1)**	**Total costs* current practice: With Abatacept Moderate and severe patients**	**Total costs* current practice: With Abatacept Moderate and severe patients (Scenario 2)**
Adalimumab	136,825,189	136,825,189	410,471,615	410,471,615
Certilizumab	12,382,370	12,382,370	37,146,735	37,146,753
Etanercept	136,825,189	136,825,189	410,471,615	410,471,615
Infliximab	35,321,793	33,555,703	105,964,359	100,666,141
Abatacept	-	2,144,488	-	6,433,402
Difference (vs. current)		**378,398**		**1,135,184**

*Total costs include drug and administration costs

7.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

There is a potential for transfer of abatacept infusion from secondary care to primary care in the future but at present it is not possible to quantify its impact.

The results of this budget impact analysis show that the net budgetary impact of abatacept on the NHS rheumatoid arthritis biologic drug costs would be minimal estimated at £378,398 (severe patients) and £1.13 million (moderate and severe patients) in the first year. Furthermore, this minimal impact is likely overestimated as conservative assumptions used in the calculations do not favour abatacept.

These results confirm that in addition to sustained/improved efficacy associated with abatacept, its proven safety and tolerability profile and its favourable cost-effectiveness profile long term compared to existing therapies, providing access to abatacept for UK patients with moderate to severe RA and an insufficient response to conventional DMARDs have minimal budgetary impact. These results further support that abatacept be recommended as a treatment option for RA after an insufficient response or intolerance conventional DMARDs.

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Please use a recognised referencing style, such as Harvard or Vancouver.

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There will be no subsequent opportunity to submit information unless it has been specifically requested by NICE.

When making a submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- an executable electronic copy of the economic model has been submitted
- the checklist of confidential information (provided by NICE along with invitation to submit) has been completed and submitted.

10.2 Disclosure of information

To ensure that the appraisal process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. NICE recognises that because the appraisal is being undertaken close to the time of regulatory decisions, the status of information may change during the STA process. However, at the point of issuing the FAD or ACD to consultees and commentators, all the evidence seen by the Committee should be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). Further instructions on the specification of confidential information, and its acceptability, can be found in the agreement between the Association of the British Pharmaceutical Industry (ABPI) and NICE (www.nice.org.uk).

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The manufacturer or sponsor must ensure that any confidential information in their evidence submission is clearly underlined and highlighted. NICE is assured that information marked ‘academic in confidence’ can be presented and discussed during the public part of the Appraisal Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as ‘academic in confidence’.

Please therefore underline all confidential information, and separately highlight information that is submitted under ‘commercial in confidence’ in red and information submitted under ‘academic in confidence’ in yellow.

The manufacturer or sponsor will be asked to supply a second version of the submission with any information that is to remain confidential removed. The confidential information should be ‘blacked out’ from this version, taking care to retain the original formatting as far as possible so that it is clear which data have been removed and where from. For further details on how the document should be redacted/stripped, see the checklist of confidential information.

The last opportunity to review the confidential status of information in an STA, before publication by NICE as part of the consultation on the ACD, is 2 weeks before the Appraisal Committee meeting; particularly in terms of ‘academic in confidence’ information. The ‘stripped’ version will be issued to consultees and commentators along with the ACD or FAD, and made available on NICE’s website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the ‘stripped’ version of the submission does not contain any confidential information. NICE will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the ERG and the Appraisal Committee. Confidential information may be distributed to all consultees with the permission of the manufacturer or sponsor. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

10.3 Equity and equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the appraisal and reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the appraisal, or if there is information that could be included in the evidence presented to the Appraisal Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE’s responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).