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Dear Dr George,

Re: Single Technology Appraisal – Abatacept for the treatment of rheumatoid arthritis after the failure of conventional disease-modifying anti-rheumatic drugs

Thank you very much for the opportunity to provide further clarification on our submission for abatacept. Please find attached our responses. We have worked through them and have tried to answer the questions as thoroughly as possible in the given time.

If you've any questions, please don't hesitate to contact me.

Yours sincerely

Maximilian Lebmeier
Associate Director Health Economics and Outcomes Research

Section A: Clarification on effectiveness data

Literature searches

A1. **Priority question:** Please clarify why only two studies of infliximab were included in the network of studies (Figure B25) when a recent systematic review of infliximab plus methotrexate vs methotrexate alone (Zintzaras et al Clinical Therapeutics 2008;30(11):1939-1955) included 12 studies. What criteria were used to select the studies included in the submission? Furthermore, please detail the criteria used to select the trials for the remaining interventions within the network meta analysis.

The search strategy was developed in order to capture all the relevant studies concerning the efficacy and safety of abatacept and alternative biologic DMARDs in the treatment of Rheumatoid Arthritis (RA) with insufficient response to methotrexate (MTX). After the completion of the systematic literature review inclusion criteria for the Mixed Treatment Comparison (MTC) analyses were developed. These inclusion criteria, listed below, have been set up to ensure more coherent a MTC analyses.

- **Patients:** Patients diagnosed with rheumatoid arthritis with an inadequate response to, or intolerance to, MTX as MTX is the first line treatment of reference.
- **Interventions:** Studies that include any of the following agents will be considered: biologic agents (abatacept, infliximab, etanercept, adalimumab, certolizumab and golimumab) in combination with MTX. Anakinra, tocilizumab and rituximab have been removed from the list of relevant interventions; since these agent are recommended for patients that have an inadequate response to TNF agents. Only results of treatments used at the licensed dosages were included in the analyses (see table 1).

Table 1. Licensed doses of the biologic agents[1]

Treatment	Licensed doses
Abatacept	10 mg/kg every 4 weeks
Infliximab	3 mg/kg every 8 weeks
Etanercept	25 mg twice weekly
Golimumab	50 mg every 4 weeks
Adalimumab	40 mg every other week
Certolizumab pegol	200 mg every other week

[1] European Medicines Agency – Summary of product characteristics

- **Comparators:** Studies that compare the agents listed under 'Interventions' either to each other or to MTX (as the 'placebo'-arm).
- **Endpoints:** Studies that include the following:

  Efficacy parameters: Change From Baseline (CFB) in Health Assessment Questionnaire (HAQ) score at 24/28 and 48/54 weeks, American College of Rheumatology 20 (ACR20) 20, ACR50, ACR70 response rates at 24/28 weeks and 48/54 weeks, Disease Activity Score 28 (DAS28) <2.6 clinical remission response rates at 24/28 weeks and 48/54 weeks

  Safety parameters: Withdrawals due to adverse events at 24/28 weeks.

- **Study designs:** Only RCTs. The inclusion of open-label studies in MTC analyses could bias the results.

The 12 infliximab studies included in Zintzaras publication are listed below along with detailed reasoning for their inclusion or exclusion:

- Maini et al: no outcomes at 24-28 weeks and infliximab not given at the recommended dosage
- Perkins et al: This is a single dose study. No outcomes at 24-28 weeks
- Antoni and Kalden: review
- Lipsky et al: This publication refers to the ATTRACT trial and is included in the meta-analysis network (figure B25)
- Kavanaugh et al: no outcomes at 24-28 weeks and infliximab not given at the recommended dosage
- St Clair et al: MTX-naïve patients
- Taylor et al: early RA, MTX-naïve patients
- Durez et al: no outcomes at 24-28 weeks
- Quinn et al: MTX-naïve patients
- Goekoop-Ruiteman et al: MTX-naïve patients
- Abe et al: no outcomes at 24-28 weeks

- Westhovens: no outcomes at 24-28 weeks

See also appendix 4; section 9.4.6 and 9.4.7

A2. Page 26: Please confirm whether any searches were undertaken for any ongoing trials in research registers or databases (for example, metaRegister of Controlled Trials, Health Technology Assessment Database)?

Searches were performed within the following databases:

- The Cochrane Library (includes the HTA database)
- Medline via Dialog Datastar.
- Embase via Dialog Datastar.
- 2 conference websites (EULAR and ACR)

No search was performed in metaRegister of Controlled Trials.

A3. Pages 67-68: In section 5.2.1, the electronic literature searches were said to have identified a total of three clinical trials and two long-term extension studies. However, the QUOROM diagram also indicates that two relevant 'clinical study reports' were also identified. Please provide details of these reports.

The clinical study reports (CSR) were identified for the AIM trial and the ATTEST trial. These CSRs were used if data was not reported or unavailable in the publicly and peer-reviewed full text publications for AIM and ATTEST.

Population

A4. Page 33: In section 2.2, it is estimated that 346,357 adults have RA; this figure appears to apply to the UK. However, in Table C 1 it appears to relate only to England and Wales. Please provide clarification on this point.

The figure 346,357 relates to the number of adults in England and Wales with RA. Please note that section 2.2 should read 'Using recent population estimates from England and Wales, this prevalence results in 346,357 RA patients'.

A5. Page 33: It is estimated in the submission that 10% of the total rheumatoid population has a DAS28 of $\geq$ 5.1 , and 30% has a DAS28 of $\geq$3.2. It is also reported that 10% of the estimated eligible population receive an IV administered biologic agent. Please provide clarification of the source of these figures.

These figures were obtained from the following sources:

1. 10% of the total rheumatoid population has a DAS28 of ≥ 5.1 – this was obtained from the costing template from TA195.

2. 30% of the total rheumatoid population has a DAS28 ≥ 3.2 – personal communication with RA specialists.

3. 10% of the estimated eligible population receive an IV administered biologic – personal communication with RA specialists.

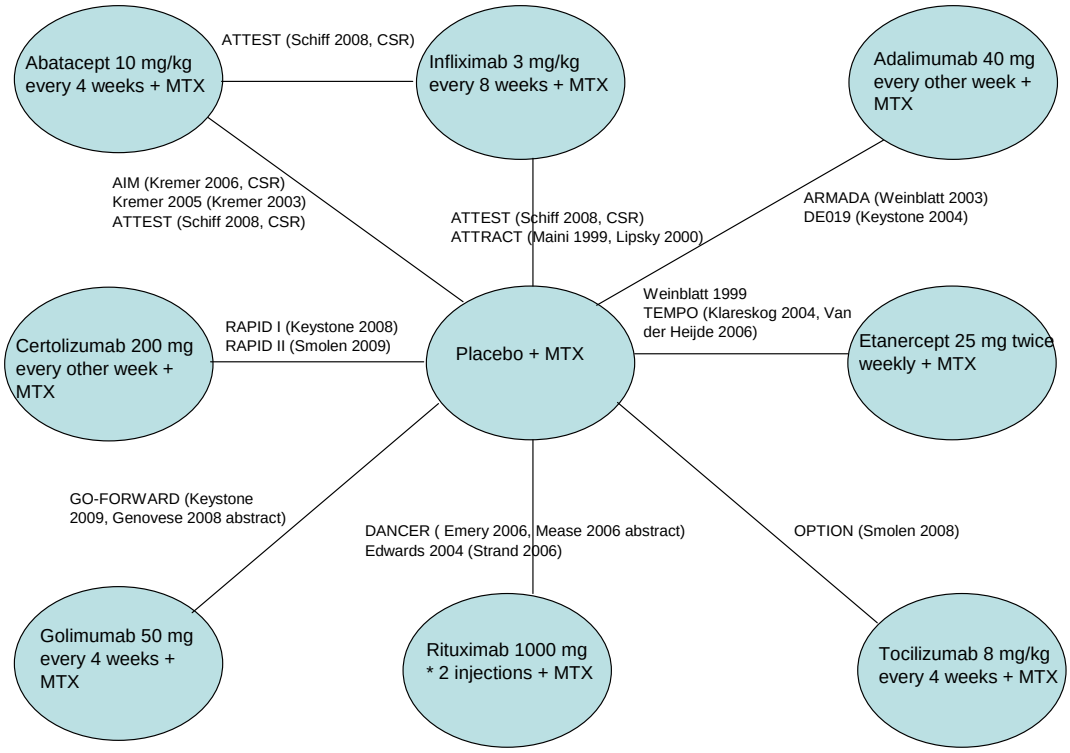
Comparators

A6. **Priority question:** Please clarify why a treatment sequence was used that did not include a second biologic agent or rituximab.

The use of a second biologic agent after the failure of a first biologic has been recently assessed within TA 195 and is not within the scope of this appraisal

A7. **Priority question:** Please explain if the inclusion of trials on ritxumab and tocilizumab would help to complete the network meta analysis, and if so please include these trials.

The inclusion of trials on rituximab and tocilizumab do not help to complete the network meta analysis. These interventions can only be added as loose ends in the network (see figure below). Therefore, the relative efficacy of abatacept compared to the other interventions does not change at all if we include these trials.



Clinical evidence

A8. **Priority question:** Please clarify the relationship assumed in the model between an increase in the dosage of infliximab and efficacy. Please confirm whether the efficacy has been taken from RCTs in which the dose of infliximab remained constant?

No relationship was assumed in the model between the increase in dosage and efficacy. Increase in dosage had only an impact on the cost. The efficacy for the HAQ CFB of infliximab has been taken from the ATTEST trial and ATTRACT, in which a dose of 3mg/kg for infliximab remained constant throughout the trial period.

A9. **Priority question:** Please provide the rationale for why the distribution for 'time on treatment' for patients whose disease responds to treatment is assumed equal for all biologics (p252), whereas the differential effects on HAQ change from baseline and in serious adverse events are not assumed equal for all biologics

The long-term treatment duration for responders was based on UK data from the British Society for Rheumatology Biologics Register (BSRBR) as the extension trials for abatacept do not capture the long-term treatment duration beyond 5 years. Long-term time on treatment was therefore based on the Kaplan-Meier plots for survival provided by the BSRBR data as cited in Malottki et al 2009.

The HAQ CFB and treatment discontinuation due to serious adverse events (SAEs) at 6 months could be estimated from the clinical trials by means of an indirect comparison.

A10. **Priority question:** Please confirm whether weight-based dosing is assumed for infliximab.

Yes, weight based dosing is assumed for infliximab.

A11. **Priority question:** Please **c**onfirm whether there are any statistically significant differences between abatacept and infliximab observed within the ATTEST trial.

As mentioned in section 5.3.6 “However, although the trial was not powered to make a formal comparison, 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.”

Based on the analysis of treatment difference between abatacept + MTX and infliximab + MTX treatment and its 95% CI, there were differences between groups with regards to following outcomes:

- ACR20 response at 1 year (presented in table B19 page 128): 72.4 vs 55.8%, difference of 16.7, 95% CI=5.5, 27.8
- DAS28(ESR) change from baseline to 1 year (presented in section 5.5.36 page 112): –2.88 vs. –2.25; estimate of difference (95% CI) = –0.62 (–0.96, –0.29)
- Proportion of subjects with a DAS change from baseline to 1 year ≥1.2 unit (presented in table B21 page 132): 75.0 vs 86.0%, difference of 11.0, 95% CI=1.4;20.6
- Proportion of subjects achieving Low Disease Activity Score (LDAS) (DAS28≤3.2) at 1 year ≥1.2 unit (presented in table B21 page 132): 35.3 vs 22.4%, difference of 12.9, 95% CI=2.1;23.7
- Mean change from baseline to 1 year in Physical Component Summary (PCS) (presented in table B22 page 133): 9.5 vs 7.6; difference of 1.93; 95% CI=0.08; 3.84.

No statistically significant differences after one year of long term extension (LTE) between patients from the original abatacept group and patients in the original infliximab group switched to abatacept the 2nd year

A12. Page 26 and 70: Please provide trial identifier codes for the AIM, ATTEST, Kremer Phase 2b and ATTAIN trials

Trial identifiers codes as mentioned in the website clinicaltrials.gov:

- Phase IIB: NCT00162266
- AIM: NCT00048568
- ATTEST: NCT00095147
- ATTAIN: NCT00048581

A13. Page 42: In section 2.8, please provide details of the location of care, staff usage, administration costs, monitoring and tests associated with the use of abatacept.

Location of care – rheumatology ward or infusion clinic.

Staff usage and administration costs – these costs are captured in cost of administration per dose £158 presented in the economic model.

Monitoring tests associated with abatacept – there is no additional monitoring associated with abatacept

A14. Pages 60/85: Table A2 states that the outcomes addressed in the submission were those specified by NICE in the scope, namely disease activity; physical function; joint damage; pain; mortality; fatigue; extra-articular manifestations of disease; adverse effects of treatment; health related quality of life. However, on pages 85-86, the outcomes discussed in considering the decision problem appear to exclude the following: pain (except inasmuch as it is included in the ACR 20/50/70 responses), mortality, and extra-articular manifestations of disease. Please provide data on these outcomes or state where data are not available. Alternatively, please provide justification for the exclusion of those outcomes.

Pain: this information was not available in a suitable format for presentation within this dossier.

Mortality – is reported in the Safety section as number of deaths.

Extra-articular manifestations – were not reported in the clinical trials

A15. Page 76: Please clarify why the primary objective of the AIM study was ACR20 at 6 months but HAQ at one year.

ACR 20 response was selected at 6 months to evaluate the short term of abatacept on signs and symptoms.

HAQ was selected at one year to evaluate the long term impact of abatacept on functional disability. However treatment with abatacept resulted in clinically and statistically significant improvements in HAQ at Day 365. Statistically

significant improvements in HAQ were observed as early as Day 29 and maintained through Day 365 indicating that abatacept had a significant impact on functional disability.

A16. Page 79: Please clarify why, in the Kremer Phase 2b study, ACR20 was assessed only at 6 months, while ACR50 and ACR70 were assessed at 6 months and 1 year. If ACR20 data are available at 1 year, please provide them.

ACR 20 response was assessed monthly during the first 6 months then every 2 months until Month 12. ACR20 response at 1 year was one of the secondary outcome efficacy criteria. Results were presented on page 127 in table B19 in the submission dossier.

A17. Page 95: Please provide a clinical rationale for the various subgroup analyses undertaken on data from the AIM and ATTEST trials.

Please see section 5.37 page 95:

"In the AIM trial, subgroup analyses were performed on; age, gender, race, geographic region, duration of RA, Swollen Joint Count (SJC), Tender Joint Count (TJC), C-reactive protein (CRP) levels, weight, Genant-modified Sharp Score (GMS) total score, Health Assessment Questionnaire Disability Index (HAQ-DI), and ACR responses at Day 169, wherever applicable.

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.

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

Subgroups analysis with regards to socio-demographics variables in the AIM and ATTEST trials were performed as these subgroup analyses are usually requested in the guidance and ethical guidelines on clinical trials.

In addition subgroup analysis by disease severity criteria and level of inflammation at baseline were performed to check the robustness of the studies and if the overall results were not driven by a specific subgroup of patients who might have more disease severity at baseline.

A18. Please provide the results from the placebo arms of the non-abatacept trials used in the network meta-analysis, with a particular focus on the infliximab trials that may be used for an indirect comparison.

The input data used in the network meta-analysis for the placebo arms as well as for all the interventions considered are reported in table 34 (for the HAQ CFB analysis), table 35 (for the ACR20 responses), table 36 (for ACR50 responses) and table 37 (for ACR70 responses), see sections 5.7.4.1 – 5.7.4. In the tables below the data for the placebo arms is provided.

HAQ CFB 24/26 weeks: infliximab studies included: ATTEST trial ATTRACT

Trial	Placebo		
treatment	mean HAQ CFB	Standard deviation	Number of patients
# AIM (CSR)	-0.4	0.59	219
# Kremer 2003	-0.14	0.49	119
# ATTEST (CSR)	-0.29	0.22	110
# ARMADA (Weinblatt 2003)	-0.27	0.57	62
# DE019 (Keystone 2004)	-0.24	0.52	200
# RAPID I (NICE Cimzia manufacturer report)	-0.17	0.56	199
# RAPID II (Smolen 2009)	-0.14	0.45	127
# Weinblatt 1999	-0.40	0.49	30
# TEMPO (Van der Heijde 2006)	-0.63	1.08	228
# GO-FORWARD (Genovese 2008)	-0.13	0.58	133
# ATTRACT (Lipsky 2000)	-0.19	0.49	88

ACR 20 24/28 weeks: infliximab studies included ATTEST and ATTRACT

Trial	Placebo		
treatment	% patients with ACR20 response	Number of patients with ACR20 response	Number of patients
# AIM (Kremer 2006)	39.7%	87	219
# Kremer 2005	35.3%	42	119
# ATTEST (Schiff 2008)	41.8%	46	110
# ARMADA (Weinblatt 2003)	14.5%	9	62
# DE019 (Keystone 2004)	29.5%	59	200
# RAPID I (Keystone 2008)	13.6%	27	199
# RAPID II (Smolen 2009)	8.7%	11	127
# Weinblatt 1999	26.7%	8	30
# TEMPO (Klareskog 2004)	73.2%	167	228
# GO-FORWARD (Keystone 2009)	27.8%	37	133
# ATTRACT (Maini 1999)	20.5%	18	88

ACR50 24/28 weeks: infliximab study included ATTEST

Trial	Placebo		
treatment	% patients with ACR50 response	Number of patients with ACR50 response	Number of patients
# AIM (Kremer 2006)	16.9%	37	219
# Kremer 2005	11.8%	14	119
# ATTEST (Schiff 2008)	20.0%	22	110
# ARMADA (Weinblatt 2003)	8.1%	5	62
# DE019 (Keystone 2004)	9.5%	19	200
# RAPID I (Keystone 2008)	7.5%	15	199
# RAPID II (Smolen 2009)	3.1%	4	127
# Weinblatt 1999	3.3%	1	30
# TEMPO (Klareskog 2004)	40.4%	92	228
# GO-FORWARD (Keystone 2009)	13.5%	18	133

ACR70 24/28 weeks: infliximab study included ATTEST

Trial	Placebo		
treatment	% patients with ACR50 response	Number of patients with ACR50 response	Number of patients
# AIM (Kremer 2006)	6.4%	14	219
# Kremer 2005	1.7%	2	119
# ATTEST (Schiff 2008)	9.1%	10	110
# ARMADA (Weinblatt 2003)	4.8%	3	62
# DE019 (Keystone 2004)	2.5%	5	200
# RAPID I (Keystone 2008)	3.0%	6	199
# RAPID II (Smolen 2009)	0.8%	1	127
# Weinblatt 1999	0.0%	0	30
# TEMPO (Klareskog 2004)	14.9%	34	228
# GO-FORWARD (Keystone 2009)	5.3%	7	133

A19. Page 100: Please clarify why, in relation to all three trials, the text of the submission states that 'it is not clear if allocation was adequately concealed' but Table B10 indicates that concealment of treatment allocation was adequate.

This is a typographical error; 'it is not clear if allocation was adequately concealed' should not be in the text and should read 'concealment of treatment allocation was adequate'.

A20. Pages 105 – 115: Please indicate the number of patients included in Figures B7, B10, B13, B16, and B19.

The intent-to-treat population represented in the Figures B7, B10, B13, B16 and B19 are for the 10 mg/kg abatacept group, n=115, for the abatacept 2 mg/kg group, n=105, and for the placebo group, n=119. Please see Figures 10.1.4.1A, 10.1.4.1B and 10.1.4.1C and also Tables 10.2.2 and 10.3.1 from the CSR [Appendix, Reference 1], for the Double-Blind (DB) period of the Ph IIb trial (IM101-100).

A21. Page 120: The text describes the number of missed infusions in the ATTEST trial. Please confirm that the mean is 0.2 and the median is 0 rather than vice versa.

Correct, please see table 9.2 page 77 in the CSR of DB period for ATTEST trial

- Mean number of missed infusion=0.2
- Median number of missed infusion=0

A22. Page 128: Table B 19 Please clarify the meaning of NR in this table? Please comment on why point estimates and 95% confidence intervals not provided, whereas p-values are given?

NR means “Not reported”. However, treatment difference vs. placebo and its 95% CI were reported in the CSR of double-blind period of Phase IIB study for ACR 20/50/70 response at 6 months and 1 year. See the corresponding tables from the CSR for your reference [Appendix, Reference 2] (see also few errors in report of number of responders, p-values on pages 127-128):

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A23. Page 140: Tables B25, B26 B27, B28, B29 and B30: The power of the test for heterogeneity between trials is low, particularly with a limited number of trials. Please present a random effects meta-analysis allowing for uncertainty in the true value of the between-study standard deviation.

Please also clarify how missing standard errors were taken into account in meta-analyses of continuous outcome measures.

The random effects meta-analyses for tables B25-30 are presented below.

For the AIM and ATTEST trials, the standard errors of the continuous outcomes were reported in the clinical study reports and used in the meta-analyses.

For the Kremer study, no information around the uncertainty was available in the publications (Kremer 2003 and Kremer 2005). The standard error (se) for these studies is therefore imputed based on the other trials as follows. For each trial/treatment combination, the standard deviation (sd) of the observations is computed, by multiplying the se with the square root of the treatment sample size. The sd is squared to obtain a variance and to be able to estimate the average (please note that the variances can be added, where sds cannot). The square root of the mean of the variances is used as sd for Kremer 2003 and Kremer 2005. The sd is divided by the square root of the treatment sample sizes to obtain an estimate of the se, permitting integration of all the data available.

Table B 25 HAQ CFB at one year

Random 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	
t^2	0

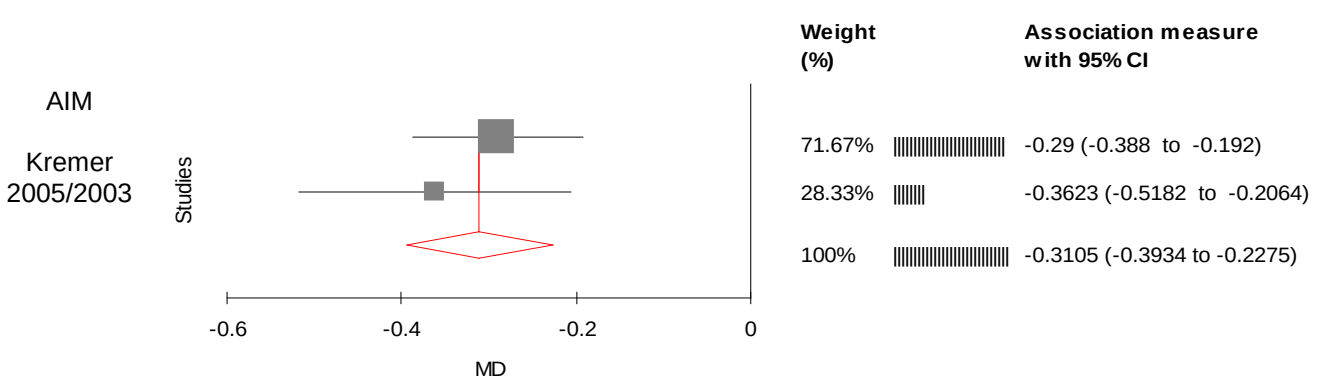


Table B 26 DAS 28 CFB at 24/28 weeks

Random 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	
t^2	0

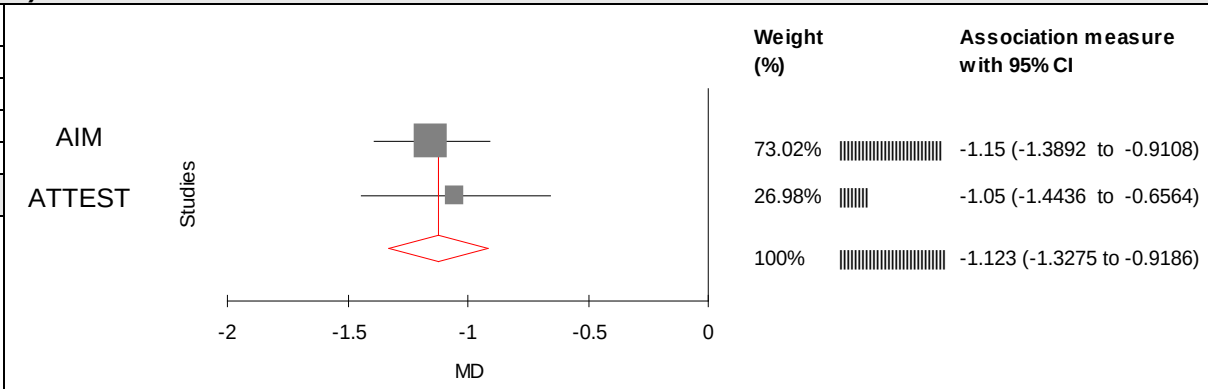
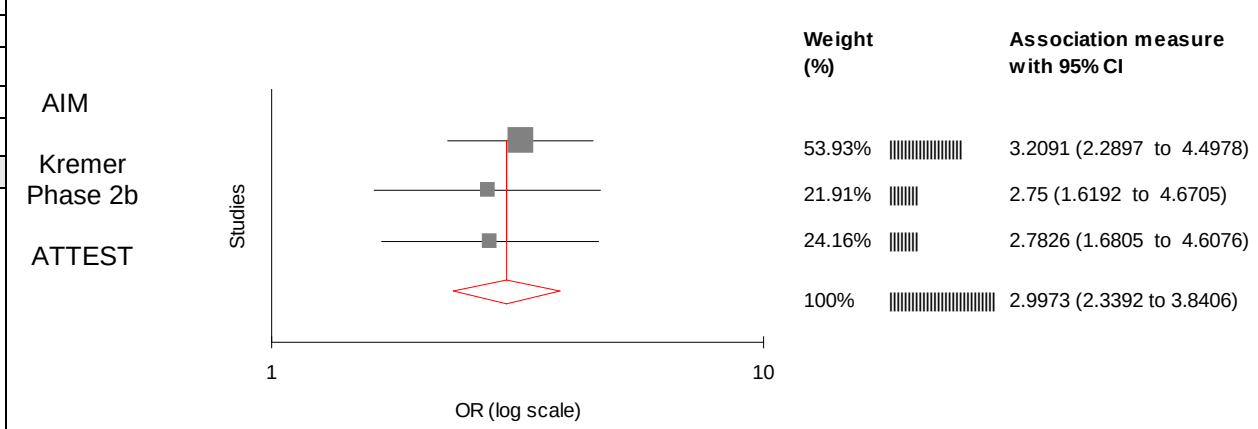


Table B 27 ACR20 at 24/28 weeks

Random effect model – Odds Ratio (OR)	
Meta-analysis outcome	2.9973
95% CI lower limit	2.3392
95% CI upper limit	3.8406
z	8.6786
p-value (two-tailed)	< 0.0001
Heterogeneity	
t^2	0



Random effect model – Relative Risk (RR)	
Meta-analysis outcome	1.6757
95% CI lower limit	1.4746
95% CI upper limit	1.9043
z	7.9125
p-value (two-tailed)	< 0.0001
Heterogeneity	
t^2	0

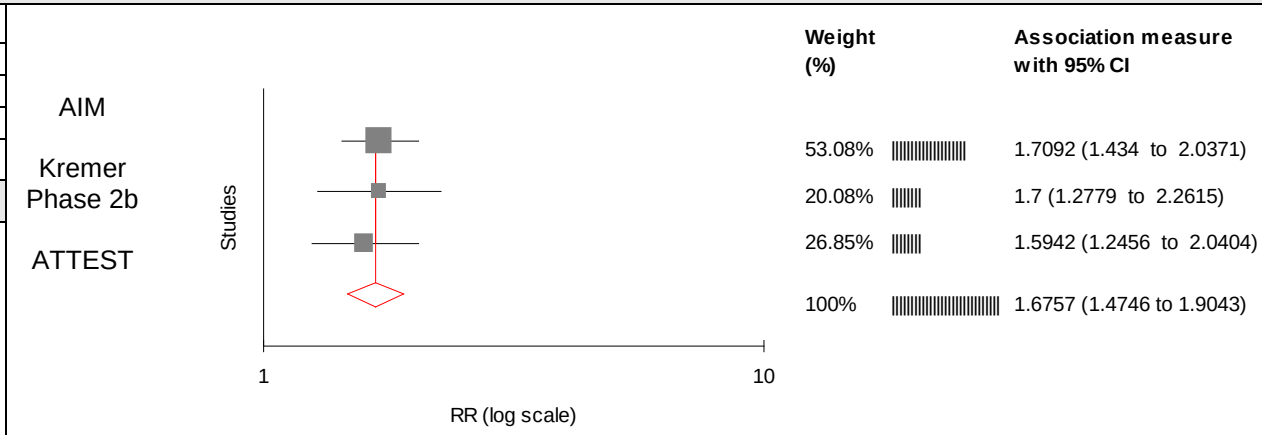
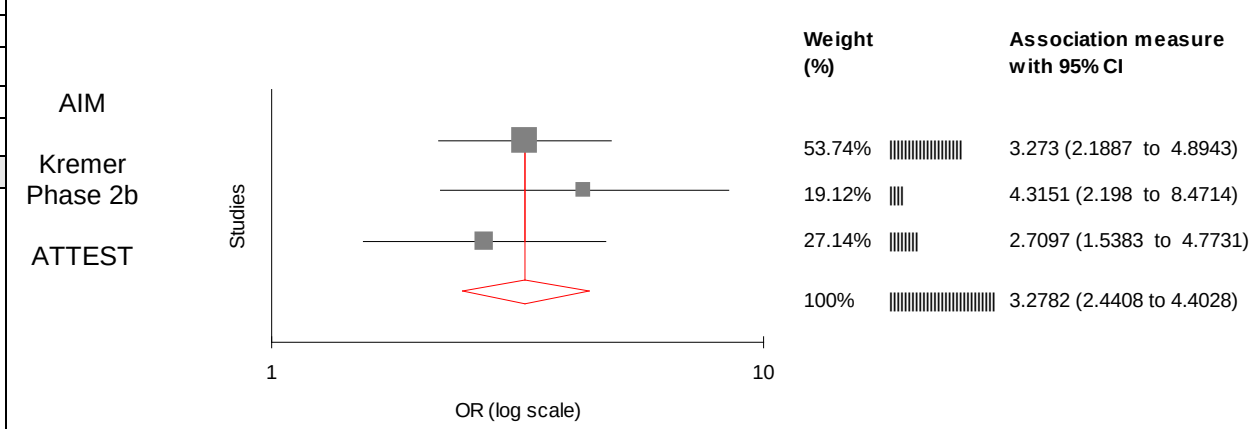


Table B28 ACR50 at 24/28 weeks

Random effect model – Odds ratio (OR)	
Meta-analysis outcome	3.2782
95% CI lower limit	2.4408
95% CI upper limit	4.4028
z	7.8891
p-value (two-tailed)	< 0.0001
Heterogeneity	
t^2	0



Random effect model – Relative Risk (RR)	
Meta-analysis outcome	2.366
95% CI lower limit	1.8815
95% CI upper limit	2.9751
z	7.3671
p-value (two-tailed)	< 0.0001
Heterogeneity	
t^2	0

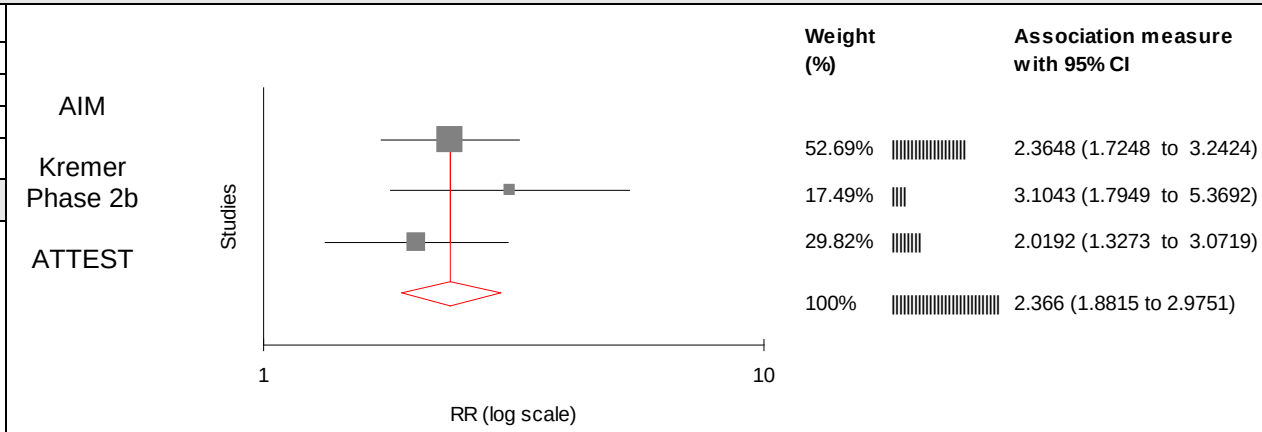
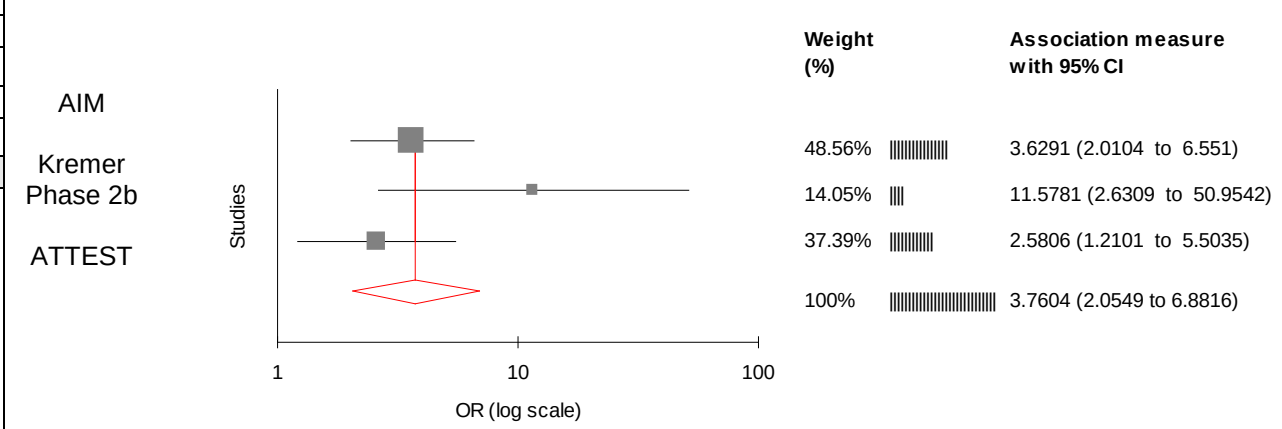


Table B29 ACR70 at 24/28 weeks

Random effect model – Odds ratio (OR)	
Meta-analysis outcome	3.7604
95% CI lower limit	2.0549
95% CI upper limit	6.8816
z	4.2958
p-value (two-tailed)	< 0.0001
Heterogeneity	
t^2	0.105



Random effect model – Relative Risk (RR)	
Meta-analysis outcome	3.1991
95% CI lower limit	1.8041
95% CI upper limit	5.6729
z	3.9789
p-value (two-tailed)	< 0.0001
Heterogeneity	
t^2	0.1032

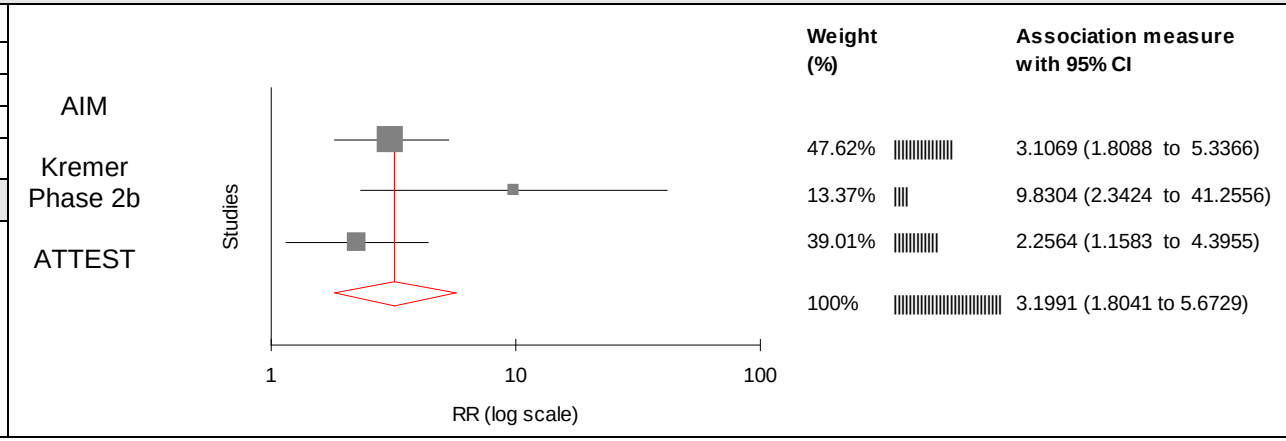
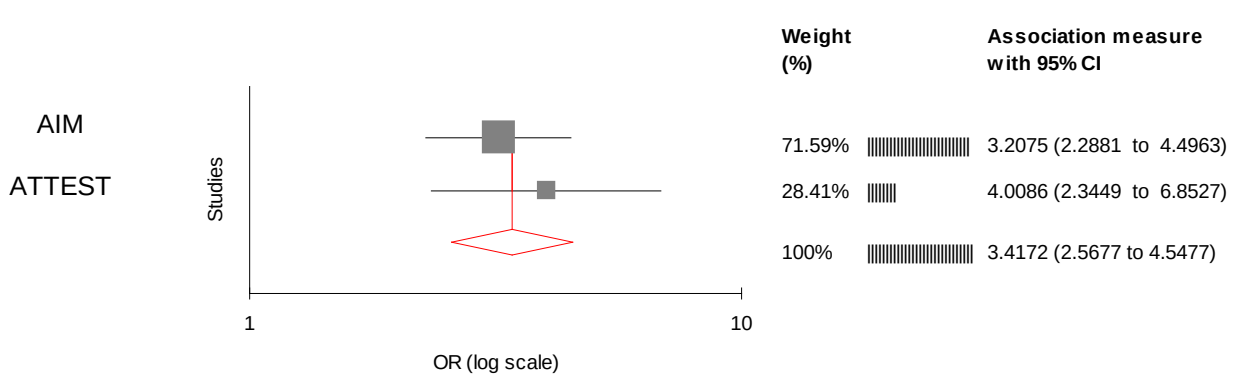
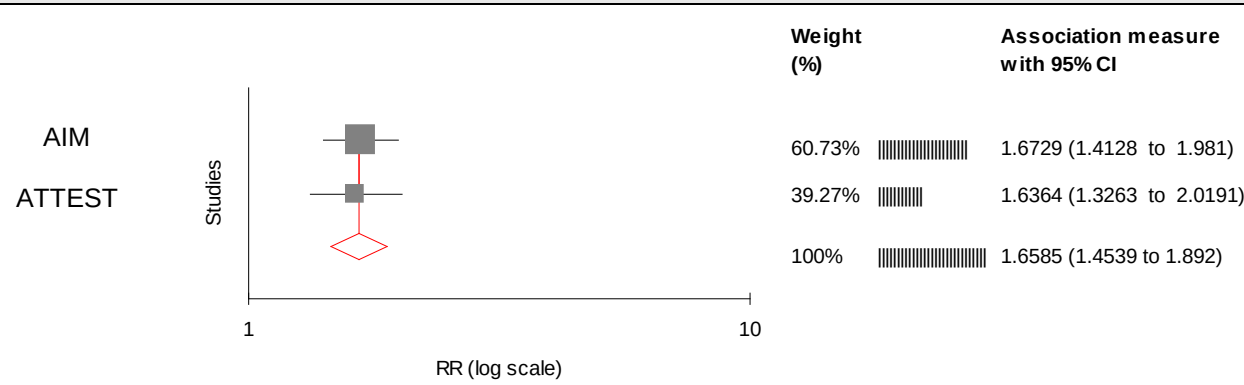


Table B30 DAS 28 improvement at 24/28 weeks

Random effect model – Odds ratio (OR)	
Meta-analysis outcome	3.4172
95% CI lower limit	2.5677
95% CI upper limit	4.5477
z	8.4272
p-value (two-tailed)	< 0.0001
Heterogeneity	
t^2	0



Random effect model – Relative Risk (RR)	
Meta-analysis outcome	1.6585
95% CI lower limit	1.4539
95% CI upper limit	1.892
z	7.529
p-value (two-tailed)	< 0.0001
Heterogeneity	
t^2	0



A24. Page 193: Table B57 describes the sustained ACR50 and ACR70 response over time. Please provide a statistical comparison of sustained response between abatacept and infliximab

Table B57 describes proportion of patients who sustained ACR50/70 response from 1 year to 2 years in patients from the original abatacept group (1 year double blind period + 1 year in open-label period) and in patients in the original infliximab group switched to abatacept the 2nd year. Thus, no statistical testing was performed during the long-term extension period since all patients were treated with abatacept. Results were reported using point estimates and corresponding 95% confidence interval.

A25. Page 199: Provide statistical evaluation and p-values for adverse events and discontinuation rate

As seen from the statistical data tables attached [Appendix, Reference 3], all 95% CI overlap between active and control arms across trials. However the studies were not powered to detect any statistical significance between treatment arms. Therefore, all that can be concluded is that abatacept does not harm versus placebo as there is no significant increase in any AE/SAE vs. control group.

Below is a table comparing safety data in the ATTEST trial with odds ratios which may be helpful.

Event	N (Proportion) with Event		Ratio of Proportions* (aba:inf)	95% CI for Ratio*
	Abatacept (N = 156)	Infliximab (N = 165)		
Related AEs	72 (0.46)	96 (0.58)	0.79	0.64, 0.98
Related SAEs	5 (0.03)	14 (0.09)	0.38	0.09, 0.99

Acute Infusional Events	11 (0.07)	41 (0.25)	0.28	0.14, 0.52
ANA Seroconversion	7/107 (0.07)	51/107 (0.48)	0.14	0.06, 0.27
Immunogenicity	0	101/163 (0.60)	-	-
SAEs of Infection	3 (0.02)	14 (0.09)	0.22	0.04, 0.72
Related SAEs of Infection	2 (0.01)	10 (0.06)	0.21	0.02, 0.84

A26. Page 200: Please confirm that the percentage urinary tract infection in the placebo arm of the AIM trial should be 5.0%.

Correct, please see table 12.1.1A page 184 in the CSR of DB period for AIM trial

- Urinary tract infection in placebo arm: 11/219 (5.0%)

Section B: Clarification on mixed treatment comparison

Page 170: Sections 5.7.6.1, 5.7.6.3, 5.7.6.5 and 5.7.6.7: Please present results compared to placebo, and present estimates of the between study standard deviation together with their 95% credible intervals. Please also clarify what measures were taken to explain the heterogeneity between trials (that is, to reduce the between-study standard deviation through methods such as meta-regression)

The results compared to placebo (all random effects models) are presented in the tables on the next page.

Estimates of the between study standard deviations are reported in the table below.

Section (endpoints)	5.7.6.1 (HAQ CFB at 24/26 weeks)	5.7.6.3 (ACR20 responses at 24/28 weeks)	5.7.6.5 (ACR50 responses at 24/28 weeks)	5.7.6.7 (ACR70 responses at 24/28 weeks)
Between study standard deviation (95% CrI)	0.077 (0.023; 0.204)	0.481 (0.083; 1.283)	0.563 (0.039; 1.655)	0.548 (0.031; 1.797)

Heterogeneity: the feasibility of meta-regressions was evaluated by adjusting for DAS28 score at baseline and differences in background MTX use. Unfortunately, performing a meta-regression with DAS28 score at baseline and MTX concomitant use dosage as covariates was severely challenged by lack of reported data. Further, the DAS28 score at baseline was only reported for 5 studies. In one study, the DAS28 C-reactive protein (CRP) was reported and in three studies, it was the DAS28 erythrocyte sedimentation rate (ESR). The fifth study reported both the DAS28 CRP and ESR.

HAQ CFB at 6 months Treatment effect relative to Placebo

	Relative difference in mean HAQ CFB	2.5% CrL	97.5% CrL
Adalimumab	-0.33	-0.51	-0.16
Certolizumab Pegol	-0.39	-0.54	-0.23
Etanercept	-0.28	-0.48	-0.08
Golimumab	-0.34	-0.58	-0.09
Infliximab	-0.19	-0.35	-0.03
Abatacept	-0.30	-0.42	-0.16

ACR 20 Treatment effect relative to Placebo

	Relative risk	2.5% CrL	97.5% CrL	Odds ratio	2.5% CrL	97.5% CrL
Adalimumab	2.49	1.76	3.21	6.19	2.54	18.50
Certolizumab Pegol	2.85	2.22	3.41	11.28	4.37	30.50
Etanercept	1.80	1.06	2.77	2.65	1.08	8.26
Golimumab	2.12	1.00	3.09	3.88	1.00	15.34

Infliximab	1.81	1.03	2.68	2.68	1.04	7.36
Abatacept	1.90	1.24	2.57	3.00	1.37	6.42

ACR 50 Treatment effect relative to Placebo

	Relative risk	2.5% CrL	97.5% CrL	Odds ratio	2.5% CrL	97.5% CrL
Adalimumab	4.50	2.23	7.62	8.54	2.63	33.09
Certolizumab Pegol	4.79	2.47	7.91	9.87	3.02	38.20
Etanercept	2.65	1.24	6.82	3.40	1.28	19.95
Golimumab	2.85	0.71	6.76	3.81	0.68	21.98
Infliximab	2.14	0.46	5.72	2.53	0.43	13.26
Abatacept	2.62	1.24	4.95	3.36	1.28	9.22

ACR 70 Treatment effect relative to Placebo

	Relative risk	2.5% CrL	97.5% CrL	Odds ratio	2.5% CrL	97.5% CrL
Adalimumab	7.17	2.21	18.88	9.59	2.31	43.09
Certolizumab Pegol	8.86	3.14	23.31	12.97	3.43	72.43
Etanercept	3.73	1.38	18.93	4.20	1.40	39.99
Golimumab	4.14	0.69	16.76	4.75	0.68	35.52
Infliximab	3.57	0.55	13.16	3.99	0.54	22.32
Abatacept	3.72	1.50	10.52	4.18	1.53	15.12

A27. Page 170: Sections 5.7.6.2, 5.7.6.4, 5.7.6.6 and 5.7.6.8: It is assumed that “adjusted mean HAQ CFB” means the presentation of absolute mean change from baseline. The estimate of the abatacept change from baseline is based on the average of the population means from each trial. Although baselines are typically assumed to be fixed when estimating treatment effects, baselines will vary across trials. Please provide a rationale for not modelling the abatacept change from baseline using a random effects model

As noted in section 5.7.6.2, 5.7.6.4, 5.7.6.6. and 5.7.6.8 of the NICE STA, a random effect model was used. All the adjusted means were calculated using the average placebo mean, plus the relative treatment effect versus placebo treatment as estimated by the MTC, using a random effect model.

A28. Page 172: Section 5.7.7: The estimates of the residual deviance are incorrect in the case of the models for continuous data because they assume that the standard errors of the means are known and equal to the sample standard errors. Please present total residual deviances for each model and discuss any large individual deviance values for treatment arms.

The residual deviances were not used for testing, but only for comparison of the fit of the fixed and random effects approach. In our opinion, changing the formula will only change the result of the comparison when the residual deviances of the models compared are about equal. In that situation, the model selection is questionable, independent of whether or not we use the correct formula. Further, this formula for residual deviance with normal data y, mean mu (μ) and known standard deviation sigma (σ) is presented in the evidence synthesis for decision modelling course given by the University of Leicester and the University of Bristol.

The total residual deviances and the individual residual deviances for each model are reported in the tables below. For the fixed effects model, we see that the large residual deviance is obtained for the AIM study and the ATTEST study. This is in line with the large difference in input of treatment effect: AIM: difference of -.19, ATTEST: difference of -.39, both adjusted for placebo. As a check of this statement, we inputted a placebo response for the AIM study, which was in line with the ATTEST study. After rerunning, we found no outliers. The random effect model is better than the fixed effects model, just because of the difference in AIM and ATTEST, as can be obtained from taking the sum of the deviances not related to AIM and ATTEST.

Fixed effects model

Model used	Fixed effects model
Total residual deviance	31.4
Deviance for each data point	
AIM, placebo	5.20
ATTEST, placebo	3.07
AIM, abatacept	2.90
ATTEST, abatacept	1.52
ATTRACT, infliximab	0.60
ATTRACT, placebo	0.59
ATTEST, infliximab	0.47
GO-FORWARD, placebo	0.46
GO-FORWARD, golimumab	0.46
Kremer 2003, placebo	0.44
Kremer 2003, abatacept	0.44
RAPID I, certolizumab	0.42
DE019, adalimumab	0.41
DE019, placebo	0.41
RAPID II, certolizumab	0.41
RAPID I, placebo	0.39
RAPID II, placebo	0.39
Weinblatt 1999, etanercept	0.37
TEMPO, etanercept	0.36
TEMPO, placebo	0.35
Weinblatt 1999, placebo	0.30
ARMADA, placebo	0.29
ARMADA, adalimumab	0.28

Random effects model

Model used	Random effects model
Total residual deviance	21.6
Deviance for each data points	
AIM, placebo	0.66
ATTEST, placebo	0.59
AIM, abatacept	0.57
ATTEST, abatacept	0.5
ATTRACT, placebo	0.47
ATTEST, infliximab	0.46
GO-FORWARD, placebo	0.46
GO-FORWARD, golimumab	0.46
ATTRACT, infliximab	0.45
DE019, adalimumab	0.44
DE019, placebo	0.43
RAPID I, certolizumab	0.43
RAPID II, certolizumab	0.43
RAPID I, placebo	0.42
RAPID II, placebo	0.41
Weinblatt 1999, etanercept	0.41
Kremer 2003, placebo	0.39
TEMPO, etanercept	0.39
Kremer 2003, abatacept	0.38
TEMPO, placebo	0.38
ARMADA, placebo	0.37
Weinblatt 1999, placebo	0.36
ARMADA, adalimumab	0.35

A29. Whilst a random effects meta-analysis quantifies the degree of heterogeneity between trials, the resulting posterior distribution in the presence of uncertainty means that the treatment effect varies with trial. Please clarify what measures were taken to evaluate differences between trials.

To evaluate differences between trials, we first performed a qualitative assessment of the study design and methodologies of the included trials as well as a qualitative assessment of the baseline population and disease characteristics (see section 5.7.3 for more details). During this process, the TEMPO trial was identified as potentially different trial design compared to the other trials included. The patient population included did not consist of inadequate responders to MTX, but inadequate responders to conventional DMARDs. Therefore, patients effectively changed their treatment from a conventional DMARD to MTX in the placebo treatment group, potentially explaining the high placebo response observed. The impact of the TEMPO trial on the result has been evaluated in a scenario analysis. As mentioned in section 5.7.8, 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.

A30. Page 174: Section 5.7.9:. Please clarify how the abatacept response rates were estimated from the MTC given that abatacept was the baseline treatment used in the meta-analysis.

The baseline treatment used in the MTC was placebo, and not abatacept, as placebo was the most common comparator across the studies. As shown in figure B25, we obtain a network of studies where all the studies were connected to each other, allowing us to estimate the relative efficacy of all pair-wise treatments. All the adjusted means were calculated using the crude average of the placebo arms, plus the relative treatment effect versus placebo treatment as estimated by the indirect treatment comparison.

A31. Page 332: Section 9.4.8: The models for continuous data (Code 1 and 2) appear to be incorrect, as they assume that the within study standard error is known and equal to the sample standard error. Please could you amend the analysis to allow for uncertainty in the between study standard deviation. The models should include the data to allow for checking of the analysis. Please also clarify how any missing standard errors to be accounted for in the analyses of continuous data e.g. Kramer, Table B20, Page 129.

Indeed, the assumption is made that the within study standard error is known and equal to the sample error. However, note that in a number of studies, the sample error is not known and we use sample errors just derived from p-values. The ‘incorrectness’ of these sample errors is in our opinion much larger than the incorrectness of the sample errors themselves. Further, the assumption that the within study standard error is known and equal to the sample error is commonly used.

All the analyses have been performed using a random effects model, therefore allowing for uncertainty in the between study standard deviation. The input data are presented in tables B34, B36, B36 and B37 in section 5.7.4, the data sets are provided in the tables below.

In the analysis of continuous data (HAQ CFB at 24/26 weeks), the following strategy has been developed when the standard deviation was missing. If a p-value was provided in the publication, the missing standard deviation was estimated based on the p-value. When the p-value was an exact number, the standard deviation estimate was expected to be very close to the true value (approach taken for Strand 2006 and Smolen 2008). When the p-value was stated to be less than a certain threshold, the standard deviation estimate was expected to be greater than the true value (approach taken for Van der Heijde 2006). When no information about the uncertainty was available, the standard errors provided in other papers was transformed into standard deviations and corresponding variances. The square root of the mean variance is divided by the square root of the sample size of the trial/treatment combination for which the standard error is missing to obtain an estimate of the standard error (approach taken for Kremer 2003, Weinblatt 1999 and Lipsky 2000), permitting integration of all the data available.

Data sets used in WinBUGS

HAQ CFB 24/26 weeks

Coding treatments		**Data**						
1=	Placebo	list(N=23, NS=11, NT=7, NT1=11)						
2=	Adalimumab	s[]	t[]	y[]	sd[]	n[]	b[]	
3=	Certolizumab Pegol	1	7	-0.59	0.62	433	1	# AIM (CSR)
4=	Etanercept	1	1	-0.4	0.59	219	1	
5=	Golimumab	2	1	-0.14	0.49	119	1	# Kremer 2003
6=	Infliximab	2	7	-0.42	0.49	115	1	
7=	Abatacept	3	7	-0.68	0.22	156	1	# ATTEST (CSR)
		3	1	-0.29	0.22	110	1	
		3	6	-0.53	0.29	165	1	
		4	1	-0.27	0.57	62	1	# ARMADA (Weinblatt 2003)
		4	2	-0.62	0.63	67	1	
		5	2	-0.56	0.52	207	1	# DE019 (Keystone 2004)

5	1	-0.24	0.52	200	1	
6	1	-0.17	0.56	199	1	# RAPID I (NICE Cimzia manufacturer report)
6	3	-0.58	0.59	393	1	
7	1	-0.14	0.45	127	1	# RAPID II (Smolen 2009)
7	3	-0.5	0.47	246	1	
8	1	-0.4	0.49	30	1	# Weinblatt 1999
8	4	-0.7	0.49	59	1	
9	1	-0.63	1.08	228	1	# TEMPO (Van der Heijde 2006)
9	4	-0.89	1.08	231	1	
10	1	-0.13	0.58	133	1	# GO-FORWARD (Genovese 2008)
10	5	-0.47	0.55	89	1	
11	1	-0.19	0.49	88	1	# ATTRACT (Lipsky 2000)
11	6	-0.31	0.49	86	1	

END

ACR 20 24/28 weeks

Coding treatments

1= Placebo
2= Adalimumab
3= Certolizumab Pegol
4= Etanercept
5= Golimumab
6= Infliximab
7= Abatacept

Data

list(N=23, NS=11, NT=7, NT1=11)

s[]	t[]	r[]	n[]	b[]	
1	9	294	433	1	# AIM (Kremer 2006)
1	1	87	219	1	
2	1	42	119	1	# Kremer 2005
2	9	69	115	1	
3	9	104	156	1	# ATTEST (Schiff 2008)
3	1	46	110	1	
3	6	98	165	1	
4	1	9	62	1	# ARMADA (Weinblatt 2003)
4	2	45	67	1	
5	2	131	207	1	# DE019 (Keystone 2004)
5	1	59	200	1	

6	1	27	199	1	# RAPID I (Keystone 2008)
6	3	231	393	1	
7	1	11	127	1	# RAPID II (Smolen 2009)
7	3	141	246	1	
8	1	8	30	1	# Weinblatt 1999
8	4	42	59	1	
9	1	167	228	1	# TEMPO (Klareskog 2004)
9	4	188	231	1	
10	1	37	133	1	# GO-FORWARD (Keystone 2009)
10	5	53	89	1	
11	1	18	88	1	# ATTRACT (Maini 1999)
11	6	42	86	1	

END

ACR 50 24/28 weeks

Coding treatments

1= Placebo
2= Adalimumab
3= Certolizumab Pegol
4= Etanercept
5= Golimumab
6= Infliximab
7= Abatacept

Data

list(N=21, NS=10, NT=7, NT1=10)

s[]	t[]	r[]	n[]	b[]	
1	7	173	433	1	# AIM (Kremer 2006)
1	1	37	219	1	
2	1	14	119	1	# Kremer 2005
2	7	42	115	1	
3	7	63	156	1	# ATTEST (Schiff 2008)
3	1	22	110	1	
3	6	61	165	1	
4	1	5	62	1	# ARMADA (Weinblatt 2003)
4	2	37	67	1	
5	2	81	207	1	# DE019 (Keystone 2004)
5	1	19	200	1	
6	1	15	199	1	# RAPID I (Keystone 2008)

6	3	146	393	1	
7	1	4	127	1	# RAPID II (Smolen 2009)
7	3	80	246	1	
8	1	1	30	1	# Weinblatt 1999
8	4	23	59	1	
9	1	92	228	1	# TEMPO (Klareskog 2004)
9	4	136	231	1	
10	1	18	133	1	# GO-FORWARD (Keystone 2009)
10	5	33	89	1	

END

ACR 70 24/28 weeks

Coding treatments

1=	Placebo
2=	Adalimumab
3=	Certolizumab Pegol
4=	Etanercept
5=	Golimumab
6=	Infliximab
7=	Abatacept

Data

list(N=21, NS=10, NT=7, NT1=10)

s[]	t[]	r[]	n[]	b[]	
1	7	86	433	1	# AIM (Kremer 2006)
1	1	14	219	1	
2	1	2	119	1	# Kremer 2005
2	7	19	115	1	
3	7	32	156	1	# ATTEST (Schiff 2008)
3	1	10	110	1	
3	6	40	165	1	
4	1	3	62	1	# ARMADA (Weinblatt 2003)
4	2	18	67	1	
5	2	43	207	1	# DE019 (Keystone 2004)
5	1	5	200	1	
6	1	6	199	1	# RAPID I (Keystone 2008)
6	3	84	393	1	
7	1	1	127	1	# RAPID II (Smolen 2009)
7	3	39	246	1	

8	1	0	30	1	# Weinblatt 1999
8	4	9	59	1	
9	1	34	228	1	# TEMPO (Klareskog 2004)
9	4	82	231	1	
10	1	7	133	1	# GO-FORWARD (Keystone 2009)
10	5	18	89	1	
END					

Section C: Clarification on health economic model

A32. **Priority question:** Please present the cost-effectiveness results incrementally (with the identification of interventions that are dominated or extendedly dominated).

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, 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 in 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. Please find presented below deterministic and probabilistic analyses.

Deterministic

All treatments

Treatment	Cost	QALY	ICER vs cDMARD	ICER (inc. analysis)
cDMARD	£76,276	4.88	Ref	
Certolizumab pegol	£103,976	6.16	£21,592	£21,592
Etanercept	£107,653	6.12	£25,361	D
Infliximab	£109,419	5.96	£30,693	D
Adalimumab	£111,922	6.29	£25,359	£64,732
Abatacept	£114,548	6.16	£29,916	D
Golimumab	£115,372	6.25	£28,592	D

cDMARD, abatacept, infliximab

Treatment	Cost	QALY	ICER vs cDMARD	ICER (inc. analysis)
cDMARD	£76,276	4.88	ref	
Infliximab	£109,419	5.96	£30,693	ED
Abatacept	£114,548	6.16	£29,916	£29,916

Probabilistic

All treatments

Treatment	Cost	QALY	ICER vs cDMARD	ICER (inc. analysis)
cDMARD	£75,095	4.75	ref	
Certolizumab pegol	£103,385	6.05	£21,833	£21,833
Etanercept	£107,067	6.02	£25,232	D
Infliximab	£108,456	5.84	£30,565	D
Adalimumab	£111,436	6.15	£25,963	£77,425
Golimumab	£114,105	6.13	£28,332	D
Abatacept	£114,596	6.07	£29,888	D

cDMARD, abatacept, infliximab

treatment	Cost	QALY	ICER vs cDMARD	ICER (inc. analysis)
cDMARD	£75,095	4.75	ref	
Infliximab	£108,456	5.84	£30,565	ED
Abatacept	£114,596	6.07	£29,888	£29,888

A33. **Priority question:** Please confirm whether the CODA (the convergence diagnostic and output) from the WinBugs output was used in the modelling, or whether the data were transformed into independent normal distributions. A proper representation of uncertainty should be based on the results of the MTC and will use samples from the joint posterior distribution, thereby preserving the unknown underlying distribution and correlation between treatments.

CODA is not used and data were not transformed. All trials are placebo-controlled and only the ATTEST trial is a three-arm trial: abatacept, infliximab and placebo. As such, only one correlation is expected to be different from 0: the correlation between the relative estimate of abatacept versus placebo and the relative estimate of infliximab versus placebo. This means, that the comment is related to the comparison of abatacept with infliximab. This comparison is indeed made in a conservative way, as abatacept has a larger effect than infliximab in the head-to-head study and due to the independent sampling method used in the economic model, this is not taken into account.

A34. **Priority question:** Please clarify the rationale for assuming that serious adverse events are not associated with a cost implication.

Treatment discontinuation due to serious adverse events was not associated with cost. This is in line with the economic analysis submitted for the abatacept for TA195. Since the serious adverse events rates for abatacept are lower compared to cDMARD and infliximab, this is a conservative approach for abatacept.

A35. **Priority question:** Please tabulate the proportion (and associated confidence intervals) of patients likely to respond to each treatment at 6 months.

The proportion of patients responding at 6 months is not an outcome of the model. The key input data to estimate the proportion of responders based on HAQ is estimated by using the data from column 2 and 3 in the table below. The proportion of patients responding at 6 months is reported in column 4.

Treatment	MEAN HAQ at 6 months	SE	% responder (HAQ 0.3)
MTX + Abatacept	1.13	0.70	65%
MTX + Etanercept	1.15	0.71	64%
MTX + Adalimumab	1.10	0.71	66%
MTX + Infliximab	1.24	0.70	59%
MTX + Certolizumab pegol	1.04	0.70	69%
MTX + Golimumab	1.09	0.71	67%
Leflunomide	1.33	0.70	54%
Gold	1.40	0.70	50%
Azathioprine	1.50	0.70	44%
Ciclosporin	1.37	0.70	52%
Penicillamine	1.50	0.70	44%
Palliative care	1.70	0.70	33%

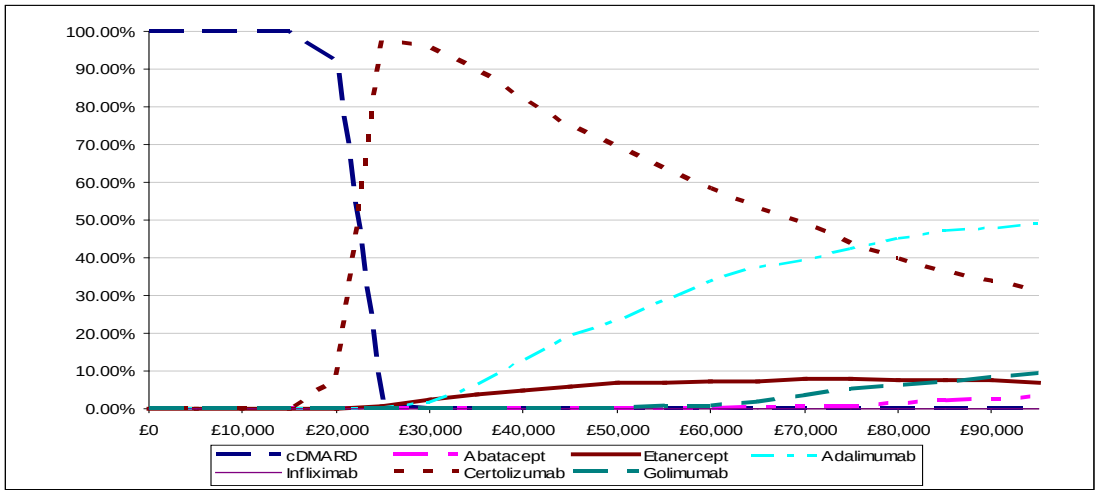
A36. **Priority question:** The Cost Effectiveness Acceptability Curve (CEAC) should detail the probability of each intervention being cost effective, and therefore the summation of the individual probabilities should equal 100%. Please provide a correct CEAC that considers the interventions simultaneously

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, 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

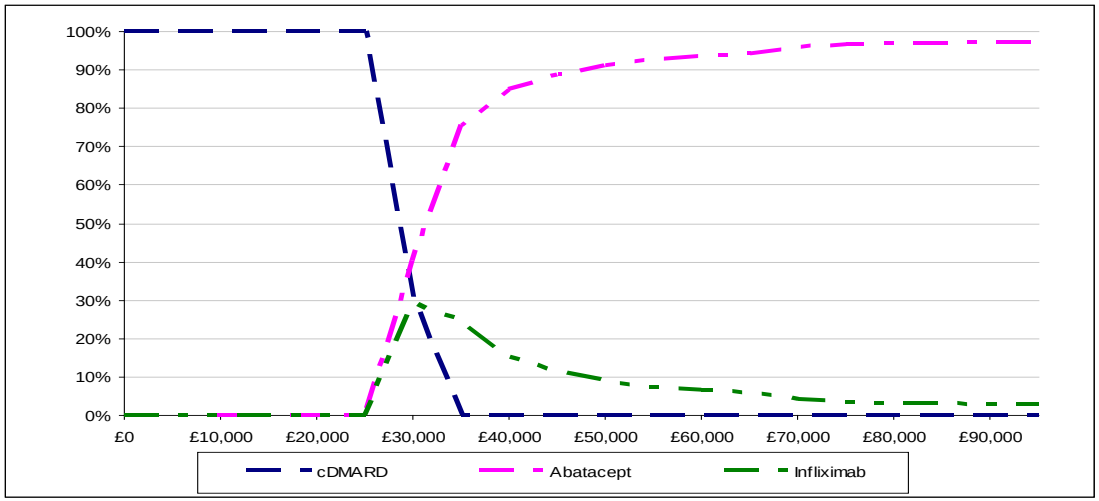
In addition, as described above in more detail in section 2, for some patients a sc administered agent provides an adequate choice of therapeutic medicine, however there are patients who would benefit more from an IV administered drug. An IV administered agent would be more appropriate for patients who; 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.

Presented below are the correct CEAC analyses.

CEA curve all treatments



CEA curve abatacept, cDMARD and infliximab



A37. Page 236: The results from the Vera Llonch study appear internally inconsistent in that an incremental cost of £68k and an incremental QALY of 1.1 does not appear to produce an ICER of £43k. Please check and clarify.

Correct, the corrected ICER is provided in the table below.

	MTX		Abatacept + MTX		Difference		ICER
	Total cost	Total QALY			Cost	QALY	
Life time	$80,096	3.9	$147,853	5.5	$67,757	1.6	$42,348
10 years	$52,175	3.0	$103,601	4.1	$51,426	1.1	$46,751

A38. Page 251: Table B75: Please provide a rationale for using results of a fixed effects model for the analysis of serious adverse events (SAEs).

The total number of studies included in this analysis was 6. As a consequence, the random effects model did not yield informative results, i.e. the relative treatment effects have an implausibly very large uncertainty. Therefore the mean results of the fixed effect model were preferred over the random effects model in order to distinguish the treatments

A39. Page 251: Please provide confidence intervals for the long-term HAQ progressions reported in Table B75.

Confidence intervals were not incorporated for the long-term HAQ progression.

A40. Page 260: Please clarify if in the citation of the Hurst et al utility equation the final term should be relates to HAQ squared rather than to HAQ alone.

Yes, utility equation is related to HAQ squared.

A41. Page 263: Please confirm that the utility derived from the HAQ score is based on the individual patient's HAQ score rather than placing the HAQ within a band (e.g. 1.25-1.50) and using the midpoint from that HAQ range. If the latter, please justify why the loss in accuracy was necessary.

Yes, utility is derived from the HAQ scores on the individual patients HAQ and not related to a mid point.

A42. Page 276: Table B84 describes the parameters in the probabilistic sensitivity analyses:

- Please confirm that there should be no value in the placebo and MTX row as this is the metric with which the other treatments are compared.

The uncertainty in the absolute response of a treatment is accumulated by the uncertainty in the relative treatment effect of the treatment effect versus placebo and the uncertainty in the placebo effect, expressed as placebo + MTX, as all treatments are added to MTX.

- Please provide a justification for the uncertainty associated with patients who fail on treatment, treatment duration, discontinue due to SAEs and have dose increases, and in the utility parameters.

Uncertainty associated with:

Failure on treatment cDMARD (HAQ CFB): no confidence intervals reported in Chen 2006, therefore assumed + and - 20% credibility limit of the mean.

Treatment duration: Biologics; no confidence intervals reported in Malottki 2009 assumed + and - 20% credibility limit on the shape and scale. For cDMARDs no confidence intervals reported in Barton 2004 assumed + and - 10% credibility limit on the shape and scale.

Discontinuation due to SAEs: Biologics; due to the very wide confidence intervals reported in the results from the indirect treatment comparison of the fixed effect model, + and – 20% CrL of the mean was assumed. For cDMARDS, no confidence intervals were reported in Chen 2006, therefore assumed + and – 20% CrL of the mean.

Dose increase: Moots 2009 did not report confidence intervals, therefore + and – 20% CrL of the mean was assumed.

Utility parameters: the standard error was calculated from the 95% confidence intervals reported in Malottki 2009, page 215.

	Hurst (quadratic)		
	mean	95% CI	se
A	0.804	0.711, 0.897	0.047449
*b*1	0.203	0.054, 0.351	0.075765
*b*2	0.045	-0.007, 0.096	0.026276

- Please clarify assumptions made about the correlation between parameters and revise the analysis if correlation is currently assumed to be zero. An analysis based on a normal distribution should model the intercept, slope and slope2 as being multivariate normally distributed.

As already mentioned previously, no correlation was applied in the model, as only the treatment effect of abatacept versus placebo and the treatment effect of infliximab versus placebo is correlated and infliximab is worse than abatacept, implying a conservative analysis. To not make the model more complex, it was decided to sample the relative treatment effects independently.

- Please clarify what 'assumed 20%CrL' and 'assumed 20%' refer to.

Assumed 20% CrL and assumes 20% means that the CrL was obtained by adding and subtracting 20% of the mean or shape and scale (e.g. mean * 0.80 and mean * 1.2).

A43. Page 281: Please confirm if the admin costs for certolizumab should be £30?

Confirmed, the administration costs for certolizumab used in the CE model are £30.

A44. Page 283: Table B88. Please confirm if the last column should be labelled the cost effectiveness of abatacept compared with the intervention.

Confirmed.

A45. Page 299: Table C3. Please confirm whether the value for infliximab in scenario 2 should be 9,321?

There is in error in Table C3, values for infliximab should be:

- Current practice; no abatacept moderate and severe patients: 10,391
- Scenario 2: with abatacept moderate and sever patients: 9,871

These value may also be viewed within the budget impact model.

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APPENDICIES

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