Golimumab for the Treatment of Rheumatoid Arthritis after Failure of Previous Disease-Modifying Antirheumatic Drugs

Submission to National Institute of Health and Clinical Excellence

Single technology appraisal (STA)

Evidence Review Group (ERG) Clarification Question Response

05 August 2010

Manufacturer

Schering-Plough Ltd (part of MSD)

22 July 2010

National Institute for Health and Clinical Excellence
NICE
Midcity Place
71 High Holborn
London
WC1V 6NA
Tel: 0161 870 3154
Fax: 020 7061 9821
Email: Kate.Moore@nice.org.uk
www.nice.org.uk

Dear Jo Annah,

Re: Single Technology Appraisal –Golimumab for the treatment of rheumatoid arthritis after failure of previous disease-modifying antirheumatic drugs

The Evidence Review Group (School of Health and Related Research [ScHARR]) and the technical team at NICE have now had an opportunity to take a look at submission received on the 2 July 2010 by Schering Plough Ltd (part of MSD). In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **17:00, 5 August 2010**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments, or sent on a CD.
Please provide an update on the status of the additional analyses that are being awaited. As previously indicated, the Evidence Review Group (ERG) cannot provide a guarantee that it will be possible to review these extra analyses.

If you have any further queries on the technical issues raised in this letter then please contact Sally Doss – Technical Lead (sally.doss@nice.org.uk) Any procedural questions should be addressed to Kate Moore – Project Manager (Kate Moore@nice.org.uk in the first instance.

Yours sincerely
Helen Chung
Associate Director – Appraisals
Centre for Health Technology Evaluation

Section A: Clarification on effectiveness data

A1. **Priority Question:** The current MS considers golimumab at two points. These are:

- as an alternative to currently available anti-TNFs in second line therapy
- as an alternative to rituximab in third line therapy

  In addition to the two comparisons currently considered, please also present comparisons against the additional treatments recommended in the draft guidance of ongoing rheumatoid arthritis appraisals of tocilizumab, and abatacept, adalimumab, etanercept and infliximab after the use of a TNF inhibitor. This would consider golimumab;

- as an alternative to anti-TNF therapy (adalimumab, etanercept, infliximab and abatacept) in patients unable to take the standard third line therapy (rituximab with methotrexate)
- as an alternative to tocilizumab with methotrexate in patients unable to take the standard third line therapy (rituximab with methotrexate)
- as an alternative to current fourth line therapy (tocilizumab with methotrexate)

  If the comparisons are not considered appropriate please provide further rationale.

  The two patient populations presented within the MS represent those assessed within the randomised clinical trials (GO-FORWARD, Kay *et al* 2008 and GO-AFTER). Populations further along the treatment pathway were considered outside the scope of this appraisal.

  The sequential use of TNFs as well as tocilizumab were not included as comparators as these appraisals remain outstanding and have not received final Technology Appraisal Guidance (TAG). The Final Appraisal Determination (FAD) for both of these appraisals was published within days of the golimumab MS and thus it was not possible to speculate which population would be most appropriately modelled.

  Within the 10 day timeframe requested by the Evidence Review Group (ERG), it is not possible to address the three additional treatment pathways above as this requires significant remodelling and systematically re-reviewing the literature for relevant comparator data.

A2. **Priority Question:** Tables 130 and 131, pages 124-126. Please a) clarify the definition of the term 'palliative care' in terms of the treatment pathway and b) describe and justify the selection of evidence to support the modelling of palliative care.

Palliative care is assumed to be following complete treatment failure on biologics. In the absence of DMARD therapy, clinical expert feedback suggested that patients

would theoretically be treated with pain relief, pain management, physiotherapy, occupational therapy and rehabilitation services where available. Patients receiving palliative care were assumed to have a one-off visit to the rheumatologist prior to cycling into palliative care. Every cycle on palliative care was assumed to have 3 rheumatologist visits and 3 specialist nurse visits, based on clinical expert opinion. The costs of drugs administered in palliative care are assumed to be zero.

Evidence for DMARD response following biologic treatment is limited and suggests may not be effective. The model conservatively estimates an improved response on DMARDs rather than palliative care. A more appropriate assumption may have been to assume that DMARDs and palliative care following biologic treatment have similar treatment responses.

A3. **Priority Question:** Please provide analyses (including use in meta-analyses, mixed treatment comparisons, indirect comparisons and use as comparators in economic analyses as directed above) comparing golimumab with tocilizumab, abatacept and the sequential use of the TNF inhibitors.

Please refer to question A1 which states that it is not feasible within the 10 day time frame to present analyses for all of the suggested comparisons above. This requires widening the systematic literature review and then updating and re-running all of the analyses.

The MS was based upon accepted clinical practice at the time of submission. Whilst several FADs were published immediately before the golimumab MS, these still remain in draft guidance, awaiting publication of the TAGs.

A4. **Priority Question:** Page 26. The decision problem lists the outcomes addressed in this assessment. The following outcomes do not appear to have been addressed: Joint damage, mortality, fatigue and radiological progression. Please provide data on these outcomes or state where data are not available. Alternatively please provide justification for the exclusion of these outcomes.

Tendor and swollen joint counts were extracted for all identified clinical trials and included within the Tables 16, 17, 116 and 121. Mortality was incorporated within the Markov model within transition states derived from UK mortality rates. Mortality figures were extracted for all RCTs but was not commonly reported and thus not included within the MS. These figures are included below in Table 1. FACIT-F and fatigue were included within the search criteria. However, this parameter was underreported in the identified RCTs. Radiological progression data was not available from the pivotal trials.

Table 1. Mortality data at 6 and 12 months for identified RCTs

Study name	Intervention, dosing	Safety population	mortality	
			6 months	12 months
(Kim *et al.*, 2007)	placebo s.c., every other week + MTX	63		

	adalimumab 40 mg s.c. every other week + MTX	65		
(van de Putte *et al.*, 2004)	placebo s.c. weekly	110		
	adalimumab 40 mg s.c. every other week (with placebo injected on the alternate week)	113		
ARMADA	placebo s.c. every other week + MTX	62		
	adalimumab 40 mg s.c. every other week + MTX	67		
CHANGE	placebo s.c. every other week	87		
	adalimumab 40 mg s.c. every other week	91		
DE019	placebo sc every other week + MTX	12	0 (12 weeks)	
	adalimumab sc 40 mg every other week + MTX	35	0 (12 weeks)	
STAR	placebo sc every other week + background DMARDs	318	0	
	adalimumab sc 40 mg every other week + background DMARDs	318	1	
(Chen *et al.*, 2009)	placebo sc every week + MTX	200		0
	adalimumab sc 40 mg every other week (placebo on non-treatment weeks) + MTX	207		1
RAPID 1	placebo sc weeks 0, 2, 4, every 2 weeks thereafter + MTX (oral)	199		1
	certolizumab sc 400 mg weeks 0, 2, 4, 200 mg every 2 weeks thereafter + MTX (oral)	392		2
RAPID 2	placebo sc weeks 0, 2, 4, every 2 weeks thereafter + MTX (oral)	125	0	
	certolizumab sc 400 mg weeks 0, 2, 4, 200 mg every 2 weeks thereafter + MTX (oral)	248	1	
TEMPO	placebo sc twice weekly + MTX (oral)	228		1
	etanercept sc 25 mg twice weekly + placebo (oral)	223		1
	etanercept sc 25 mg twice weekly + MTX (oral)	231		1
(Combe *et al.*, 2006)	placebo sc twice weekly + sulfasalazine (oral)	50	0	
	etanercept sc 25 mg twice weekly + placebo (oral)	103	0	
	etanercept sc 25 mg twice weekly + sulfasalazine (oral)	101	0	
(Moreland *et al.*, 1999)	placebo twice weekly for 26 weeks	80		
	etanercept sc 25 mg twice weekly for 26 weeks	78		
(Weinblatt *et al.*, 1999)	placebo sc twice weekly for 24 weeks + MTX (oral or sc)	30	0	
	etanercept sc 25 mg twice weekly for 24 weeks + MTX (oral or sc)	59	0	
GO-FORWARD	placebo sc + MTX (oral)	134	0	
	golimumab sc 50 mg every 4 weeks + MTX (oral)	212	0	
(Kay *et al.*, 2008)	placebo (sc every 2 weeks); open-label infliximab 3 mg/kg at week 20, 22, 28, every 8 weeks thereafter + MTX (oral ≥ 10 mg/week)	34	0	0
	golimumab 50 mg/4 weeks; placebo every other 2 weeks + MTX (oral ≥ 10 mg/week)	37	0	0
ATTEST	placebo i.v. (all infusion days) + MTX	110	0	
	infliximab i.v. 3 mg/kg day 1, 14, 43, 85, every 56 days + MTX	165	1	2
ATTRACT	placebo i.v. week 0, 2, 6, every 4 weeks after + MTX (oral)	86		3
	infliximab i.v. 3 mg/kg week 0, 2, 6, every 4 weeks after + MTX (oral)	86		

	infliximab i.v. 3 mg/kg week 0, 2, 6, every 8 weeks after + MTX (oral)	88		
START	placebo i.v. week 0, 2, 6, 14 + MTX (oral); other DMARDs as necessary	361		1
	infliximab i.v. 3 mg/kg week 0, 2, 6, 14 + MTX (oral); other DMARDs as necessary	360		1
(Abe *et al.*, 2006)	placebo i.v. week 0, 2, 6 + MTX (oral)	47	0	
	infliximab i.v. 3 mg/kg week 0, 2, 6 + MTX (oral)	49	0	

A5. **Priority Question:** Page 28 onwards. ACR70 data are reported in the study publications for the GO-FORWARD, Kay *et al.* (2008) and GO-AFTER trials. Please provide a justification for the omission of this outcome. Please provide full additional analyses (with incorporation into meta-analyses, mixed treatment comparisons, indirect comparisons and economic analysis), incorporating this outcome.

Meta analyses for comparators and golimumab for ACR70 at 24 weeks are presented in the below tables for both a DMARD experienced population and TNFα inhibitor experienced population. Adalimumab, certolizumab, etanercept (excluding TEMPO), infliximab, rituximab and golimumab were all found to be statistically superior to placebo.

DMARD EXPERIENCED POPULATION

ADALIMUMAB

Table 2. Adalimumab studies included within meta-analysis (ACR70 at 24 wks in DMARD experienced population)

			treatment		**comparator**	
study	**treatment**	**comparator**	**n**	**total**	**n**	**total**
ARMADA	adalimumab	placebo	18	67	3	62
CHANGE	adalimumab	placebo	11	91	1	87
DE019	adalimumab	placebo	43	207	5	200
Kim	adalimumab	placebo	14	65	5	63
STAR	adalimumab	placebo	47	318	11	318
Van de Putte	adalimumab	placebo	14	113	2	110

Global analysis

The results of the meta-analyses are:

Table 3. Adalimumab meta-analysis RR results (ACR70 at 24 wks in DMARD experienced population)

Study	**RR**	**95% CI**	**Weights fixed-effect meta-analysis (%)**	**Weights random-effect meta-analysis (%)**
ARMADA	5.55	1.72, 17.93	11.4	11.7
CHANGE	10.52	1.39, 79.75	3.7	3.9
DE019	8.31	3.36, 20.55	18.6	19.7

Kim	2.71	1.04, 7.09	18.6	17.5
STAR	4.27	2.26, 8.09	40.2	39.6
Van de Putte	6.81	1.59, 29.29	7.4	7.6
Pooled RR			**5.30 (3.56, 7.90)**	**4.98 (3.33, 7.44)**
p-value pooled RR			**<0.001**	**<0.001**
Heterogeneity			**I^2=0%, chi-square p-value=0.577**	

There is no heterogeneity in this meta-analysis. The fixed-effect model is therefore the most appropriate. It shows that patients on adalimumab are 5.3 times more likely to achieve an ACR70 response at 6 months than patients on placebo.

CERTOLIZUMAB

Table 4. Certolizumab studies included within meta-analysis (ACR70 at 24 wks in DMARD experienced population)

			treatment		**comparator**	
study	**treatment**	**comparator**	**n**	**total**	**n**	**total**
RAPID 1	certolizumab	placebo	84	393	6	199
RAPID 2	certolizumab	placebo	39	246	1	127

Global analysis

The results of the meta-analyses are:

Table 5. Certolizumab meta-analysis RR results (ACR70 at 24 wks in DMARD experienced population)

Study	**RR**	**95% CI**	**Weights fixed-effect meta-analysis (%)**	**Weights random-effect meta-analysis (%)**
RAPID 1	7.09	3.15, 15.94	85.8	85.6
RAPID 2	20.13	2.8, 144.86	14.2	14.4
Pooled RR			**8.94 (4.23, 18.90)**	**8.24 (3.89, 17.44)**
p-value pooled RR			**<0.001**	**<0.001**
Heterogeneity			**I^2=0%, chi-square p-value=0.326**	

There is no heterogeneity in this meta-analysis, which shows that patients on certolizumab are nearly 9 times more likely to achieve an ACR70 response at 6 months than patients on placebo.

ETANERCEPT (excluding TEMPO trial)

Table 6. Etanercept studies included within meta-analysis (ACR70 at 24 wks in DMARD experienced population)

			treatment	**comparator**

study	treatment	comparator	n	total	n	total
Combe	etanercept	placebo	47	204	1	50
Moreland (monotherapy)	etanercept	placebo	12	78	1	80
Weinblatt	etanercept	placebo	9	59	0	30

Global analysis

The results of the meta-analyses are:

Table 7. Etanercept meta-analysis RR results (ACR70 at 24 wks in DMARD experienced population)

Study	RR	95% CI	Weights fixed-effect meta-analysis (%)	Weights random-effect meta-analysis (%)
Combe	11.52	1.63, 81.49	49.4	41.2
Moreland	12.31	1.64, 92.41	30.4	38.8
Weinblatt	9.82	0.59, 163.15	20.3	20.0
Pooled RR			**11.41 (3.19, 40.83)**	**11.45 (3.26, 40.20)**
p-value pooled RR			**<0.001**	**<0.001**
Heterogeneity			**I^2=0%, chi-square p-value=0.992**	

There is no heterogeneity in this meta-analysis. The fixed-effect model is therefore the most appropriate one. It shows that patients on etanercept are 11.4 times more likely to achieve an ACR70 response at 6 months than patients on placebo.

GOLIMUMAB

Table 8. Golimumab studies included within meta-analysis (ACR70 at 24 wks in DMARD experienced population)

			treatment		comparator	
study	**treatment**	**comparator**	**n**	**total**	**n**	**total**
GO-FORWARD	golimumab	placebo	18	89	7	133
Kay	golimumab	placebo	7	35	2	35

Global analysis

The results of the meta-analyses are:

Table 9. Golimumab meta-analysis RR results (ACR70 at 24 wks in DMARD experienced population)

Study	RR	95% CI	Weights fixed-effect meta-analysis (%)	Weights random-effect meta-analysis (%)
GO-FORWARD	3.84	1.67, 8.82	73.7	76.5
Kay	3.50	0.78, 15.69	26.3	23.5

Pooled RR			**3.75 (1.81, 7.77)**	**3.76 (1.82, 7.78)**
p-value pooled RR			**<0.001**	**<0.001**
Heterogeneity			**I^2=0%, chi-square p-value=0.915**	

There is no heterogeneity in this meta-analysis. The fixed-effect model is therefore the most appropriate. It shows that patients on golimumab are 3.75 times more likely to achieve an ACR70 response at 6 months than patients on placebo.

INFLIXIMAB

Table 10. Infliximab studies included within meta-analysis (ACR70 at 24 wks in DMARD experienced population)

			treatment		**comparator**	
study	**treatment**	**comparator**	**n**	**total**	**n**	**total**
ATTEST	infliximab	placebo	40	165	10	110
ATTRACT	infliximab	placebo	16	172	0	88
START	infliximab	placebo	48	360	16	361

Global analysis

The results of the meta-analyses are:

Table 11. Infliximab meta-analysis RR results (ACR70 at 24 wks in DMARD experienced population)

Study	**RR**	**95% CI**	**Weights fixed-effect meta-analysis (%)**	**Weights random-effect meta-analysis (%)**
ATTEST	2.67	1.39, 5.11	41.9	40.6
ATTRACT	16.98	1.03, 279.7	2.3	2.2
START	3.01	1.74, 5.2	55.8	57.3
Pooled RR			**3.19 (2.11, 4.83)**	**2.97 (1.97, 4.50)**
p-value pooled RR			**<0.001**	**<0.001**
Heterogeneity			**I^2=0%, chi-square p-value=0.427**	

There is no in this meta-analysis. The fixed-effect model is therefore the preferred one and shows that patients on infliximab are 3.19 times more likely to achieve an ACR70 response at 6 months than patients on placebo.

TNFα INHIBITOR EXPERIENCED PATIENTS

ACR70 data for golimumab and rituximab at 24 weeks are presented below. The relative risk for both treatments versus placebo was found to be statistically superior.

Table 12. TNFα inhibitor experienced studies assessed for ACR70 at 24 wks

			treatment		comparator	
study	**treatment**	**comparator**	**n**	**total**	**n**	**total**
GO-AFTER	golimumab	placebo	18	153	5	155
REFLEX	rituximab	placebo	36	298	2	201

Data are only available in one study for each treatment. Therefore no meta-analyses are needed.The RRs for each treatment are presented in the table below:

Table 13. RR for each treatment (ACR70 at 24 wks for TNFα experienced)

Treatment	**RR**	**95% CI**	**p-value**
golimumab	3.65	1.39, 9.58	0.009
rituximab	12.14	2.96, 49.86	0.001

This shows that patients on all treatments are significantly more likely to achieve an ACR70 response at 6 months than patients on placebo.

The MTC for both DMARD experienced and TNFα inhibitor experienced found no significant difference between the golimumab and any of the biologics as shown in the below table.

Table 14. MTC results RR (DMARD experienced population)

			FIXED EFFECT MODEL (DIC=171.2)			RANDOM EFFECT MODEL (DIC=172.7)		
			mean	**median**	**95% credibility interval**	**mean**	**median**	**95% credibility interval**
golimumab	vs	placebo	4.47	4.17	2.05, 8.66	4.59	4.20	1.79, 9.68
golimumab	vs	golimumab	1.00	1.00	-	1.00	1.00	-
golimumab	vs	adalimumab	0.82	0.76	0.34, 1.70	0.83	0.75	0.28, 1.86
golimumab	vs	certolizumab	0.53	0.48	0.19, 1.19	0.54	0.47	0.16, 1.35
golimumab	vs	etanercept	0.38	0.32	0.09, 1.03	0.40	0.32	0.09, 1.15
golimumab	vs	infliximab	1.32	1.21	0.53, 2.75	1.29	1.16	0.40, 3.00

Table 15. IC results RR with the Bucher method as in the MS (TNFα inhibitor experienced population)

Outcome	**Mean indirect estimate Golimumab vs Rituximab**	**95% confidence interval**
ACR70 at 6 months	0.30	0.05, 1.66

In line with other ERG clarification questions within the MTC section, a network analysis, fixed-effect model was also run in addition to the Bucher method. Table 16 shows that there is minimal difference between the IC or NA results.

Table 16. Network analysis, fixed effect model results RR (DMARD experienced population)

Outcome	Mean indirect estimate Golimumab vs Rituximab	95% confidence interval
ACR70 at 6 months	0.31	0.05, 1.38

A6. **Priority Question:** We are aware that open label extension data for the included golimumab studies are due to be published in abstract form in quarter 4 2010. Please specify whether data are available currently, and if so please provide.

As presented briefly in the MS executive summary and clinical write-up of GO-FORWARD, 52 week open label extension data is reported within Keystone et al 2010 (attached).

104 week GO-FORWARD data and 100 week GO-AFTER data was presented at EULAR, Rome in June 2010 (abstracts attached).

A7. **Priority Question:** Please state whether any trials of the efficacy and safety of golimumab in combination with methotrexate in patients with RA after failure of previous disease-modifying antirheumatic therapy are ongoing. If so, please provide data where available.

Table 17 presents the ongoing/recruiting clinical trials which assess the efficacy and/or safety of golimumab. Abstracts for the following trials accompany this document:

- NCT00771251 (CiC abstract awaiting acceptance to ACR Conference)
- NCT00264550 (EULAR Conference abstract for 104-week data; Keystone et al 2010 52-week data)
- NCT00299546 (EULAR Conference abstract for 100-week data)

Table 17. Ongoing and recruiting golimumab clinical trials

Clinicaltrials.gov Identifier	Study Title	Status	Reference
NCT01004432	Golimumab in Rheumatoid Arthritis Patients With an Inadequate Response to Etanercept (ENBREL) or Adalimumab (HUMIRA)	Recruiting. Estimated study completion date: July 2012	http://clinicaltrials.gov/ct2/show/NCT01004432?term=golimumab&rank=1
NCT00973479	An Efficacy and Safety Study of Intravenous Golimumab in Patients With Active Rheumatoid Arthritis (RA) Despite Treatment With Methotrexate, Non Steroidal Pain Medications and/or Corticosteroids	Recruiting. Estimated study completion date: Dec 2012	http://clinicaltrials.gov/ct2/show/NCT00973479?term=golimumab&rank=6
NCT00975130	Subcutaneous Golimumab (GLM) Plus DMARDs for Rheumatoid Arthritis, Followed by Intravenous/Subcutaneous GLM Strategy (P06129AM2) (GO-MORE)	Recruiting. Estimated study completion date: May 2012	http://clinicaltrials.gov/ct2/show/NCT00975130?term=golimumab&rank=8
NCT00264550	GO-FORWARD: A Study of the Safety and Efficacy of Golimumab in Subjects With Active Rheumatoid Arthritis Despite Methotrexate Therapy	Ongoing. Open label extension until 5 years (May 2012). (Abstract attached)	http://clinicaltrials.gov/ct2/show/NCT00264550?term=golimumab&rank=9
NCT00727987	A Safety and Efficacy Study of Golimumab (CNTO 148) in Patients With Active Rheumatoid Arthritis Despite Methotrexate Therapy	Ongoing. Estimated study completion date: March 2012	http://clinicaltrials.gov/ct2/show/NCT00727987?term=golimumab&rank=16

NCT00299546	GO-AFTER: A Study of the Safety and Efficacy of Golimumab (CNTO 148) in Subjects With Active Rheumatoid Arthritis Previously Treated With Biologic Anti-TNFα Agent(s)	Ongoing. Open label extension until 5 years (July 2012). (Abstract attached)	http://clinicaltrials.gov/ct2/show/NCT00299546?term=golimumab&rank=14
NCT00771251	A Safety and Efficacy Study of Golimumab (CNTO148) in Patients With Active Rheumatoid Arthritis (RA)	Primary results reporting. Estimated study completion date: October 2011. (CiC abstract attached)	http://clinicaltrials.gov/ct2/show/NCT00771251?term=golimumab&rank=15

A8. **Priority Question:** Please provide a) full up-to-date adverse events data available subsequent to the reporting of GO-FORWARD, Kay *et al.* (2008) and GO-AFTER for the use of golimumab in patients with rheumatoid arthritis. b) full up-to-date adverse events data relating to the use of golimumab in rheumatoid arthritis.

An open label extension of GO-FORWARD (NCT00264550) in DMARD experienced RA patients reported the following safety data at week 104 (Keystone et al 2010, EULAR 2010 abstract):

Patients were randomised to the following 4 groups:

- Group 1: n=133; Placebo + methotrexate
- Group 2: n=133; Golimumab 100mg + Placebo
- Group 3: n=89; Golimumab 50mg + methotrexate
- Group 4: n=89; Golimumab 100mg + methotrexate

Serious adverse events (per 100 patient-years (95% CI)) were reported as:

- Group 1: 15 (6.28, 28.68)
- Group 2: 27 (20.37, 35.97)
- Group 3: 16 (12.16, 21.47)
- Group 4: 25 (19.35, 32.23)

Serious infections (per 100 patient-years (95% CI)) were reported as:

- Group 1: 2 (0.05, 10.14)
- Group 2: 6 (3.33, 11.24)
- Group 3: 4 (1.76, 6.30)
- Group 4: 6 (3.66, 10.39)

Active tuberculosis occurred in 2 patients: 1 patient (Taiwan) in Group 3 and 1 patient (Poland) in Group 4.

Four deaths occurred through week 104: 1 each of sepsis, fulminant hepatic failure, and complicated respiratory distress in Group 2 and 1 circulatory insufficiency in Group 4.

A total of 15 malignancies occurred through week 104: 1 event in Group 1, 3 events in Group 2, 6 events in Group 3, and 5 events in Group 4.

An open label extension of GO-AFTER (NCT00299546) in TNFα inhibitor experienced RA patients reported the following safety data at week 100 (EULAR 2010 abstract):

Patients were randomised to the following 3 groups (detail in Table 18):

- Group 1: n=150; Placebo
- Group 2: n=147; Golimumab 50mg + methotrexate
- Group 3: n=148; Golimumab 100mg + methotrexate

Table 18. GO-AFTER open label extension (up to week 100) patient detail

Assessment	Group 1	Group 2	Group 3
Randomized pts (n):	150	147	148
Pts who entered EE at Wk 16	70(46.7%)	41(28.1%)	-
Pts who were receiving GLM 50 mg at Wk 24	120	96	-
Pts who had an opportunity to receive a dose escalation after DBL	107(89.2%)	78(81.3%)	-
Pts who received a dose escalation at anytime through Wk 100	78(72.9%)	41(52.6%)	-
No. swollen joints at Wk 100 % improvement from baseline	60.0 (10.00, 86.36)	64.52 (25.00, 86.36)	71.13 (28.57, 95.45)

Serious adverse events at week 100 were reported as:

- Group 2: 16.1%
- Group 3: 16.6%

Serious infections at week 100 were reported as:

- Group 2: 5.0%
- Group 3: 5.7%

Injection site reactions at week 100 were reported as:

- Group 2: 0.8%
- Group 3: 1.3%

No cases of tuberculosis were reported.

One death (pancreatic cancer) occurred through week 100 in Group 1.

A total of 6 malignancies occurred through week 100: 1 event in Group 1, 2 events in Group 2, and 3 events in Group 3.

A9. **Priority Question:** Appendix 7, Page 224 onwards. The number of records from the adverse events searches appear to be very small for the seven interventions searched (i.e. 37 in Medline and 36 in Embase). Please clarify why these numbers are so low.

The systematic literature search was re-run in MEDLINE on 04 August 2010 and found similar results. The updated systematic literature search was restricted to those interventions of interest (ie, excluded abatacept) and added the search term 'rituxan' as suggested within the ERG clarification questions. As depicted in Table 19 the updated search resulted in 101 hits. After further restrictions (English language, full text availability and humans) the number of hits reduced to 56. As these numbers are in line with the similar search conducted nearly 8 months ago, it is reasonable to consider that the EMBASE results will not change sufficiently. The search was further restricted (in accordance with inclusion criteria) to included 'rheumatoid arthritis' as a search term and resulted in 26 hits. This was to assist in addressing question A10 where those studies excluded were to explicitly state the reasoning; the

majority of studies were originally excluded as they were not in reference to the assessed indication. Therefore, inclusion of 'rheumatoid arthritis' as a search term removed the majority of those studies due to 'different indication'.

Table 19. Updated Ovid MEDLINE Search (conducted: 4 August 2010)

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1950 to Present>		
#	**Search Statement**	**Results**
1	(etanercept or enbrel).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	2705
2	(infliximab or remicade).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	5894
3	(adalimumab or humira).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	1696
4	(golimumab or simponi).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	81
5	(certolizumab or cimzia).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	148
6	(rituximab or mabthera or rituxan).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	6674
7	or/1-6	14629
8	Safety/	28637
9	(safe or safety).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	346190
10	side effect$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	141867
11	emergency treatment.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	9340
12	undesirable effect$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	1612
13	tolerability.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	22664
14	Drug Toxicity/	3620
15	toxicity.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	198848
16	Adverse Drug Reaction Reporting Systems/	4270
17	adrs.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	1172
18	(adverse adj3 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	174195
19	(undesire$ adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	1092
20	Drug Hypersensitivity/	18209
21	(hypersensit$ or hyper sensit$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	123561
22	harm$.mp. [mp=title, original title, abstract, name of substance word,	69615

	subject heading word, unique identifier]	
23	or/8-22	940760
24	7 and 23	3956
25	exp infection/ci [Chemically induced]	3071
26	exp urinary tract infections/ci [Chemically induced]	64
27	exp respiratory tract infections/ci [Chemically induced]	3871
28	exp bone diseases, infectious/ci [Chemically induced]	139
29	exp arthritis, infectious/ci [Chemically induced]	57
30	exp neoplasms/ci [Chemically induced]	51755
31	exp tuberculosis/ci [Chemically induced]	336
32	or/25-31	58437
33	24 and 32	101
34	limit 33 to (english language and full text and humans)	56
35	rheumatoid arthritis.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]	64384
36	34 and 35	26

A10. **Priority Question:** Appendix 8, Page 227. The ERG considers non-randomised controlled trials to be a valid and important source of evidence for the evaluation of adverse events. Please describe any identified non-randomised controlled trial evidence relating to adverse events. If any such evidence was excluded, please justify in full reasons for exclusion.

Table 20 presents the adverse event trials which were identified from the 26 results depicted in Table 19.

Table 20. Inclusion and exclusion of adverse event trials

Author	Year	Title	Inclusion/Exclusion
Alldred	2001	Etanercept in rheumatoid arthritis	Excluded - review
Baeten	2003	Systematic safety follow up in a cohort of 107 patients with spondyloarthropathy treated with infliximab: a new perspective on the role of host defence in the pathogenesis of the disease?	Excluded - different indication
Bongartz	2009	Etanercept therapy in rheumatoid arthritis and the risk of malignancies: a systematic review and individual patient data meta-analysis of randomised controlled trials	Excluded - review
Brown	2002	Tumor necrosis factor antagonist therapy and lymphoma development: twenty-six cases reported to the Food and Drug Administration	Included
Burmester	2009	Adalimumab safety and mortality rates from global clinical trials of six immune-mediated inflammatory diseases	Included
Criscione	2002	Tumor necrosis factor-alpha antagonists for the treatment of rheumatic diseases	Excluded - review

Fleischmann	2005	Long term safety of etanercept in elderly subjects with rheumatic diseases	Included
Flendrie	2003	Survival during treatment with tumour necrosis factor blocking agents in rheumatoid arthritis	Included
Genovese	2009	Safety of biological therapies following rituximab treatment in rheumatoid arthritis patients	Excluded - different population
Hyrich	2004	Anti-tumour necrosis factor alpha therapy in rheumatoid arthritis: an update on safety	Excluded - review
Kaur	2007	Pneumocystis jiroveci (carinii) pneumonia after infliximab therapy: a review of 84 cases	Excluded - review
Keane	2001	Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent	Excluded - review
Klapman	2003	A lupus-like syndrome associated with infliximab therapy	Excluded - different indication
Klareskog	2006	A long-term, open-label trial of the safety and efficacy of etanercept (Enbrel) in patients with rheumatoid arthritis not treated with other disease-modifying antirheumatic drugs	Included
Koike	2009	Japan College of Rheumatology 2009 guidelines for the use of tocilizumab, a humanized anti-interleukin-6 receptor monoclonal antibody, in rheumatoid arthritis	Excluded - not intervention of interest
Lee	2007	Cutaneous side-effects in patients with rheumatic diseases during application of tumour necrosis factor-alpha antagonists	Excluded - different indication
Listing	2005	Infections in patients with rheumatoid arthritis treated with biologic agents	Included
Mayordomo	2002	Pulmonary miliary tuberculosis in a patient with anti-TNF-alpha treatment	Exclude - review
Mikuls	2003	Lessons learned in the use of tumor necrosis factor-alpha inhibitors in the treatment of rheumatoid arthritis	Excluded - review
Mohan	2004	Tuberculosis following the use of etanercept, a tumor necrosis factor inhibitor	Exclude - review
Nam	2010	Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA	Excluded - review
Neven	2005	Adverse events in patients with rheumatoid arthritis treated with infliximab in daily clinical practice	Excluded - letter; insufficient data
Saba	2008	Adalimumab-induced acute myelogenic leukemia	Exclude - review of single case study; n=1
Salliot	2007	Infections during tumour necrosis factor-alpha blocker therapy for rheumatic diseases in daily practice: a systematic retrospective study of 709 patients	Included

Scheinfeld	2004	A comprehensive review and evaluation of the side effects of the tumor necrosis factor alpha blockers etanercept, infliximab and adalimumab	Excluded – review
Voulgari	2005	Infliximab therapy in established rheumatoid arthritis: an observational study	Included

For those included trials, a quality assessment checklist was adapted from Downs & Black (1998) and presented in Table 21.

Table 21. Adverse event quality assessment checklist

Clinical Study	**Brown 2002**	**Burmester 2009**	**Fleischmann 2005**	**Flendrie 2003**	**Klareskog 2006**	**Listing 2005**	**Salliot 2007**	**Voulgari 2005**
Objective stated?	Y	Y	Y	Y	Y	Y	Y	Y
Main outcomes described?	Y	Y	Y	Y	Y	Y	Y	Y
Patient characteristics described ?	Y	Y	Y	Y	Y	Y	Y	Y
Interventions of interest described ?	Y	Y	Y	Y	Y	Y	Y	Y
Distributions of principal confounders in each group of subjects to be compared described?	NC	Y	Y	NC	Y	Y	N	N
Main findings described?	Y	Y	Y	Y	Y	Y	Y	Y
Were the participating subjects representative of the entire population from which they were recruited?	NC	Y	Y	Y	Y	Y	Y	Y
Subjects blinded?	N	Y	Y	NA	Y	N	NA	N
Investigators blinded?	N	Y	Y	NA	Y	N	NA	N
Time periods between intervention / outcome same for cases and controls?	Y	Y	Y	NC	Y	N	N	Y
Appropriate statistical tests conducted?	Y	Y	Y	Y	Y	Y	Y	Y
Compliance with the interventions reliable?	Y	NC	Y	NC	NC	NC	Y	Y
Reliability and validity of main outcome measures?	N	Y	Y	N	N	N	N	N
Lost to follow-up accounted for?	N	Y	Y	N	Y	Y	N	Y
Sufficient power?	NC	NC	Y	NC	Y	Y	N	NC

A11. **Priority Question:** Page 86. Please clarify how 'serious adverse events' have been defined in this assessment.

Figures for frequency of serious adverse events were directly extracted from the identified randomised clinical trials. The majority of RCTs do not specifically define 'serious adverse events' but provide absolute and proportional figures for ' ≥ 1 SAE'.

[redacted]

GO-FORWARD (C0524T06) and GO-AFTER (C0524T11) both include the following reported SAEs (with classification groupings):

Infections and infestions

- Sepsis
- Urinary tract infection
- Arthritis bacterial
- Cellulitis
- Lower / upper respiratory tract infection
- Arthritis infective
- Subcutaneous abscess
- Bronchitis
- Pneumonia
- Gastroenteritis
- Herpes zoster
- Pelvic inflammatory disease

Gastrointestinal disorders

- Gastric ulcer
- Colitis
- Diarrhoea
- Nausea
- Vomiting

Musculoskeletal and connective tissue disorders

- Arthritis
- Arthralgia
- Bursitis
- Rheumatoid arthritis
- Acquired claw toe
- Toe deformity

Neoplasms benign, malignant and unspecified (including cysts and polyps)

- Breast cancer
- Bowen's disease
- Squamous cell carcinoma
- Lymphoma

Respiratory, thoracic and mediastinal disorders

- Pulmonary embolism

Cardiac disorders

- Myocardial infarction
- Angina pectoris
- Coronary artery disease

Endocrine disorders

- Goitre

Injury, poisoning and procedural complications

- Femur fracture
- Dislocation of joint prosthesis
- Laceration

Vascular disorders

- Deep vein thrombosis
- Aortic thrombosis

Nervous system disorders

- Cerebrovascular accident
- Paraesthesia

Renal and urinary disorders

- Renal disorder

Blood and lymphatic system disorders

- Anaemia

Hepatobiliary disorders

- Hepatotoxicity

Metabolism and nutrition disorders

- Diabetes mellitus inadequate control
- Diabetic ketoacidosis

A12. **Priority Question:** Please provide a full breakdown of the number and types of serious adverse events reported by treatment arm for the following golimumab trials: GO-FORWARD (including for published 52 week data [Keystone *et al.*, 2010]), Kay *et al.* (2008), GO-AFTER.

Kay et al (2008) lists the following as reported SAEs: worsening of RA activity, congestive heart failure, cardiac tamponade, lung cancer,squamous cell carcinoma, peripheral arterial occlusive disease, pyelonephritis and pneumonia. The below listed SAE (reported through week 20)does not equal the total patients reported with ≥1 SAE as due to gaps in Kay et al (2008):

- Placebo arm (n=34) reported 2 SAE,
- GOL50mg+MTX every 4 weeks arm (n=37) reported 4 SAE (congestive heart failure, basal cell carcinoma and pneumonia),
- GOL50mg+MTX every 2 or 4 weeks arm (n=32) reported 3 SAE (lung cancer, squamous cell carcinoma, pneumonia)
- GOL100mg+MTX every 4 weeks arm (n=33) reported 2 SAE (basal cell carcinoma)
- GOL100mg+MTX every 2 or 4 weeks arm (n=35) reported 3 SAE (cardiac tampnade and pneumonia)

Keystone et al (2010) provided the below figures for SAE through week 52 in DMARD experienced patients:

- Placebo+MTX → GOL50mg+MTX
    - Early escape weeks 16-52: 5 SAE
    - Crossover weeks 24-52: 3 SAE
- GOL100mg+Placebo: 16 SAE
- Early escape (Weeks 16-52): GOL100mg+Placebo → GOL100mg+MTX: 7 SAE
- GOL50mg+MTX: 9 SAE
- Early escape (Weeks 16-52): GOL50mg+MTX → GOL100mg+MTX: 3 SAE
- GOL100mg+MTX: 16 SAE

A full breakdown of GO-FORWARD (C0524T06) data is presented below in Table 22. These events form the basis of those SAE presented in Table 4 of Keystone et al (2009) and include patients with early escape who switched treatment at week 16 (some patients counted in > 1 group). These figures were normalised to events per patient-year.

Table 22. GO-FORWARD (C0524T06) Golimumab SAE data – up to week 24 per treatment arm (DMARD experienced)

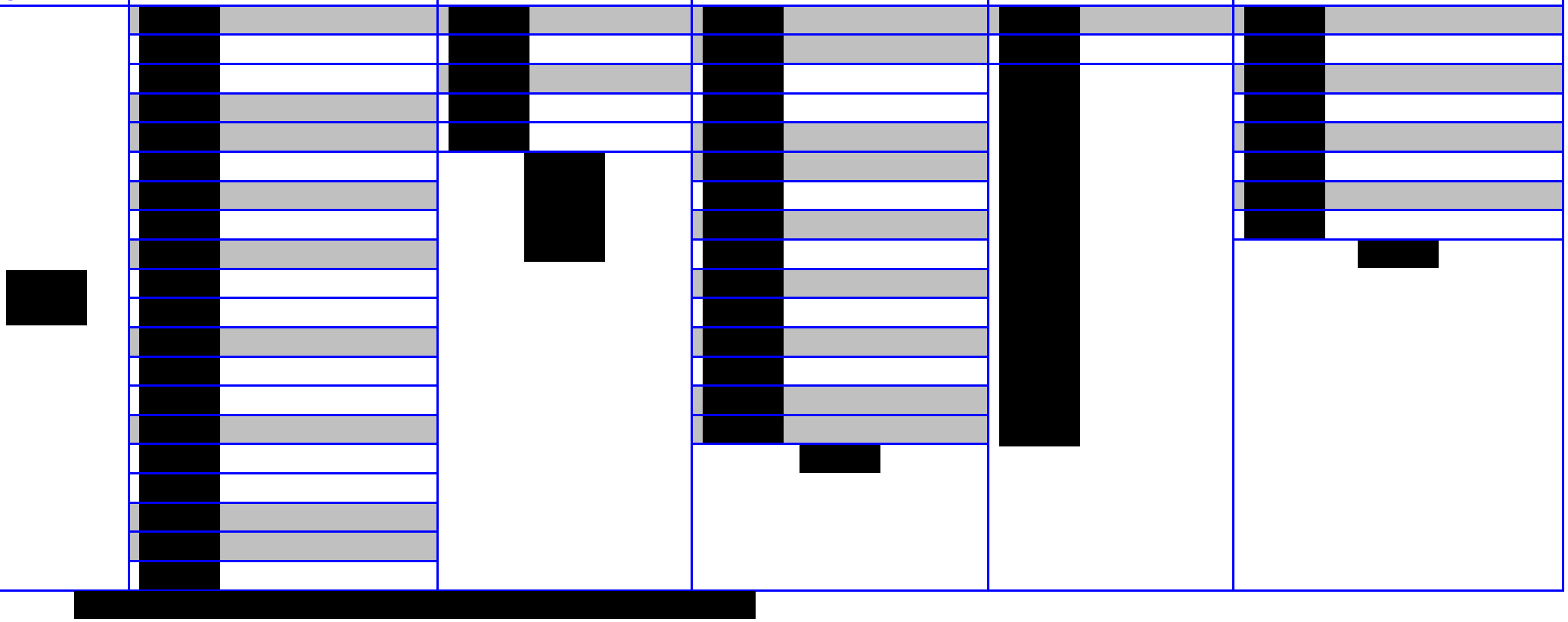
GO-FORWARD treatment arm	Placebo + MTX	Placebo+MTX --> GOL50mg + MTX	GOL100mg+Placebo	GOL100mg+Placbo --> GOL100mg+MTX	GOL50mg+MTX	GOL50mg+MTX --> GOL100mg+MTX	GOL100mg+MTX
Number of patients with ≥1 SAE	n=5		n=6		n=6		n=11
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

** Denotes a SAE which was also considered as a serious infection.*

A full breakdown of GO-AFTER (C0524T11) data is presented below in Table 23. These events form the basis of those SAE presented in Table 4 of Keystone et al (2009) and include patients with early escape who switched treatment at week 16 (some patients counted in > 1 group). These figures were normalised to events per patient-year.

Table 23. GO-AFTER (C0524T11) Golimumab SAE data – up to week 24 per treatment arm (TNFα inhibitor experienced)

GO-AFTER treatment arm	Placebo + MTX	Placebo+MTX --> GOL50mg + MTX	GOL50mg+MTX	GOL50mg+MTX --> GOL100mg+MTX	GOL100mg+MTX
Number of patients with ≥1 SAE	n=14		n=11		n=7



A13. **Priority Question:** Page 89. Please clarify how 'serious infections' have been defined in this assessment.

Figures for frequency of serious infections were directly extracted from the identified randomised clinical trials. The majority of RCTs do not specifically define 'serious infections' but provide absolute and proportional figures for ' ≥ 1 Serious Infection'.

GO-FORWARD (C0524T06), GO-AFTER (C0524T11) and Kay et al (2008) all include the following reported serious infections:

- Bacterial arthritis
- Bronchitis
- Cellulitis
- Colitis
- Diarrhoea
- Fever
- Gastroenteritis
- Infected cystic lymphangioma
- Infective arthritis
- Lower / upper respiratory tract infection
- Lung disorder
- Pelvic inflammatory disease
- Pneumonia
- Sepsis
- Sinusitis
- Skin laceration
- Subcutaneous abscess
- Urinary tract infection
- Urosepsis

A14. **Priority Question:** Please provide a full breakdown of the number and types of a) infections and b) serious infections reported by treatment arm for the following golimumab trials: GO-FORWARD (including for published 52 week data (Keystone *et al.*, 2010)), Kay *et al.* (2008), GO-AFTER.

All serious infections are recorded in Table 22 and Table 23 and denoted with the symbol '*'.

GO-FORWARD: 24 weeks

Twelve subjects, including only 1 subject in the placebo + MTX group had ≥1 SAE that was also reported as a serious infection through Week 24. Of the 11 subjects with serious infections in golimumab treatment groups, all but 2 received golimumab 100 mg with or without MTX.

GO-FORWARD: 52 weeks

Through Week 52, 14 (4.2%) of 337 subjects in the all golimumab + MTX group experienced serious infections. A greater proportion of subjects with serious infections were observed in the golimumab 100 mg + MTX group (7.9%) as compared with the golimumab 50 mg + MTX only (2.2%) and golimumab 100 mg + placebo groups (3.8%).

GO-AFTER

Twelve subjects, including only 1 subject in the placebo + MTX group had 1 or more SAE that was also reported as a serious infection through Week 24. Of the 11 subjects with serious infections in golimumab treatment groups, all but 2 received golimumab 100 mg with or without MTX.

Twelve subjects, including 5 subjects in the placebo + MTX group had 1 or more SAE that was also reported as a serious infection through Week 24. The proportions of subjects reporting at least 1 infection that was also reported as an SAE in the golimumab 50 mg and 100 mg groups were 3.3% and 0.7%, respectively [redacted]

A15. **Priority Question:** Table 126, Page 114. Please a) define the malignancies referred to in this table, b) state whether these malignancies occurred in patients with other significant co-morbidities (eg. asthma) (as referred to the European Medicines Agency assessment report for Simponi), and c) provide any supporting up-to-date data on the occurrence of malignancies in patients receiving golimumab. Please also d) define the malignancies referred to in the published 52 week data (Keystone *et al.*, 2010) and e) state whether these malignancies occurred in patients with other significant co-morbidities (eg. asthma, as above).

[redacted]

[redacted]

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[redacted]		[redacted]	
[redacted]		[redacted]	

A16. **Priority Question:** Please provide a full breakdown of all adverse events reported by treatment arm in the Kay *et al.* (2008) trial.

Table 24 presents adverse events through week 20 prior to cross over which occurred at greater than 10% frequency.

Table 24. Adverse events (with greater than 10% frequency) reported through week 20

	Placebo	50mg q4 weeks	50mg q2 weeks	100mg q4 weeks	100mg q2 weeks
Patients treated	34	37	32	33	35
Avg duration of follow-up (weeks)	18.2	17.8	20.0	18.5	20.2
Avg exposure (number of administrations)	8.7	8.5	9.7	8.5	9.6
Patients with ≥1 AE	29 (85.3%)	34 (91.9%)	24 (75.0%)	29 (87.9%)	31 (88.6%)
AE with frequency of ≥10%					
Nausea	1 (2.9%)	2 (5.4%)	7 (21.9%)	6 (18.2%)	8 (22.9%)

Headache	7 (20.6%)	6 (16.2%)	5 (15.6%)	7 (21.2%)	3 (8.6%)
Injection site erythema	4 (11.8%)	5 (13.5%)	2 (6.3%)	3 (9.1%)	10 (28.6%)
RA	7 (20.6%)	6 (16.2%)	3 (9.4%)	4 (12.1%)	3 (8.6%)

A17. **Priority Question:** Page 86 onwards. Please provide all available information on numbers of and causes of death by treatment arm for the following golimumab trials: GO-FORWARD (including for published 52 week data [Keystone *et al.*, 2010]), Kay *et al.* (2008), GO-AFTER.

GO-FORWARD

There was 1 death in the golimumab 100 mg + placebo group up to week 24. The subject involved was hospitalised with diarrhea and dehydration [redacted] After hospitalisation, the patient developed an ileus and aspiration pneumonia and died due to sepsis, during week 9 of the study. The last administration of golimumab prior to death was in week 4. After Week 24 through Week 52, one death was reported in the golimumab 100 mg + placebo group. The subject died due to fulminant hepatic failure [redacted]

Kay et al (2008)

No deaths occurred during the 52-week study period. One patient in the group receiving 100 mg golimumab every 2 weeks, a 44-year-old law enforcement officer, died in the line of duty 119 days after receiving the last dose of golimumab. The primary cause of death was acute cardiac failure due to coronary insufficiency secondary to atherosclerotic cardiovascular disease. This patient received protocol-specified treatment through week 52.

GO-AFTER

Smolen et al (2009) reported only 1 death during the study. A patient within the placebo + MTX arm developed pancreatic cancer at week 23 that resulted in death.

A18. **Priority Question:** Please provide all available information on the impact of golimumab on liver enzyme levels and liver function.

Table 25 and **Table 26** present data from GO-FORWARD and GO-AFTER at both week 16 (prior to early escape or crossover) and week 24. [redacted]

Table 25. GO-FORWARD liver function test results up to 16 and 24 weeks (DMARD experienced population)

GO-FORWARD treatment arm	Placebo + MTX	Placebo+MTX --> GOL50mg + MTX	GOL100mg + Placebo	GOL100mg+Placbo --> GOL100mg+MTX	GOL50mg+MTX	GOL50mg+MTX --> GOL100mg+MTX	GOL100mg + MTX
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 26. GO-AFTER liver function test results up to 16 and 24 weeks (TNFα inhibitor experienced population)

GO-AFTER treatment arm	Placebo + MTX	Placebo+MTX --> GOL50mg + MTX	GOL50mg+MTX	GOL50mg+MTX --> GOL100mg+MTX	GOL100mg+MTX
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A19. **Priority Question:** Page 86 onwards. Please present all available data on the impact of steroid use on adverse events among patients receiving golimumab (as referred to the European Medicines Agency assessment report for Simponi).

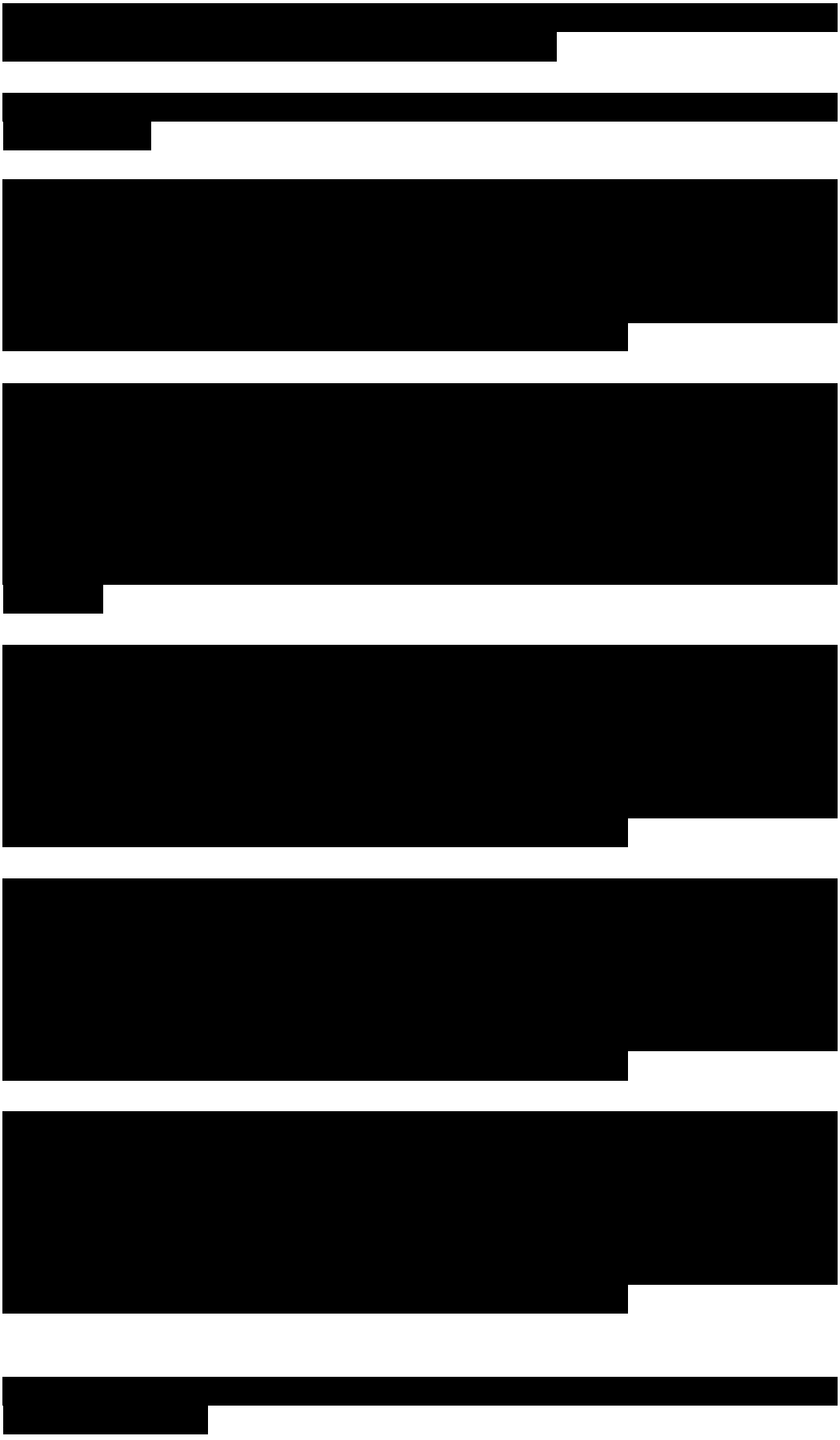
The EMEA Assessment Report for golimumab states, 'In the five Phase 3 studies through Week16, subjects on corticosteroids at baseline were more likely to have a serious infection (1.4% placebo, 2.1% golimumab 50 mg, 2.5% golimumab 100 mg) compared with subjects who did not receive corticosteroids at baseline (1.1% placebo, 0.3% golimumab 50 mg, 1.1% golimumab 100 mg).'

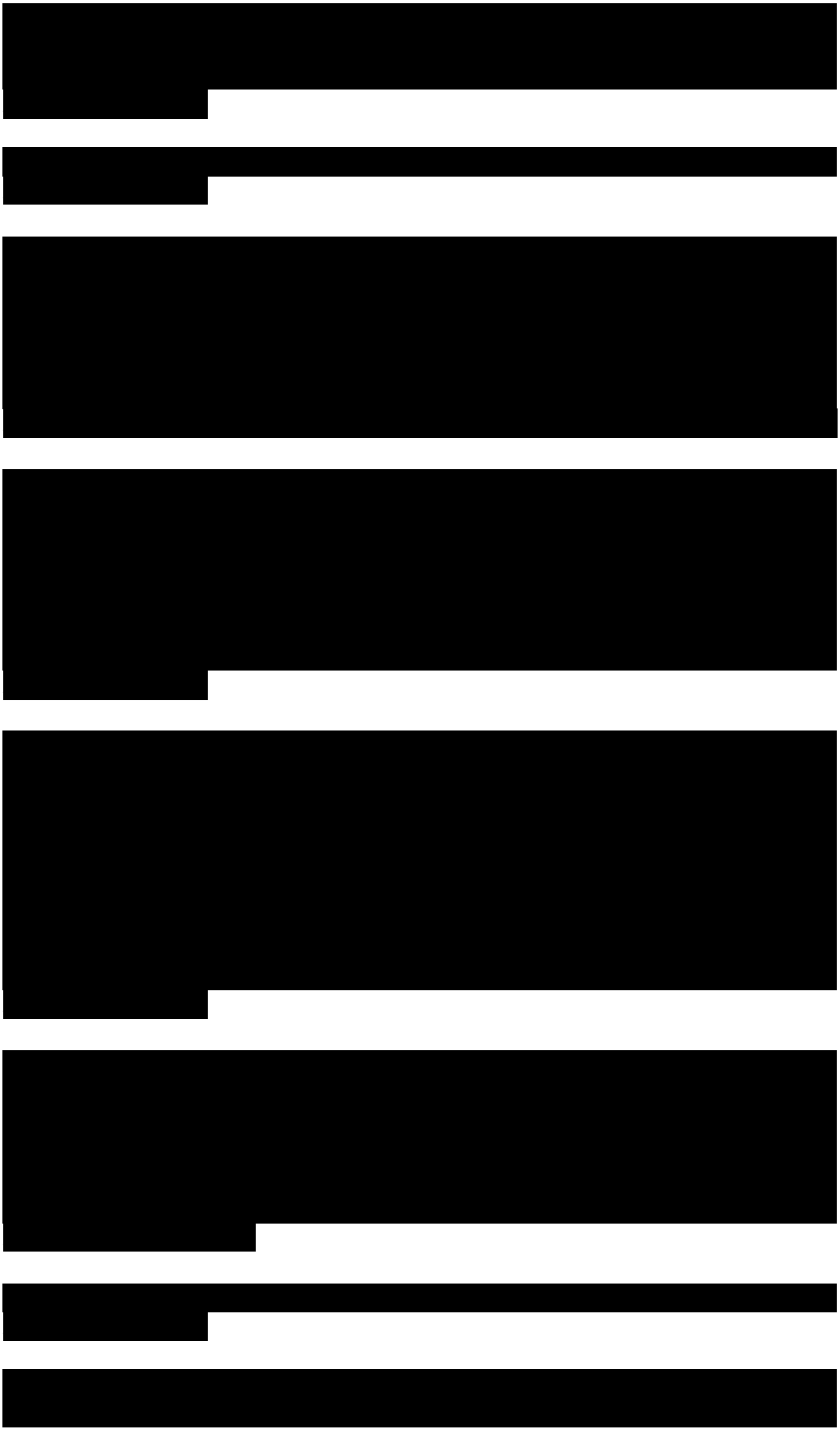
[redacted]

[redacted]				

A20. **Priority Question:** Page 86 onwards. Please provide any available information on the management of and outcomes in patients for whom golimumab has been discontinued due to the development of infection.

[redacted]





[redacted]

A21. **Priority Question:** Table 14, Table 15, Table 176. Please provide trial identifier codes for included and excluded golimumab trials

Table 27 presents clinicaltrials.gov identifiers for golimumab trials reported in Table 14, Table 15 and Table 176 of the MS.

Table 27. Golimumab clinical trial identification codes

Trial	Protocol Number	Clinicaltrials.gov Identifier
Included Trials (Table 14, Table 15)		
GO-FORWARD	C0524T06	NCT00264550
GO-AFTER	C0524T11	NCT00299546
Kay 2008	CR005263	NCT00207714
Excluded Trials (Table 176)		
Kremer 2010	C0524T12	NCT00361335

GO-BEFORE	C0524T05	NCT00264537

A22. Section 2.7, page 23. The submission states that no significant adverse reactions of these treatments are known. The clinical advisors to the ERG group do not agree with this statement, on the basis that a range of significant adverse events, including serious infections, are known. Please comment.

Please refer to clarification question A20 which discusses patient-level treatment strategies for those patients which discontinued the study agent due to serious adverse events.

A23. Page 14 and subsequently throughout document. The executive summary states that robust clinical and safety evidence is presented in the form of '2 large RCTs'; however 3 randomised controlled trials are described (GO-FORWARD, Kay *et al.* (2008), GO-AFTER) in the submission. Please clarify and correct this point.

In comparison to C0524T06 (GO-FORWARD) and C0524T11 (GO-AFTER), Kay et al (2008) has a much smaller sample size and thus was not referred to within these statements throughout the MS.

A24. Page 28 onwards. Please confirm whether any searches were undertaken for any ongoing trials in research registers or databases (e.g. metaRegister of Controlled Trials, Health Technology Assessment Database)?

CRD Health Technology Assessment (HTA) Database and CRD Database of Abstracts of Reviews of Effectiveness (DARE) were searched for cost-effectiveness publications. No trials were included for ongoing trials which have not reported at least intermediate endpoints. Many of the identified trials (ie, C0524T06 and C0524T11) have reported primary or secondary endpoints but are still ongoing over the next 5 years.

A25. Appendices relating to all search strategies, page 221 onwards. Please state the coverage dates for searches in PubMED and EMBASE.

No date restrictions were placed on searches. The PubMED and EMBASE databases were searched from origin to the date the searches were conducted (3rd week March 2010).

A26. Please clarify why the searches for adverse events data were carried out in a different platform (Ovid) compared to the efficacy searches.

Both efficacy and adverse events searches included MEDLINE, EMBASE and Cochrane. Access to OVID was unavailable during the former searches and thus PubMed (which includes MEDLINE) was used as the search database.

A27. Appendices relating to search strategies, page 221 onwards. Please state the coverage date for searches in Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R).

No date restrictions were placed on searches. The MEDLINE database was searched from 1950 to the date the searches were conducted (3rd week March 2010).

A28. Appendices relating to search strategies, page 221 onwards. Please provide the search strategy used for the Cochrane Library.

As presented in section 8.2.4, the following search strategy was conducted within Cochrane:

Cochrane Central Register of Controlled Trials search strategy (3rd week March 2010)

1 rheumatoid NEXT arthritis
2 MeSH descriptor Arthritis, Rheumatoid, explode all trees
3 #1 OR #2
4 adalimumab OR humira
5 certolizumab OR cimzia
6 etanercept OR enbrel
7 golimumab OR simponi
8 infliximab OR remicade
9 rituximab OR mabthera OR rituxan
10 tumor necrosis factor
11 tumour necrosis factor
12 anti TNF
13 anti tumor necrosis factor
14 anti interleukin
15 anti CD20
16 TNFR-Fc fusion protein
17 biologic DMARD
18 biologic agent
19 Mesh descriptor Receptor, Tumor Necrosis Factor, explode all trees
20 #4–19/OR
21 #3 AND #20 (408 references in total)

A29. Appendices relating to search strategies, page 221 onwards. Please clarify whether the below terms were used in the adverse events searches. If not, please justify their omission:

Rituxan

Tocilizumab or Atlizumab or Actemra or Roactemra

Rituxan was incorporated into the adverse events search strategy as presented in clarification A9 and A10. As discussed in A1, tocilizumab was not included within the search strategy as it was beyond the scope of the appraisal.

A30. Appendices relating to search strategies, page 221 onwards. Please clarify the use of statement 35 in the EMBASE search strategy (adverse events searches).

Statement 35 reads: "26 or 34" which was inserted to incorporate all of the adverse event search terms (statements 9 to 25) as well as all the biologics of interest (statements 28-33).

A31. Please clarify why the cost-effectiveness searches were carried out in a different platform (OVID) compared to the efficacy searches.

Access to OVID was not available at the time of the clinical searches. PubMed (which includes MEDLINE) was searched alternatively. Both efficacy and cost-effectiveness searches were conducted in MEDLINE and EMBASE. Similar to previous appraisals, additional searches within economic specific databases were also included (ie, NHS EED).

A32. Appendices relating to search strategies, page 221 onwards. Please clarify whether the following terms were used in the cost-effectiveness searches. If not, please justify their omission:

Simponi
Abatacept or Orencia
Certolizumab or Cimzia
Rituximab or Mabthera or Rituxan
Tocilizumab or Atlizumab or Actemra or Roactemra

The following search terms were considered outside the scope of this assessment as they were either (a) not recommended by NICE or (b) the TAG remained outstanding: Abatacept or Orencia, Tocilizumab or Atlizumab or Actemra or Roactemra.

The MEDLINE and EMBASE systematic searches were updated on 03 August 2010 as shown in Table 28 and Table 29. No additional publications were identified.

Table 28. MEDLINE search strategy: cost-effectiveness

#	Search Statement	Results
1	GOLIMUMAB.mp.	81
2	SIMPONI.mp.	3
3	CIMZIA.mp.	9
4	CERTOLIZUMAB.mp.	146
5	INFLIXIMAB.mp.	5884
6	REMICADE.mp.	182
7	ETANERCEPT.mp.	2687
8	ENBREL.mp.	151
9	ADALIMUMAB.mp.	1699
10	HUMIRA.mp.	80
11	RITUXIMAB.mp.	6663

12	RITUXAN.mp.	183
13	MABTHERA.mp.	98
14	OR/1-13	14670
15	ANTI-TUMOR NECROSIS FACTOR.mp.	1339
16	ANTI-TNF-ALPHA.mp.	2324
17	ANTI-TNF.mp.	4365
18	TUMOR NECROSIS FACTOR.mp.	106019
19	or/15-18	106634
20	RHEUMATOID ARTHRITIS.mp.	64521
21	COST.mp.	245979
22	COST-EFFECTIVENESS.mp.	23091
23	COST-BENEFIT ANALYSIS.mp.	49624
24	COST UTILITY ANALYSIS.mp.	794
25	COST ESTIMATE.mp.	120
26	ECONOMIC EVALUATION.mp.	3589
27	HEALTH ECONOMIC.mp.	1239
28	ECONOMIC MODEL.mp.	694
29	ECONOMIC.mp.	98825
30	OR/21-29	319130
31	QUALITY OF LIFE.mp.	132750
32	HEALTH STATUS.mp.	76848
33	HEALTH STATUS INDICATORS.mp.	15266
34	VALUE OF LIFE.mp.	5305
35	OR/31-34	198691
36	14 AND 19 AND 20 AND 30 AND 35	35
37	limit 36 to human	32

Table 29. EMBASE search strategy: cost-effectiveness

#	Search Statement	Results
1	GOLIMUMAB.mp.	380
2	SIMPONI.mp.	59
3	CIMZIA.mp.	220
4	CERTOLIZUMAB.mp.	1080
5	INFLIXIMAB.mp.	16367
6	REMICADE.mp.	2762
7	ETANERCEPT.mp.	10878
8	ENBREL.mp.	2163
9	ADALIMUMAB.mp.	6231
10	HUMIRA.mp.	1403
11	RITUXIMAB.mp.	18409
12	RITUXAN.mp.	1734
13	MABTHERA.mp.	1210
14	OR/1-13	37650
15	ANTI-TUMOR NECROSIS FACTOR.mp.	1485
16	ANTI-TNF-ALPHA.mp.	2420
17	ANTI-TNF.mp.	4950
18	TUMOR NECROSIS FACTOR.mp.	154412
19	or/15-18	155151

20	RHEUMATOID ARTHRITIS.mp.	80167
21	COST.mp.	348703
22	COST-EFFECTIVENESS.mp.	51198
23	COST-BENEFIT ANALYSIS.mp.	48834
24	COST UTILITY ANALYSIS.mp.	3452
25	COST ESTIMATE.mp.	151
26	ECONOMIC EVALUATION.mp.	8341
27	HEALTH ECONOMIC.mp.	1547
28	ECONOMIC MODEL.mp.	854
29	ECONOMIC.mp.	136264
30	OR/21-29	443386
31	QUALITY OF LIFE.mp.	177939
32	HEALTH STATUS.mp.	68502
33	HEALTH STATUS INDICATORS.mp.	220
34	VALUE OF LIFE.mp.	213
35	OR/31-34	234531
36	14 AND 19 AND 20 AND 30 AND 35	137
37	limit 36 to human	133

A33. Please provide a full study description of the Kay *et al.* (2008) study.

Protocol: C0524T02

Title of the study: A Randomized, Double-blind, Dose-ranging Trial of CNTO 148 Subcutaneous Injection Compared with Placebo in Subjects With Active Rheumatoid Arthritis Despite Treatment With Methotrexate

Objectives: The primary objective of this dose-ranging study was to assess the efficacy of SC injections of golimumab 50 or 100 mg, at either 2-week or 4-week intervals in subjects with active RA despite methotrexate (MTX) therapy.

The secondary objectives of the study were:
• To assess the safety of different doses of GOL administered by SC injection in combination withMTX.
• To assess the pharmacokinetics (PK) of different doses of GOL administered by SC injection.

Methodology: Multicenter, randomized, double-blind, placebo-controlled, 5-arm, dose-ranging study

Diagnosis and Main Criteria for Inclusion: Men or women aged 18 years or older who:

• had a diagnosis of RA (as defined by the American College of Rheumatology [ACR]) for at least 3 months prior to screening.

• had active RA – persistent disease activity in subjects on a stable dose of at least 10 mg/week of MTX for the previous 4 weeks with at least 6 swollen and 6 tender joints and at least 2 of the following 3 criteria:

1. C-reactive protein (CRP) ≥ 1.5 mg/dL
2. Erythrocyte sedimentation rate by Westergren method of ≥ 28 mm in the first hour
3. Morning stiffness of ≥ 30 minutes

• had tolerated MTX at a dose of at least 10 mg/week for at least 3 months prior to being treated with first dose of study drug

• had not previously been treated with anti-tumor necrosis factor α (TNFα) therapy

Product, Dose and Mode of Administration: 50 or 100 mg GOL SC injections q2 or q4 weeks to Week 20; then q4 weeks through Week 48

Duration of Treatment: 48 weeks

Reference Therapy, Dose and Mode of Administration: Placebo SC injections at Weeks 0,2, 4, 6, 8, 10, 12, 14, 16, and 18; Infliximab 3 mg/kg IV infusions at Weeks 20, 22, 28 and then q8 weeks through Week 44

Efficacy: ACR response (20, 50, or 70 percent improvement in multiple disease assessment criteria), percentage ACR improvement (ACRn), and Disease Activity Score 28 (DAS28) were analyzed.

Safety: AEs (including injection-site reactions and infections), routine laboratory tests, development of antinuclear antibodies (ANA), anti-double-stranded DNA (anti-dsDNA) antibodies, and antibodies to GOL were summarized.

Study Population Results:
• Demographic characteristics were generally well balanced across the randomized groups given the small number of subjects per treatment group.
• The majority (76.7%) of subjects were women, and most subjects were Caucasian (87.8%). The median age of the sample was 53.5 years, and the median duration of RA was 7.8 years.
• Baseline clinical characteristics from the ACR core set of outcome measurements were as expected in this subject population and generally similar across the treatment groups.

Efficacy Results:
• The combined GOL plus MTX group had a statistically significantly higher proportion of subjects ($p = 0.010$) achieving ACR 20 response at Week 16 than the placebo plus MTX group despite a relatively high placebo response (37.1%). Furthermore, the 100 mg q2 weeks treatment group achieved statistical significance

compared with placebo plus MTX ($p < 0.001$). Thus the primary endpoint was achieved.
• The median ACRn was significantly higher for the combined GOL plus MTX group at Week 16 compared with the placebo plus MTX group ($p = 0.001$). Furthermore, the median ACRn was significantly greater for the 50 mg q4 weeks ($p = 0.006$), 100 mg q4 weeks ($p = 0.010$), and 100 mg q2 weeks ($p < 0.001$) groups compared with the placebo plus MTX group. Thus the major secondary endpoint ACRn was achieved.
• ACR 50 response at Week 16 was significantly higher in all GOL plus MTX treatment groups compared with the placebo plus MTX group.
• In general, the percentage of subjects in ACR 20 response in the combined GOL plus MTX group did not differ by antibody status through Week 52: 73.7% of subjects positive for antibodies to GOL, 74.3% of subjects negative for antibodies to GOL, and 71.4% of subjects with undetectable antibody status were in ACR 20 response.
• All GOL dose groups tested were effective in maintaining clinical response through Week 52.
• In general, the percentage of DAS28 responders in each of the GOL plus MTX groups was greater than in the placebo plus MTX group. In addition, the percentage of subjects in DAS28 remission in each of the GOL plus MTX groups was greater than in the placebo plus MTX group.
• The efficacy of GOL plus MTX in reducing joint swelling, joint tenderness, and CRP levels was evident as early as Week 2.

Safety Results:
Over the 52-week period of evaluation, SC injections of GOL 50 mg or 100 mg administered every 2 or 4 weeks were generally well tolerated.
• Any AE – Through Week 20, the proportion of subjects who had at least 1 AE was comparable in the combined GOL plus MTX (86.1%) and the placebo plus MTX (85.3%) groups. Through Week 52, the most frequently reported AEs in the combined GOL plus MTX group were: RA (21.2%; only worsening of RA was considered an AE), nausea (20.4%), headache (19.0%), injection site erythema (17.5%), nasopharyngitis and upper respiratory tract infection (each 15.3%).
• AEs Leading to Discontinuation – Prior to crossover at Week 20, 7.3% of subjects in the combined GOL plus MTX group and 5.9% in the placebo plus MTX group discontinued study agent administration due to AEs. Through Week 52, 8.0% of subjects in the combined GOL plus MTX group discontinued study agent administration due to AEs.
• SAEs – No deaths occurred during the 52-week study period. One subject died approximately 4 months after the last GOL administration as a result of acute cardiac failure due to coronary insufficiency secondary to atherosclerotic cardiovascular disease. Through Week 20, SAEs were reported for 8.8% of subjects in the combined GOL plus MTX group and 5.9% in the placebo plus MTX group. Through Week 52, at least 1 SAE was reported for 16.1% of subjects in the combined GOL plus MTX group.
• Injection Site Reactions – Through Week 20, 21.9% and 14.7% of subjects in the combined GOL plus MTX and placebo plus MTX groups, respectively, experienced an injection site reaction. Through the final injection at Week 48, 24.8% of subjects in

the combined GOL plus MTX group experienced an injection site reaction. There were no serious injection-site reactions reported.

Efficacy Conclusion

• The primary endpoint was achieved: A statistically significantly greater proportion of subjects achieved ACR 20 response at Week 16 in the combined GOL plus MTX group and in the 100 mg q2 weeks treatment group than in the placebo plus MTX group.
• The major secondary endpoint was achieved: A significantly greater median ACRn was observed at Week 16 for the combined GOL plus MTX group as well as for the 50 mg q4 weeks, 100 mg q4 weeks, and 100 mg q2 week groups compared with the placebo plus MTX group.
• Greater improvements in the signs and symptoms of RA were observed in the combined GOL plus MTX group compared with the placebo plus MTX group across the ACR 50, ACR 70, ACR components, DAS28 response, and DAS28 remission measures of efficacy.

Safety

• There were no cases of TB; there was 1 opportunistic infection (pneumonia Legionella) reported for a subject treated with GOL and 1 (Listeria sepsis) reported for a subject in the placebo group who had crossed over to infliximab.
• Malignancies were reported for 4 subjects treated with GOL plus MTX.
• The overall incidence of subjects with antibodies to GOL was approximately 8% through Week 52 and 17% at Week 68.

Overall Conclusion

• All GOL dose groups tested were generally well tolerated and effective in maintaining clinical response through Week 52.

A34. Page 107 onwards. Please state whether the analyses from the GO-AFTER study are presented in original form or in re-analysed form following the exclusion of patients from a single trial site in the efficacy analyses (as referred to in the European Medicines Agency document entitled: 'Simponi: procedural steps taken and scientific information after the authorisation').

The GO-AFTER data presented within the MS is extracted directly from the clinical study report and thus does not exclude 16 patients as discussed within the EMEA document and resulting updated Summary of Product Characteristics. However, it should be noted that the reanalysis of efficacy data did not change the overall conclusion for key efficacy parameters but rather the significance of some of the secondary endpoints was slightly changed.

A35. Page 100 onwards. Please a) clarify in full the handling of data from patients who received rescue therapy in golimumab trials and b) describe in full how these data were handled when deriving estimates for the economic model.

Please see clarification question B16.

A36. Page 59 onwards. Please provide raw and meta-analysed data (with full heterogeneity estimates) for the etanercept analyses with the exclusion of the TEMPO study.

The below tables present etanercept meta-analyses excluding the TEMPO trial. Section 5.6.8 (page 82-83) of the MS presents the mixed treatment comparison excluding TEMPO.

Table 30. Etanercept studies included within meta-analysis (ACR20 at 24 wks in DMARD experienced population)

			treatment		comparator	
study	**treatment**	**comparator**	**n**	**total**	**n**	**total**
Combe	ETN	placebo	150	204	14	50
Combe (excluding monotherapy)	ETN	placebo	74	101	14	50
Moreland (monotherapy)	ETN	placebo	46	78	9	80
Weinblatt	ETN	placebo	42	59	8	30

Table 31 and Table 32 present the ACR20 and ACR50 (respectively) results at 24 weeks for etanercept (excluding TEMPO). Both analyses found etanercept to be statistically superior to placebo.

Table 31. Etanercept meta-analysis results RR (ACR20 at 24 wks in DMARD experienced population)

Study	**RR**	**95% CI**	**Weights fixed-effect meta-analysis (%)**	**Weights random-effect meta-analysis (%)**
Combe	2.63	1.67, 4.13	53.6	42.2
Moreland	5.24	2.76, 9.97	21.2	28.1
Weinblatt	2.67	1.44, 4.94	25.3	29.7
Pooled RR			**3.19 (2.33, 4.37)**	**3.20 (2.11, 4.87)**
p-value pooled RR			**<0.001**	**<0.001**
Heterogeneity			**I^2=39.9%, chi-square p-value=0.189**	

Table 32. Etanercept meta-analysis results RR (ACR50 at 24 wks in DMARD experienced population)

Study	**RR**	**95% CI**	**Weights fixed-effect meta-analysis (%)**	**Weights random-effect meta-analysis (%)**
Combe	3.50	1.74, 7.06	68.1	54.7
Moreland	7.95	2.94, 21.47	23.9	34.3
Weinblatt	11.69	1.66, 82.47	8.0	11.0
Pooled RR			**5.22 (3.04, 8.98)**	**5.29 (2.70, 1.40)**
p-value pooled RR			**<0.001**	**<0.001**
Heterogeneity			**I^2=22.8%, chi-square p-value=0.274**	

Table 33 presents discontinuation figures at 24 weeks due to adverse events and found no statistically significant difference bettwen placebo and etanercept.

Table 33. Etanercept meta-analysis results (Discontinuation due to adverse events at 24 wks in DMARD experienced population)

Study	RR	95% CI	Weights fixed-effect meta-analysis (%)	Weights random-effect meta-analysis (%)
Combe	0.57	0.15, 2.13	57.1	48.1
Moreland	1.71	0.42, 6.91	35.1	42.7
Weinblatt	2.58	0.13, 52.16	7.8	9.2
Pooled RR			**1.13 (0.47, 2.72)**	**1.05 (0.42, 2.61)**
p-value pooled RR			**0.788**	**0.918**
Heterogeneity			**I^2=0%, chi-square p-value=0.437**	

A37. Page 95 onwards. Please describe in full the number of and reasons for golimumab discontinuations due to adverse events.

GO-FORWARD

[redacted]

[redacted]

A38. Page 107. Please clarify how upper respiratory tract infection, cough, nasopharyngitis and infections differ in terms of classification.

[redacted]

A39. Table 120, Page 107. Please clarify what the term adverse events and the numbers (placebo n=90, golimumab 50mg n=65) relate to in this table.

90 patients (67.7%) within the placebo group and 65 patients (73.0%) within the GOL 50mg + MTX group experienced ≥1 adverse event through week 24

[redacted]

[redacted]

[redacted]

A40. Table 126, Page 114. Please clarify how upper respiratory tract infection, nasopharyngitis, cough, sinusitis and infections differ in terms of classification.

Please see the response for A38. Sinusitis is also classified under 'Infections and Infestations within the MedDRA system-organ classification.

A41. Page 77 onwards. Please complete the labelling of tables to accompany the mixed treatment comparison and indirect comparison sections and confirm whether relative risk data are presented.

Relative risks are presented in page 77 onwards in tables 52-115.

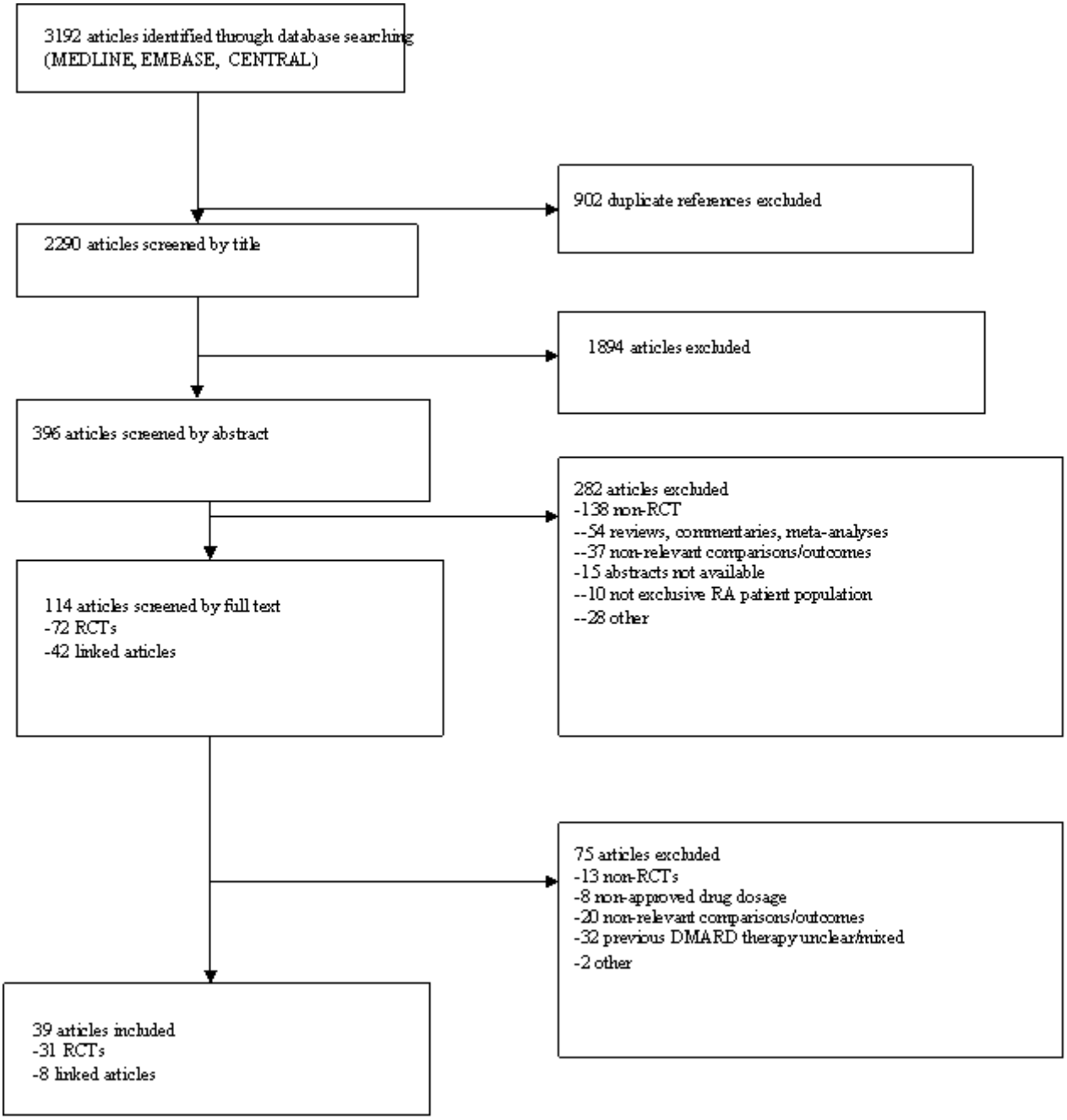
A42. Table 12, page 29. Not all outcomes listed in the decision problem are included in this table. Please provide justification for their omission.

Please refer to clarification question A4.

A43. Page 31. Please note that the top box of the QUOROM flowchart appears to be incomplete. Please amend as appropriate.

Figure 1 has been stretched below to display all text in the top box.

Figure 1. Flow diagram of study selection process



A44. Please note that Section 2.8 (as referred to in the NICE specification) is absent in the submission document. Therefore, 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.

Question 2.8 has been addressed below.

Question 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.

As this technology attempts to replace an existing TNF alpha inhibitor, no additional costs are involved. Please check economic section for details.

A45. Table 66, page 87. The table heading states that these data relate to adalimumab. Please check and confirm whether this should read certolizumab.

Table 66 was incorrectly labelled as 'adalimumab' and should reflect 'certolizumab'.

A46. Table 166. This appears to be an accidental repeat of Table 164. Please clarify.

Table 166 is identical to Table 164 and should be deleted or ignored.

A47. Page 168. The value of 42% of existing and newly diagnosed patients being eligible for biologics was considered to be rather high. Please a) justify the choice of this value and b) describe the applicability of this value to the UK setting.

The table on page 168 of the MS has been replicated below in Table 35.

[redacted]

Table 34. Newly diagnosed rheumatoid arthritis patients

INCIDENCE BASED	Percentage	2010	2011	2012	2013	2014
[redacted]						

A48. Section 8.2.7, page 190. The description of the data abstraction strategy states that outcomes listed in Table 175 were sought. However, this table does not include all outcomes specified in the decision problem (and only lists measures of treatment efficacy: ACR responses, mean DAS or DAS28, number of patients achieving low DAS (<3.2), or DAS remission (<2.6), HAQ-D1; and measures of safety of safety and tolerability: adverse events, treatment discontinuations). Please clarify whether all outcomes specified in the decision problem were included in the systematic review and if any were omitted please justify their omission.

All outcomes that were included within the final, presented efficacy search strategy are listed within Table 175 of the MS. Please refer to clarification question A4 on reasonings behind exclusion of particular outcomes specified in the decision problem.

Indirect / mixed treatment comparison

A49. Section 5.6. The TNF inhibitor-experienced data is analysed in an indirect comparison using the Bucher method. Please clarify why a network mixed treatment comparison approach was not used (as in the DMARD-experienced population) and please provide a network mixed treatment comparison for this population.

Only 2 studies were available in the TNF inhibitor experienced population, one comparing golimumab to placebo and one comparing rituximab to placebo.

Given only 2 treatments needed to be indirectly compared, and both used the same common comparator, it was not deemed necessary to implement a full network analysis. Besides, a bayesian model based on only 2 studies might have struggled with the estimation of all the parameters. For these 2 reasons, it was decided to use a much simpler approach, and the Bucher method was chosen.

However, following the ERG's comments, the network analysis was implemented and its results are shown below. Due to the limited amount of data, only the fixed-effect model was run.

Table 35. Network analysis (relative risk) (TNFα inhibitor experienced)

	RR Median indirect estimate	
Outcome	**Golimumab vs Rituximab**	**95% credibility interval**
ACR20 at 6 months	0.70	0.46, 1.04
ACR50 at 6 months	0.66	0.28, 1.56

These estimates are very close to the ones obtained with the Bucher method and lead to the same conclusions.

A50. Page 82. I^2 Statistics are not provided in the mixed treatment comparison output. Please provide these values, and provide a comment on the estimate of heterogeneity.

The I^2 statistics measure the amount of heterogeneity present in a meta-analysis. It is produced in the direct meta-analysis setting, and shown in the submission for each treatment versus placebo.

It does not apply to the network analysis framework. By definition, the fixed-effect model considers that there is no heterogeneity at all between studies. In the random-

effect model, heterogeneity is quantified and accounted for by the component σ^2, as defined in section 5.6.5 on page 79. It is assumed to be the same for all comparisons. These values are available should the evaluators wish to request them.

However, rather than a global estimate standardised across treatments, it is believed that the I^2 values for the meta-analyses of each treatment versus placebo provide a more accurate and more meaningful description of how much heterogeneity there is in this selection of studies and where it lays.

Section B: Clarification on cost-effectiveness data

B1. **Priority Question:** Tables 130 and 131. In the DMARD experienced population, patients whose disease does not respond adequately to golimumab or a TNF inhibitor progress to leflunomide. However, as modelled in the TNF inhibitor experienced population, patients in UK clinical practice will progress to rituximab therapy. Please can you amend the DMARD experienced model to include rituximab at the appropriate position as determined by NICE appraisal TA126.

The DMARD experienced model includes a scenario which allows for use of rituximab following TNFα inhibitor failure. The treatment pathways are presented below in Table 36. The DMARD only arm contains rituximab as 2nd line therapy as the assessment question within a DMARD experienced population is the cost-effectiveness of golimumab as 1st line therapy rather than assessing the cost-effectiveness of golimumab followed by rituximab versus solely DMARDs. The ICERs reduce slightly from the base case, as seen in Table 37.

Table 36. Sensitivity Analysis: Treatment sequence including rituximab as 2nd line therapy

	Comparator 1	Comparator 2	Comparator 3	Comparator 4	Comparator 5	Comparator 6
1st Line	Golimumab	adalimumab	infliximab	etanercept	Certolizumab	Methotrexate
2nd Line	rituximab	rituximab	rituximab	rituximab	rituximab	rituximab
3rd Line	leflunomide	leflunomide	leflunomide	leflunomide	leflunomide	leflunomide
4th Line	Gold	Gold	Gold	Gold	Gold	Gold
5th Line	azathioprine	azathioprine	azathioprine	azathioprine	azathioprine	azathioprine
6th Line	ciclosporin	ciclosporin	ciclosporin	ciclosporin	ciclosporin	ciclosporin
7th Line	Palliative Care	Palliative Care	Palliative Care	Palliative Care	Palliative Care	Palliative Care

Table 37. Sensitivity Analysis: Incremental cost-effectiveness results with rituximab as 2nd line therapy (DMARD experienced population)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus Baseline (MTX)	Incremental analysis
Methotrexate	£40,855	4.451	-	-	-	-
Adalimumab	£71,542	5.690	£30,687	1.239	£24,763	£24,768
Golimumab	£72,379	5.726	£837	0.036	£24,722	£23,250
Infliximab	£74,660	5.545	£2,281	-0.181	£30,882	Dominated

Certolizumab	£77,817	5.720	£3,157	0.175	£29,127	£18,040
Etanercept	£74,208	6.133	£637	0.365	£24,514	£1,745

B2. **Priority Question:** Table 137. Please can you provide more detail on the Kristensen *et al* (2006) study used to estimate the long-term discontinuation rates and justify this choice of evidence. Please can you clarify how the estimate of 20 years (mean) is derived for methotrexate from the Edwards *et al* (2005) study. Please provide the calculation method and worked formula.

A review of the literature found limited sources for quality long-term withdrawal rates for the biologics. Kristensen (2006) provided 5 year withdrawal rates for infliximab and etanercept over a 5 year time period. This data was used to estimate the longer-term discontinuation rates over a lifetime horizon. Kristensen (2006) is an observational study, prospectively conducted in Sweden with 949 enrolled patients with active RA. The investigators introduced LUNDEX, an index which takes the proportion of patients fulfilling a set of criteria (ie, ACR response) into account and the proportion of patients adhering to a specific intervention. The LUNDEX calculation can be found below:

LUNDEX =

[(Fraction of starters still in the study at time T) x (Fraction responding at time T)]

Appendix 16 (Section 8.16) of the MS presents the calculations applied to determine the long term drop rates for infliximab, etanercept and methotrexate from the Kaplan-Meier survival estimates in Edwards 2005 (figure 2 and table 1) and Kristensen 2006 (figure 3c).

B3. **Priority Question:** Section 6. ACR70 response rates are not incorporated into the cost effectiveness analysis, and therefore underestimate the benefits of all treatments. Please incorporate ACR70 into your analysis, or justify your reasoning for not doing so.

Clarification A5 presents meta-analyses for ACR70 at 24 weeks which found all biologics to be statistically superior to placebo. Mixed treatment comparisons for both DMARD experienced and TNFα inhibitor experienced found all biologics to not have a significantly different risk ratio. An indirect comparison for the TNFα inhibitor experienced population was also run which confirmed the mixed treatment comparison results of no significant difference between golimumab and rituximab for ACR70 at 24 weeks. Any differentiation between the biologic ICERs driven by the ACR70 response point estimates is therefore not statistically significant and only adds an additional element of uncertainty around the model outputs. The inclusion of ACR20 and ACR50 is in line with current UK clinical practice and seen as a conservative estimate as inclusion of ACR70 would most likely favour biological therapy.

B4. **Priority Question:** Page 128, Table 145, and Table 168. Please can you clarify the dosing regimen provided for rituximab, (whether it is re-administered every 6 (as referred to on page 126) or every 9 months (as referred to in table 145)) and the justification for this regimen. The submission refers to a number of international surveys to determine the frequency between rituximab infusions, please can you provide further justification with specific reference to UK clinical practice.

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

B5. **Priority Question:** Page 137. Please justify the selection of a 0.09 HAQ progression rate on palliative care, 0.045 on DMARDs, and 0 on TNF inhibitors. Please provide full details of any published evidence to support these rates.

The model assumes that there is a constant risk of HAQ progression for RA patients. The rate of increase in the HAQ for patients receiving DMARDs is taken from the NICE appraisal model (Chen et al 2006). In the MS model the HAQ score declines at a rate of 0.045 per year if a patient is receiving normal DMARDs. Patients receiving palliative care have a HAQ progression two times that of patients responding to DMARDs, at 0.09 per year. The model assumes that anti-TNF treatment halts disease progression. This assumption is aligned with comments from the NICE technology appraisal TA130 which states that it is "appropriate to primarily examine the estimates of cost-effectiveness based on the assumption of no HAQ progression while on TNF- α inhibitor therapy, while acknowledging the effects on the estimates of incorporating different assumptions of HAQ progression" (NICE, TA130, 2007). Alternative assumptions were explored in the sensitivity analysis of the MS.

B6. **Priority Question:** The HAQ progression rate for rituximab is not provided. However the model suggests that the assumed rate is that of conventional DMARDs

rather than the TNF inhibitors. Please clarify the assumed HAQ progression rate for patients on rituximab therapy and provide further justification for its use. Please provide a sensitivity analysis using a value equal to the assumed HAQ progression rate for patients on any TNF inhibitor therapy.

The base case of the model assumes rituximab has the same HAQ progression rate as DMARDs (0.0225 per cycle of 6 months). Most of the previous NICE RA appraisals have suggested a zero progression whilst on TNFα inhibitor treatment and not biologics as a whole. A sensitivity analysis was conducted in which rituximab is assumed to have the same HAQ progression rate as TNFα inhibitors. The sensitivity analysis presented in Table 38 suggests that the model is very sensitive to the HAQ progression rate. It is more likely that the rituximab HAQ progression rate falls in between the TNFα inhibitors and conventional DMARD therapy.

Table 38. Sensitivity Analysis: Rituximab HAQ progression rate (change from 0.0225 to 0.0000 per 6 month cycle)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus Baseline (Methotrexate)	Incremental analysis
Methotrexate	£33,673	3.899	-	-	-	-
Golimumab	£50,175	3.712	£16,502	0.583	£28,286	£28,286
Rituximab	£50,206	3.523	£32	0.187	£21,465	Cost saving / < responders

B7. **Priority Question:** Section 6.5. Please clarify why a systematic search for resource used was not conducted. Please justify the choice of evidence used to model resource use.

Preliminary searches of the literature found the majority of articles were not from the UK perspective and therefore differed in their resource use. To ensure that resource use inputs were tailored to clinical practice within the UK, expert clinicians were consulted. Initial estimates from the BRAM were used as a gauge and adjusted based on clinical feedback during consultation. The current ACR and BSR guidelines on best practice within RA were also reviewed for consistency with the model's assumptions to ensure consistency.

B8. **Priority Question:** Table 146. Please provide further justification for the administration and infusion costs for infliximab, rituximab. Please compare to values accepted by appraisal committees when appraising these therapies previously and where these differ, please conduct a sensitivity analysis.

The most recent appraisal of infliximab and rituximab was for the use of biologics after the failure on a TNF α inhibitor. Both biologics were assumed to have a cost per infusion of £284.73. The annual cost for infliximab was assumed to be £3,777 for the loading dose (year 1) and ranging from £7,553-£8,812. A number of one way

sensitivity analyses were conducted varying the price of infliximab with the understanding that vial optimisation which results in cost savings may occur in clinical practice. Rituximab was assumed to have a cost of £3,492 per single course which consists of two 1000mg IV infusions. Dosing frequency was ranged from 6 months to 11.6 months.

Adjusting the IV infusion cost from £55 to £248.73 for infliximab substantially increases infliximab's total cost and resulting cost per QALY as shown in Table 39 and Table 40.

Table 39. Sensitivity Analysis: Adjusting infliximab infusion cost

	Total Cost	Total QALYs
Golimumab	£67,747	5.827139687
Adalimumab	£66,875	5.79240144
Infliximab	£87,046	5.650986033
Etanercept	£74,208	6.133375929
Certolizumab	£73,571	5.768428442
methotrexate	£35,869	4.569436133

Table 40. Sensitivity Analysis: Incremental cost-effectiveness results after adjusting infliximab infusion cost

Comparisons	Inc. Costs	Inc. QALYs	Cost per QALY
Golimumab vs. methotrexate	£31,878	1.257703553	**£25,346**
Adalimumab vs. methotrexate	£31,006	1.222965307	**£25,353**
Infliximab vs. methotrexate	£51,176	1.0815499	**£47,317**
Etanercept vs. methotrexate	£38,339	1.563939796	**£24,514**
Certolizumab vs. methotrexate	£37,701	1.198992309	**£31,444**
Golimumab vs. Adalimumab	£872	0.034738246	**£25,097**
Golimumab vs. Infliximab	-£19,298	0.176153654	**GOL Dominates**

Adjusting the IV infusion cost from £76 to £248.73 for rituximab increases rituximab's total cost and resulting cost per QALY as shown in Table 41 and Table 42.

Table 41. Sensitivity Analysis: Adjusting rituximab infusion cost

	Total Cost	Total QALYs
Golimumab	£50,175	3.712
Rituximab	£55,679	3.523
Methotrexate	£33,673	3.129

Table 42. Sensitivity Analysis: Incremental cost-effectiveness results after adjusting rituximab infusion cost

Comparisons	Inc. Costs	Inc. QALYs	Cost per QALY
Golimumab vs. methotrexate	£16,502	0.583	**£28,286**
Rituximab vs. methotrexate	£22,006	0.394	**£55,814**

Golimumab vs. rituximab	-£5,504	0.189	**GOL Dominates**

Rituximab pricing included with the MS base case is the same as that presented in previous appraisals and thus does not require a sensitivity analysis. Increasing the price of infliximab from the base case of 2.67 vials to 3.00 vials slightly increased the total cost and cost per QALY of infliximab as shown in Table 43 and Table 44.

Table 43. Sensitivity Analysis: Adjusting infliximab unit cost

	Total Cost	**Total QALYs**
Golimumab	£67,747	5.827
Adalimumab	£66,875	5.792
Infliximab	£68,440	5.651
Etanercept	£74,208	6.133
Certolizumab	£73,571	5.768
methotrexate	£35,869	4.569

Table 44. Sensitivity Analysis: Incremental cost-effectiveness results after adjusting infliximab unit cost

Comparisons	Inc. Costs	Inc. QALYs	Cost per QALY
Golimumab vs. methotrexate	£31,878	1.258	**£25,346**
Adalimumab vs. methotrexate	£31,006	1.223	**£25,353**
Infliximab vs. methotrexate	£32,570	1.082	**£30,114**
Etanercept vs. methotrexate	£38,339	1.564	**£24,514**
Certolizumab vs. methotrexate	£37,701	1.199	**£31,444**
Golimumab vs. Adalimumab	£872	0.035	**£25,097**
Golimumab vs. Infliximab	-£693	0.176	**GOL Dominates**
Golimumab vs. Etanercept	-£6,461	-0.306	**Cost saving/<QALYs**
Golimumab vs. Certolizumab	-£5,824	0.059	**GOL Dominates**

B9. Please can you confirm there are no other differences between the two submitted Excel files other than the patient population group selected/treatment sequence modelled?

This is correct. In selecting a different patient population group, an alternative treatment sequence is modelled and thus all the parameters (clinical and cost) are altered. However, all of the data within the backsheets of both models are identical. Two models were submitted for ease in viewing the probabilistic sensitivity analysis outputs.

B10. Sections 6.4.6, 6.4.7. A search for HRQoL data has not been conducted; instead a search for functions that map HAQ to HRQoL has been conducted. Please summarise the SF-36 data in the golimumab trials, and please provide a full justification for choosing to use a HAQ to utility mapping function to estimate utilities in the model.

[redacted]The SF-6D would appear to suffer from a floor effect at the lower end when mapping from HAQ (Marra 2005). A recent analysis found that utilities per HAQ intervals using SF-6D did not differentiate across the different levels of disease severity (HAQ scores from 0 to >3.0), but EQ-5D did differentiate more across the severity groups. Therefore EQ-5D from HAQ may be the appropriate instrument (Benito-Garcia 2009).

As discussed in Section 6.4.3, studies have shown that the HAQ is strongly correlated with measures of health-related quality of life (Hurst 1997). Linear transformations between the HAQ and utility have been widely used in rheumatoid arthritis cost-effectiveness models.

B11. Page 152. Please justify the dosage used in the model of methotrexate as 7.5mg per week.

The dose of methotrexate for moderate to severe RA patients is stated in the British National Formulary 59 as 7.5 mg once weekly, adjusted according to response with a maximum weekly dose of 25 mg. The lower bound of this dose range was conservatively inputted into the economic analyses. Increasing the weekly dose to the upper bound of 25 mg has minimal implications on the total cost and QALYs as depicted in Table 46 and Table 48.

DMARD experienced patient population: Sensitivity analysis varying MTX dose from 7.5 mg once weekly (base case displayed in Table 45) to 25 mg once weekly (maximum dose displayed in Table 46).

Table 45. Basecase Incremental cost effectiveness results – 7.5mg/week MTX (DMARD experienced RA patient population)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus Baseline (Methotrexate)	Incremental analysis
Methotrexate	£35,869	4.569	-	-	-	-
Adalimumab	£66,875	5.792	£31,006	1.223	£25,353	£25,353
Golimumab	£67,747	5.827	£872	0.035	£25,346	£24,914
Infliximab	£69,899	5.651	£2,152	-0.176	£31,464	Dominated
Certolizumab	£73,571	5.768	£3,672	0.117	£31,444	£31,385
Etanercept	£74,208	6.133	£637	0.365	£24,514	£1,745

Table 46. Sensitivity Analysis Incremental cost effectiveness results – 25mg/week (DMARD experienced RA patient population)

Technologies	Total	Total	Incremental	Incremental	ICER (£)	Incremental

	costs (£)	QALYs	costs (£)	QALYs	versus Baseline (Methotrexate)	analysis
Methotrexate	£36,005	4.569	-	-	-	-
Adalimumab	£67,064	5.792	£31,059	1.223	£25,396	£25,396
Golimumab	£67,941	5.827	£877	0.035	£25,392	£25,057
Infliximab	£70,075	5.651	£2,134	-0.176	£31,501	Dominated
Certolizumab	£73,571	5.768	£3,496	0.117	£31,331	£29,880
Etanercept	£74,436	6.133	£865	0.365	£24,573	£2,370

TNFα inhibitor experienced patient population: Sensitivity analysis varying MTX dose from 7.5 mg once weekly (base case displayed in Table 47) to 25 mg once weekly (maximum dose displayed in Table 48).

Table 47. Basecase Incremental cost effectiveness results – 7.5mg/week (TNFα inhibitor experienced RA patient population)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus Baseline (Methotrexate)	Incremental analysis
Methotrexate	£33,673	3.129	-	-	-	-
Golimumab	£50,175	3.712	£16,502	0.583	£28,286	£28,286
Rituximab	£50,206	3.523	£31	-0.189	£41,935	Dominated

Table 48. Sensitivity Analysis Incremental cost effectiveness results – 25mg/week (TNFα inhibitor experienced RA patient population)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus Baseline (Methotrexate)	Incremental analysis
Methotrexate	£33,757	3.129	-	-	-	-
Golimumab	£50,289	3.712	£16,532	0.583	£28,338	£28,338
Rituximab	£50,206	3.523	-£83	-0.189	£41,721	£439

B12. Table 1. Please clarify that the model operates using a 24 week/6 month cycle length. The golimumab key features table (Table 1) suggests that response should be assessed at 12 weeks. Please could you clarify when assessment(s) take place and when a patient will be considered a non-responder. If it is more appropriate, then please adjust the model cycle length to incorporate a 12 week period.

Based on current clinical practice where a follow-up visit is not scheduled until week 24 and previously submitted models for RA Sequential Use, BRAM and BSRBR, a 24

week cycle is considered most appropriate. The text within Table 1 of the MS is extracted from the EMEA license and therefore not tailored solely to UK clinical practice.

B13. Section 6.3. Please could you clarify how the results of the mixed treatment comparison have been incorporated in the economic analysis, and why the CODA samples from the MTC using WinBUGS have not been used to maintain the correlation between parameters within the PSA. Please amend the model to incorporate the CODA samples.

Whilst the Convergence Diagnostic and Output Analysis is available for the 50,000 iterations after convergence, it is improbable to assume that a large correlation may exist between the parameters as the analyses assess multiple treatments compared to placebo. It is therefore presumed sufficient to solely use the mean + precision to place distributions around each parameter in the probabilistic sensitivity analysis.

B14. The economic model incorporate 2006 Reference Costs and 2008 Unit Costs. Please can you amend the model with the most up-to-date Reference and Unit Costs?

Both models have been updated to include the most recently available reference and unit costs as show in Table 49. The resulting total costs, QALYs and resulting ICERs are presented in
Table 50 and

Table 51.

Table 49. Unit costs of health care resources UK (£)

Health care resource	Unit cost	Source
Rheumatologist	£128.19	NHS Reference Costs 2008-2009
General practitioner	£39.00	PSSRU 2009
Specialist nurse	£36.00	PSSRU 2009
Nurse practitioner	£11.00	PSSRU 2009
Full blood count	£2.71	NHS PbR tariff 2008-2009
Erythrocyte Sedimentation rate	£2.71	NHS PbR tariff 2008-2009
Biochemistry profile	£1.42	NHS PbR tariff 2008
C—reactive protein	£2.71	NHS PbR tariff 2008
TB test	£3.48	NHS PbR tariff 2008
Hep B and Hep C	£3.48	NHS PbR tariff 2008
Urinalysis	£1.07	NHS PbR tariff 2008
Chest X-ray	£36.00	NHS Reference Costs 2008-2009

Table 50. Incremental cost effectiveness results – updated reference and unit costs (DMARD experienced RA patient population)

Technologies	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus Baseline	Incremental analysis

	(£)				(Methotrexate)	
Methotrexate	£39,589	4.569	-	-	-	-
Adalimumab	£70,376	5.792	£30,787	1.223	£25,211	£25,211
Golimumab	£71,229	5.827	£853	0.035	£25,193	£24,371
Infliximab	£75,904	5.651	£4,675	-0.176	£33,628	Dominated
Certolizumab	£76,868	5.768	£964	0.117	£31,086	£8,239
Etanercept	£77,548	6.133	£680	0.365	£24,301	£1,863

Table 51. Incremental cost effectiveness results – updated reference and unit costs (TNFα inhibitor experienced RA patient population)

Technologies	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£) versus Baseline (Methotrexate)**	**Incremental analysis**
Methotrexate	£37,134	3.129	-	-	-	-
Golimumab	£53,519	3.711	£16,385	0.583	£28,115	£28,115
Rituximab	£53,530	3.522	11	-0.189	£41,622	DOMINATED

B15. Section 6.6. Please clarify how many PSA simulations are run. The model suggests 2000 runs and so please can you confirm how this number was estimated, and if appropriate increase the number of simulations and show stability in the mean results.

The models submitted with the MS ran 2,000 PSA simulations. The PSA for both populations has been re-run with 5,000 simulations to show stability in the mean results. The below tables suggest that there is minimal difference when increasing the number of PSA simulations, thus it can be concluded that the mean estimates are stable.

Table 52. 2000 PSA Simulations: Basecase incremental cost-effectiveness results (DMARD experienced population)

Options	**Mean Expected Cost**	**Mean Expected QALYs**	**Cost per QALY vs. MTX**	**λ = £20,000**		**λ = £30,000**	
				ENB(£)	**Probability CE**	**ENB(£)**	**Probability CE**
Golimumab	£67,670	5.834	£25,757	£19,615	0.047	£42,982	0.079
adalimumab	£68,990	5.902	£25,433	£19,739	0.136	£43,378	0.182
Infliximab	£71,547	5.779	£30,247	£17,637	0.038	£40,760	0.081
Etanercept	£76,142	6.245	£24,483	£19,524	0.169	£44,582	0.317
Methotrexate	£35,763	4.596	--	£22,541	0.558	£40,980	0.243
Certolizumab	£76,320	5.912	£30,811	£16,783	0.053	£40,414	0.100

Table 53. 5000 PSA Simulations: Basecase incremental cost-effectiveness results (DMARD experienced population)

Options	Mean Expected Cost	Mean Expected QALYs	Cost per QALY vs. MTX	λ = £20,000		λ = £30,000	
				ENB(£)	Probability CE	ENB(£)	Probability CE
Golimumab	£68,076	5.902	£25,646	£49,390	0.048	£108,048	0.084
adalimumab	£69,438	5.986	£25,040	£49,711	0.122	£109,001	0.181
Infliximab	£72,041	5.832	£30,529	£44,243	0.037	£102,221	0.074
Etanercept	£76,631	6.311	£24,471	£49,125	0.156	£111,873	0.317
Methotrexate	£36,083	4.654	--	£56,662	0.579	£102,959	0.237
Certolizumab	£76,443	5.983	£30,365	£42,480	0.058	£101,749	0.107

Table 54. 2000 PSA Simulations: Basecase incremental cost-effectiveness results (TNFα inhibitor experienced population)

Options	Mean Expected Cost	Mean Expected QALYs	Cost per QALY vs. MTX	λ = £20,000		λ = £30,000	
				ENB(£)	Probability CE	ENB(£)	Probability CE
Golimumab	£50,078	3.771	£29,123	£9,949	0.046	£25,013	0.460
Rituximab	£48,294	3.508	£48,499	£8,547	0.054	£22,540	0.099
Methotrexate	£33,563	3.204	--	£11,974	0.901	£24,745	0.442

Table 55. 5000 PSA Simulations: Basecase incremental cost-effectiveness results (TNFα inhibitor experienced population)

Options	Mean Expected Cost	Mean Expected QALYs	Cost per QALY vs. MTX	λ = £20,000		λ = £30,000	
				ENB(£)	Probability CE	ENB(£)	Probability CE
Golimumab	£50,447	3.852	£28,629	£26,119	0.045	£64,285	0.458
Rituximab	£48,833	3.602	£45,448	£22,704	0.050	£58,197	0.100
Methotrexate	£33,841	3.272	--	£31,201	0.905	£63,636	0.442

B16. Page 144. Please clarify how patients who receive rescue therapy are handled when estimating mean HAQ by health state from the golimumab trials.

The model accounts for patients within the crossover groups by adjusting the HAQ score for each cycle to account for the HAQ score of patients transitioning into the health state from previous lines of therapy. Current HAQ score for each health state and cycle number is therefore a function of response status and HAQ decrement from baseline. HAQ decrement from baseline is estimated as a function of time on treatment with DMARDs and TNFα inhibitors. No differentiation was made between patients increasing from GOL50mg + MTX to GOL100mg + MTX.

B17. Table 142. Table 142 appears to be mislabelled as some rows have same health state but different data. Please correct or explain as appropriate.

Table 142 has been amended and reproduced below with more clarification. The change in HAQ for methotrexate was taken from the placebo arm of the GO-FORWARD trial and is reflected in the last three rows of Table 56 below. The figures within Table 56 were included in the model within the sheet titled, 'HAQ scores'.

Table 56. HAQ scores

Health state	Methotrexate experienced (GO-FORWARD)	Anti-TNF experienced (GO-AFTER)
Treatment HAQ scores		
Baseline	1.41	1.59
GOL treated Non responder	1.23	1.49
GOL treated ACR 20	0.86	1.21
GOL treated ACR 50	0.69	0.89
Methotrexate HAQ scores		
GOL treated Non responder	1.44	N/A
GOL treated ACR 20	1.01	N/A
GOL treated ACR 50	0.68	N/A