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12th July 2010

Lori Farrar
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Dear Ms. Farrar:

RE: STA FOR GOLIMUMAB FOR THE TREATMENT OF PSORIATIC ARTHRITIS: CLARIFICATION LETTER

Please find attached MSD's response to the clarification letter for the appraisal of golimumab in psoriatic arthritis. As suggested in my previous e-mail, we have provided all the available information in our response. There are two outstanding requests relating to 52 week safety data for GO-REVEAL clinical trial and revised mixed treatment comparison. I will forward this information as soon as we receive it.

Please do not hesitate to contact me in case of any questions or any additional request for further data or analyses during this appraisal.

Kind regards,

Yogesh Punekar
Senior Health Economist, Market Access
MSD

Section A: Clarification on effectiveness data

Outcomes

A1. **Priority question**: [P32, Table B3] The details of GO-REVEAL trial specify the modified van der Heijde-Sharp score at 24 weeks as a primary outcome measure. Please provide further summary data for this outcome at 24 weeks and 52 weeks if available or explain what happened to this primary outcome.

Study results on van der Heijde-Sharp score for golimumab RCT

Timepoint	Placebo	Golimumab 50 mg*	Golimumab 100 mg*	RR or mean difference (95% CI)	RR or mean difference (95% CI)
Baseline total vdH-S score					
Baseline	n=111	n=143	n=143		
	18.15 ± 27.76	23.85 ± 35.41	23.37 ± 35.38		
Change from baseline in total vdH-S score					
24 weeks	n=113	n=146	n=146		
52 weeks§					
Patients with change ≤ 0 in total vdH-S score from baseline§§					
24 weeks	n=102	n=132	n=137		
Patients with progression based on total vdH-S score > SDC§§,†					
24 weeks	n=102	n=132	n=137		

*All p values are compared to placebo; §No statistical analysis was performed at 52 weeks due to lack of adequate control arm; ‡These are patients who switched to golimumab at weeks 16/24; §§These results are not available for week 52; †SDC - Smallest Detectable Change (=2.21)

A2. **Priority question**: [P46, Table B6] Please provide data on the mean number of prior DMARDs and the proportion of patients with numbers of previous DMARDs for each arm of the GO-REVEAL trial.

No information on the mean number of previous DMARDs is available. The proportion of patients with numbers of previous DMARDs has been outlined in the table below.

	Placebo (n=113)	Golimumab (50mg) (n=146)	Golimumab (100mg) (n=146)
Subjects who took any DMARDs	85 (75.2%)	110 (75.3%)	119 (81.5%)
1 – 2 DMARDs	75 (66.4%)	101 (69.2%)	109 (74.7%)
> 2 DMARDs	10 (8.8%)	9 (6.2%)	10 (6.8%)
Main DMARDs			
Methotrexate	76 (67.3%)	97 (66.4%)	106 (72.6%)
Sulfasalazine	28 (24.8%)	45 (30.8%)	50 (34.2%)
Leflunomide	7 (6.2%)	2 (1.4%)	6 (4.1%)

A3. **Priority question**: [P68, Table B10] Please provide 95% confidence intervals for the relative risks and mean differences in the result sections of the GO-REVEAL trial. Please also provide the standard deviations for the mean values (e.g. HAQ changes from baseline).

Table B1: Study results for golimumab RCT

Trial	Duration	Outcomes	Placebo	Golimumab 50 mg	Golimumab 100 mg	RR or mean difference (95% CI)	
						50 mg	100 mg
GO REVEAL	14 weeks	PsARC	24/113 (21.2%)	107/146 (73.3%)	105/146 (71.9%)	3.451 (2.49 - 4.87)	3.386 (2.43 - 4.80)
		ACR 20					
		All pts	10/113 (8.8%)	74/146 (50.7%)	66/146 (45.2%)	5.727 (3.24 - 10.56)	5.108 (2.86 - 9.48)
		+MTX	8/55 (14.5%)	38/71 (53.5%)	32/71 (45.1%)	3.680 (1.98 – 7.25)	3.099 (1.63 – 6.22)
		-MTX	2/58 (3.4%)	36/75 (48.0%)	34/75 (45.3%)	13.920 (4.13 – 51.64)	13.147 (3.88 – 48.88)
		ACR 50					
		All pts	2/113 (1.8%)	44/146 (30.1%)	41/146 (28.1%)	17.027 (4.81 – 63.32)	15.866 (4.47 – 59.11)
		ACR 70					
		All pts	1/113 (0.9%)	18/146 (12.3%)	25/146 (17.1%)	13.932 (2.46 – 81.82)	19.349 (3.48 – 112.44)
		HAQ change from baseline (mean (SD))	N/A	N/A	N/A		
		PASI 50					
		All pts	7/73 (9.6%)	63/106 (59.4%)	83/107 (77.6%)	6.198 (3.22 – 12.7)	8.089 (4.38 – 16.04)
		PASI 75					

		All pts	2/79 (2.5%)	44/109 (40.4%)	63/108 (58.3%)	15.945 (4.62 – 59.11)	23.042 (6.85 – 84.59)
		PASI 90 All pts	0/73 (0.0%)	22/106 (20.8%)	26/107 (24.3%)	Inf (4.21 – Inf)	Inf (4.95 – Inf)
	24 weeks‡		n = 113	n = 146	n = 146		
		PsARC	33/113 (29.2%)	102/146 (69.9%)	124/146 (84.9%)	2.392 (1.81 – 3.20)	2.908 (2.28 – 3.68)
		ACR 20 All pts	14/113 (12.4%)	76/146 (52.1%)	89/146 (61.0%)	4.202 (2.60 – 7.03)	4.920 (3.09 – 8.13)
		ACR 50 All pts	4/113 (3.5%)	47/146 (32.2%)	55/146 (37.7%)	9.094 (3.62 – 23.94)	10.642 (4.27 – 27.85)
		ACR 70 All pts	1/113 (0.9%)	27/146 (18.5%)	31/146 (21.2%)	20.897 (3.77 – 121.19)	23.993 (4.35 – 138.68)
		HAQ change from baseline (mean (SD))	- 0.01 ± 0.49	0.33 ± 0.55 p < 0.001	0.39 ± 0.50 p < 0.001		
		PASI 50 All pts	6/73 (8.2%)	77/102 (75.5%)	87/106 (82.1%)	9.185 (4.69 – 19.45)	9.986 (5.21 – 20.76)
		PASI 75 All pts	1/73 (1.4%)	57/102 (55.9%)	70/106 (66.0%)	40.794 (7.86 – 232.88)	48.208 (9.44 – 274.39)
		PASI 90					

		All pts	0/73 (0.0%)	33/102 (32.4%)	34/106 (32.1%)	Inf (6.65 – Inf)	Inf (6.59 – Inf)
	52 weeks		GLM 50mg only† n = 102	GLM 50=>100mg†† n = 26	GLM 100mg only††† n = 115		
	104 weeks		GLM 50mg only† n = 70	GLM 50=>100mg†† n = 76	GLM 100mg only††† n = 130		

‡At wk24 all pts randomised to the respective treatment arm are included; †Includes patients randomised to golimumab 50mg and did not change dose; ††Includes patients on placebo at baseline who entered early escape or crossed over to golimumab 50mg and later dose escalated to 100mg and patients randomised to golimumab 50mg who entered early escape or dose escalated to golimumab 100mg; †††Includes patients randomised to golimumab 100mg and did not change dose.

A4. **Priority question**: [P68, Table B10] Please provide tabulated efficacy data of golimumab for the open-label extension at 52 weeks in the GO-REVEAL trial.

Results presented in response to question A3.

A5. **Priority question**: [P69, Table B10] Please provide comprehensive efficacy data (means and standard deviations, mean differences with 95% confidence intervals; event rates, relative risks with 95% confidence intervals) for the treatment arm receiving 100 mg golimumab at 14, 24 and 52 weeks in the GO-REVEAL trial.

Results presented in response to question A3.

A6. **Priority question**: [P90, Table B17] Please provide 95% confidence intervals for the relative risks for adverse events in the GO-REVEAL trial.

Adverse event	Placebo	Placebo => GLM 50mg	GLM 50mg	GLM 50mg => GLM 100mg	GLM 100mg	Combined 50mg & 100mg	All GLM
Week 16	n = 113		n = 146		n = 146	n = 292	
Patients with ≥ 1 AE	63/113 (55.8%)		85/146 (58.2%) 1.044 (0.85-1.30)		82/146 (56.2%) 1.007 (0.81-1.26)	167/292 (57.2%) 1.026 (0.86-1.26)	
+MTX	27/54 (50.0%)		36/71 (50.7%) 1.521 (1.04-2.22)		39/69 (56.5%) 1.696 (1.18-2.43)	75/140 (53.6%) 1.607 (1.16-2.28)	
-MTX	36/59 (61.0%)		49/75 (65.3%) 1.071 (0.83-1.39)		43/77 (55.8%) 0.915 (0.70-1.22)	92/152 (60.5%) 0.992 (0.80-1.29)	
Patients with ≥ 1 serious AE	6/113 (5.3%)		3/146 (2.1%) 0.387 (0.11-1.39)		2/146 (1.4%) 0.258 (0.06-1.10)	5/292 (1.7%) 0.322 (0.11-0.98)	
+MTX	1/54 (1.9%)		2/71 (2.8%) 1.521 (0.20-11.56)		1/69 (1.4%) 0.771 (0.08-7.36)	3/140 (2.1%) 1.133 (0.17-7.88)	
-MTX	5/59 (8.5%)		1/75 (1.3%) 0.157 (0.02-0.98)		1/77 (1.3%) 0.153 (0.02-0.96)	2/152 (1.3%) 0.155 (0.04-0.68)	
Patients with ≥ 1 serious infections	3/113 (2.7%)		1/146 (0.7%) 0.258 (0.04-1.78)		0/146 (0.0%) 0.000 (0.00-0.98)	1/292 (0.3%) 0.129 (0.02-0.89)	
+MTX	0/54 (0.0%)		1/71 (1.4%) Inf (0.2 – Inf)		0/69 (0.0%) -	1/140 (0.7%) Inf (0.10 – Inf)	

-MTX	3/59 (5.1%)		0/75 (0.0%) 0.000 (0.00-1.04)		0/77 (0.0%) 0.000 (0.00-1.01)	0/142 (0.0%) 0.000 (0.00-0.55)	
AE leading to discontinuation	4/113 (3.5%)		2/146 (1.4%) 0.387 (0.08-1.78)		2/146 (1.4%) 0.387 (0.08-1.78)	4/292 (1.4%) 0.387 (0.11-1.40)	
+MTX	0/54 (0.0%)		2/71 (2.8%) -		0/69 (0.0%) -	2/140 (1.4%) -	
-MTX	4/59 (6.8%)		0/75 (0.0%) 0.000 (0.00-0.73)		2/77 (2.6%) 0.383 (0.08-1.74)	2/152 (1.3%) 0.194 (0.04-0.89)	
Subjects with ≥ 1 injection site reactions	3/113 (2.7%)		5/146 (3.4%) 1.290 (0.35-4.84)		5/146 (3.4%) 1.290 (0.35-4.84)	10/292 (3.4%) 1.290 (0.39-4.32)	
Subjects with tuberculosis	0/113 (0.0%) -		0/146 (0.0%) -		0/146 (0.0%) -	0/292 (0.0%) -	
Week 24	n = 113	n = 51	n = 146	n = 28	n = 146	n = 292	n = 343
Patients with ≥ 1 AE	67/113 (59.3%)	26/51 (51.0%)	99/146 (67.8%) 1.144 (0.95-1.38)	4/28 (14.3%)	95/146 (65.1%) 1.097 (0.91-1.33)	196/292 (67.1%) 1.132 (0.96-1.36)	222/343 (64.7%) 1.092 (0.93-1.31)
+MTX	30/54 (55.6%)	10/25 (40.0%)	45/71 (63.4%) 1.141 (0.86-1.54)	1/14 (7.1%)	44/69 (63.8%) 1.148 (0.86-1.55)	89/140 (63.6%) 1.144 (0.90-1.53)	99/165 (60.0%) 1.08 (0.85-1.44)
-MTX	37/59 (62.7%)	16/26 (61.5%)	54/75 (72.0%) 1.148 (0.91-1.46)	3/14 (21.4%)	51/77 (66.2%) 1.056 (0.83-1.36)	107/152 (70.4%) 1.123 (0.92-1.42)	123/178 (69.1%) 1.102 (0.91-1.40)

Patients with ≥ 1 AE of severe intensity	12/113 (10.6%)	1/51 (2.0%)	8/146 (5.5%) 0.516 (0.22-1.19)	0/28 (0.0%)	8/146 (5.5%) 0.516 (0.22-1.19)	16/292 (5.5%) 0.516 (0.26-1.05)	17/343 (5.0%) 0.467 (0.23-0.94)
Patients with ≥ 1 serious AE	7/113 (6.2%)	0/51 (0.0%)	3/146 (2.1%) 0.332 (0.09-1.15)	0/28 (0.0%)	4/146 (2.7%) 0.442 (0.14-1.38)	7/292 (2.4%) 0.387 (0.14-1.04)	7/343 (2.0%) 0.329 (0.12-0.89)
+MTX	1/54 (1.9%)	0/25 (0.0%)	2/71 (2.8%) 1.521 (0.20-11.56)	0/14 (0.0%)	1/69 (1.4%) 0.783 (0.08-7.46)	3/140 (2.1%) 1.157 (0.17-8.05)	3/165 (1.8%) 0.982 (0.14-6.83)
-MTX	6/59 (10.2%)	0/26 (0.0%)	1/75 (1.3%) 0.131 (0.02-0.80)	0/14 (0.0%)	3/77 (3.9%) 0.383 (0.11-1.35)	4/152 (2.6%) 0.259 (0.08-0.83)	4/178 (2.2%) 0.221 (0.07-0.71)
Patients with ≥ serious infections	4/113 (3.5%)	0/51 (0.0%)	1/146 (0.7%) 0.193 (0.03-1.27)	0/28 (0.0%)	1/146 (0.7%) 0.193 (0.03-1.27)	2/292 (0.7%) 0.193 (0.04-0.89)	2/343 (0.6%) 0.165 (0.04-0.76)
+MTX	0/54 (0.0%)	0/25 (0.0%)	1/71 (1.4%) Inf (0.2-Inf)	0/14 (0.0%)	0/69 (0.0%) -	1/140 (0.7%) Inf (0.10-Inf)	1/165 (0.6%) Inf (0.09-Inf)
-MTX	4/59 (6.8%)	0/26 (0.0%)	0/75 (0.0%) 0.000 (0.00-0.73)	0/14 (0.0%)	1/77 (1.3%) 0.192 (0.03-1.24)	1/152 (0.7%) 0.097 (0.02-0.63)	1/178 (0.6%) 0.083 (0.01-0.54)
AE leading to discontinuation	5/113 (4.4%)	0/51 (0.0%)	2/146 (1.4%) 0.310 (0.07-1.36)	0/28 (0.0%)	6/146 (4.1%) 0.929 (0.31-2.82)	8/292 (2.7%) 0.619 (0.22-1.78)	8/343 (2.3%) 0.527 (0.19-1.51)
+MTX	0/54 (0.0%)	0/25 (0.0%)	2/71 (2.8%) -	0/14 (0.0%)	2/69 (2.9%) -	4/140 (2.9%) -	4/165 (2.4%) -
-MTX	5/59 (8.5%)	0/26 (0.0%)	0/75 (0.0%) 0.000 (0.00-0.58)	0/14 (0.0%)	4/77 (5.2%) 0.613 (0.18-2.05)	4/152 (2.6%) 0.311 (0.09-1.04)	4/178 (2.2%) 0.265 (0.08-0.89)
Subjects with ≥ 1	3/113 (2.7%)	0/51 (0.0%)	7/146 (4.8%)	0/28 (0.0%)	7/146 (4.8%)	14/292 (4.8%)	14/343 (4.1%)

injection site reactions			1.806 (0.52-6.35)		1.806 (0.52-6.35)	1.806 (0.57-1.83)	1.537 (0.49-4.96)
Subjects with tuberculosis	0/113 (0.0%) -		0/146 (0.0%) -		0/146 (0.0%) -	0/292 (0.0%) -	

A7. **Priority question**: [P90, Table B17] Please provide tabulated adverse event data for the open-label extension at 52 weeks in the GO-REVEAL trial.

We do not have this information as this is still being analysed by clinical trials team. We will provide this information as soon as it becomes available.

A8. **Priority question**: [P96, Section 5.9.3] Please provide further summary data on the adverse events of serious infections and tuberculosis for the GO-REVEAL trial.

The detailed adverse event data has been presented in A6. No active tuberculosis was reported in any arms of the GO-REVEAL trial.

A9. **Priority question**: [P166, Section 7.8] The manufacturer's submission (MS) states that golimumab is associated with a lower incidence of injection site reactions compared with other TNF-alpha inhibitors. Please provide summary supporting evidence.

Injection site reactions are a common adverse events associated with the subcutaneous (SC) biologic DMARDs. Patients receiving TNF-α inhibitor products have a 3-times higher risk of developing injection-site reactions (localized erythema and/or itching, hemorrhage, pain, or swelling) compared with control groups in randomized clinical trials (relative risk [RR] 3.0; 95% confidence interval [CI]: 1.0-8.6) [Alonso-Ruiz, 2008]. The assessment by the National Institute for Health and Clinical Excellence (NICE) found that injection-site reaction are the most commonly reported adverse events for agents given subcutaneously [NICE, 2008]. The rate of injection-site reactions published in the respective product labels for etanercept or adalimumab are shown in table below [Enbrel® package insert; Humira® package insert; Alonso-Ruiz, 2008].

Injection-site Reactions with Etanercept and Adalimumab

Rate of Injection-Site Reactions [a]	Etanercept		Adalimumab	
	Etanercept	Placebo	Adalimumab	Placebo
Package Insert	37%	10%	20%	14%
Summary of Product Characteristics	36%	9%	14%	8%

[a]Erythema and/or itching, hemorrhage, pain, or swelling

In addition, etanercept has also been associated with localized reactions at sites where administered previously, even if the last injection was given at a different site ("recall" injection-site reactions). Patients may develop these recall injection-site reactions at multiple previous sites of injections [Gonzalez-Lopez, 2007; Zeltser, 2001].

In some patients, the injection-site reactions can be bothersome and more severe, requiring attention and management, and may even result in treatment

discontinuation or switching. Case reports indicate that some patients experience a worsening of injection-site reactions with continued etanercept use, requiring premedication with antihistamines and acetaminophen, and dose reductions [Edwards, 2003]. Case reports of severe cutaneous reactions to adalimumab have also been reported to require permanent treatment discontinuation [Beuthien, 2004; Nikas, 2007]. Based on data from the BSR Biologics Registry, of 22 patients with injection-site reactions, 2% discontinued therapy due to the reaction; 15 patients (68%) switched to another anti-TNFα due to the reaction [Hyrich, 2007].

The injection site reactions with golimumab have been displayed in A6. They are comparable to placebo suggesting no additional burden of injection site reactions on patients. They are significantly lower than other TNF-α inhibitors as outlined in table above.

Methods

A10. **Priority question**: Please provide full details of the intention to treat (ITT) method used in the analysis of GO-REVEAL trial at 14 & 24 weeks. Please clarify which method (e.g. last observation carried forward) was used to handle missing data, and whether the approach differed for different outcomes. Please provide full details on the methods used to deal with crossing over data in analyses.

All efficacy analyses were based on randomized subjects; ie, the intent-to-treat population. Based on the intent-to-treat principle, subjects randomly assigned to a treatment group were included in the efficacy analyses according to their assigned treatment group whether or not they received the assigned treatment.

Clinical pharmacology and safety analyses were based on treated subjects; ie, subjects who received at least 1 study agent administration. Treated subjects were included in a specific treatment group if they met the definition of that group.

Treatment Failure Rules

Treatment failure rules were applied in the primary analysis. These rules superseded the actual clinical response status value (yes/no) based on the ACR 20. Subjects were considered to have not achieved an ACR 20 response at Week 14 if, prior to Week 14, they:

Initiated any DMARDs, biologics, systemic immunosuppressives for PsA or increased MTX dose above baseline level for PsA.

Initiated treatment with oral, IV, or IM corticosteroids for PsA, or increased the dose of oral corticosteroids for PsA above baseline dose.

Discontinued study agent injections due to unsatisfactory therapeutic effect.

Missing Data Rules

Subjects with missing data for all of the ACR components at Week 14, were considered as ACR 20 nonresponders at Week 14. If subjects had data for at least 1 ACR component at Week 14, the following rules were applied:

Percent improvement from baseline at Week 14 was imputed as 0% for any ACR component, if the component values were missing from baseline through Week 14.

Any missing ACR component value at Week 14 was replaced by the last nonmissing observation (including baseline).

Any missing baseline ACR component value (needed for computing percent improvement from baseline) was imputed as the median value of that component from all subjects with baseline data in the same stratum (baseline MTX use yes/no).

For the other endpoints, early escape rules were applied to data after Week 16; ie, subjects who increased dose at Week 16 had their last observation prior to change in the treatment carried forward for Week 24 analyses.

A11. **Priority question**: [P27 & 28, Sections 5.2.1 & 5.2.2] The flow chart in section 5.2.2 describes two searches (efficacy and adverse events). Please clarify whether the study selection criteria described in section 5.2.1 relate to both types of searches. If not, please provide full details on the inclusion/exclusion criteria for the evaluation of adverse events.

The study selection criteria refer to both efficacy and adverse events searches.

A12. **Priority question**: [P28, Figure B1] Study selection flow diagram: Please provide all the references for the studies that are included in the evaluation of efficacy (n=43) and adverse events (n=32).

The excluded studies have been provided in Appendix A.

A13. **Priority question**: [P69, Table B10] Based on Table B10 and Figure B2 (p.60), it appears that the numbers included in the analyses of GO-REVEAL trial do not indicate an intention-to-treat method. Please provide full clarification on how the numbers included in the analyses of GO-REVEAL trial in Table B10 correspond to those reported in Figure B2 (p.60).

The numbers reported in Table B10 of the original submission correspond to per protocol population. The data for the detailed efficacy results (ACR50, ACR70, PASI50, PASI90 etc) has been analysed per protocol and was therefore presented as per-protocol in our original submission. The intention-to-treat analysis is available for co-primary endpoint and major secondary endpoints and has been presented in this response under responses to questions A1, A3 and A6.

A14. **Priority question**: [P97] The MS states that 'in the RCT considered, golimumab has been administered for a period of 24 weeks before the non-responders switched to a higher dose'. However, based on the CONSORT flow chart for the GO-REVEAL trial (p.60), it appears that non-responders switched to a higher dose at week 16. Therefore please confirm whether the time for those non-responders switching to a higher dose was at week 16.

This is correct. The non-responders, defined as <10% improvement from baseline in both swollen and tender joint count qualified to enter early escape at week 16 in a double blind fashion. Treatment for subjects who entered early escape was as follows:

Placebo to golimumab 50 mg SC injections at Weeks 16 and 20

Golimumab 50 mg to golimumab 100 mg SC injections at Weeks 16 and 20

Golimumab 100 mg to No change (golimumab 100 mg SC injections at Weeks 16 and 20)

Week 24 was the point of placebo crossover where all participants on placebo switched to golimumab 50 mg SC injections.

Mixed Treatment Comparison

A15. [P83, Section 5.7.5] Figure B9 and Table B15 imply that the analysis assumes that the change in HAQ and change in PASI are independent. The ERG would like further data to support this assumption. Please provide 2x2 tables for each treatment showing the number of patients with psoriasis at baseline who achieved PsARC response with and without achieving PASI 75 response, for golimumab and for placebo, in the GO-REVEAL trial.

A16. [P83, Section 5.7.5] For the reasons mentioned in the above point (A15), please also conduct a statistical test to show that the differences in mean PASI change are the same in PsARC responders and non responders.

This information has been presented in response to A15.

A17. [P84, Section 5.7.5] The MS used the last randomised endpoint before week 24 to measure the change in HAQ and PASI. The ERG would like to check if this assumption is important. Please re-estimate the meta-analysis using data from the time point closest to 3 months.

We have considered this request. In relation to the HAQ endpoint, the 24 week data from Mease 2005 (adalimumab) is almost exactly the same as the 12 week data, the only difference is on one of the standard errors. We do not anticipate a significant impact of this change on the results of mixed treatment comparison results.

With regards to the PASI endpoint, the original MS analysis uses figure 2B in the Mease 2005 paper (adalimumab) for PASI at 24 weeks. The PASI response at 12 weeks is a little bit weaker, and may results in a lower estimate for adalimumab in terms of PASI (compared to the results using the 24 week endpoint). From Mease 2004 (etanercept), it appears that they only report a 24-week endpoint. No information is available for 12-week response. This will necessitate us to delete Mease 2004 from the evidence base which may result in additional uncertainty for

etanercept. Therefore, we have not revised our analysis in response to this clarification request.

A18. **Priority question**: [P86, Section 5.7.6] Results of Winbugs analyses are shown as absolute probabilities or changes from baseline for each drug for each outcome. It is difficult to use this table to assess a) Heterogeneity of relative treatment effects between the trials for each outcome b) Whether the pooled relative effects calculated by the analysis are in fact consistent with the original data from the RCTs. Given the complexity of the Winbugs code, the ERG would like to check that assumptions about priors or the structure of the analyses are not dominating the data. Please present relative treatment effects for each drug compared with placebo, for each outcome. To make comparison with trial results straightforward, relative risks or weighted mean differences (95% CIs) would be best.

RRs of PsARC response vs placebo				
	Infliximab	Etanercept	Adalimumab	Golimumab
mean				
SE				
2.5%				
97.5%				

HAQ change in the responders groups, mean difference to placebo				
	Infliximab	Etanercept	Adalimumab	Golimumab
mean				
SE				
2.5%				
97.5%				

HAQ change in the non-responders groups, mean difference to placebo				
	Infliximab	Etanercept	Adalimumab	Golimumab
mean				
SE				
2.5%				
97.5%				

HAQ change unconditional on response, weighted mean difference to placebo

	Infliximab	Etanercept	Adalimumab	Golimumab
mean				
SE				
2.5%				
97.5%				

Quality Assessment

A19. [P66, Section 5.4.3] There is insufficient information to allow for proper evaluation on the quality assessment of the GO-REVEAL trial in the submission. Please provide details of information relating to the randomisation method (e.g. centralised randomisation), concealment of allocation, and blinding (of patients, investigators and assessors).

Randomized treatment allocation via a centralized IVRS was provided by ClinPhone Inc (Princeton, NJ). Sites placed a telephone call to the IVRS to randomly assign a subject to a treatment group after the informed consent had been obtained and the subject had met all screening criteria.

Subjects were to be randomized in a 1:1.3:1.3 ratio to one of three treatment groups: placebo, golimumab 50 mg, and golimumab 100 mg. In order to ensure relatively even treatment balance within sites, within baseline MTX usage (yes/no), and within the study overall, subject allocation to a treatment group was performed using an adaptive stratified randomization design.

Randomization files containing treatment assignments for individual subjects were maintained in limited-access directories within the electronic data filing system at the central randomization center. Johnson & Johnson Global Clinical Operations Integrated Data Services (IDS) group performed data management activities and were unblinded to the treatment group of the subjects. IDS received the randomization and dosing assignment files from ClinPhone periodically for purposes of data cleaning.

Identification of sponsor personnel with access to the unblinded subject level data for the 24-week report was documented prior to unblinding. All Centocor personnel having contact with study sites, including the medical monitor, were to remain blinded to the treatment assignment of individual subjects until the 24-week database lock. All site monitors, site personnel, and subjects were to remain blinded to treatment assignment until the last subject completes Week 52 evaluations and the database is locked.

Unblinding of the investigator was to be done only for compelling safety reasons. To request the unblinding of treatment assignment for a subject, the investigator was required to contact Centocor, who would review the request and, if necessary, authorize the randomization center to provide the information to the investigator. Additionally, a given subject's treatment assignment could be unblinded to the

sponsor, IRB/EC, and site personnel to fulfil regulatory reporting requirements for serious, unexpected, drug related AEs. Data that could potentially unblind the treatment assignment (eg, study agent serum concentrations, antibodies to study agent, treatment allocation, and study agent preparation/accountability data) were handled with special care, so that prior to unblinding, such data were to be available only to IDS staff for purposes of data cleaning.

A20. [P66, Section 5.4.3] For the reasons mentioned in the above point (A19), please provide details of the number of drop-outs in the different arms in the GO-REVEAL trial, to give evidence to support the MS statement that there were unexpected imbalances in drop-outs between groups for the GO-REVEAL trial.

Discontinuation	Placebo	GLM 50mg	GLM 100mg	Combined 50mg & 100mg
Week 14	n = 113	n = 146	n = 146	n = 292
Subjects discontinuing treatment	10 (8.8%)	7 (4.8%)	2 (1.4%)	9 (3.1%)
Reasons				
AEs	4 (3.5%)	2 (1.4%)	2 (1.4%)	4 (1.4%)
Unsatisfactory response	2 (1.8%)	1 (0.7%)	0 (0.0%)	1 (0.3%)
Loss to follow-up	1 (0.9%)	1 (0.7%)	0 (0.0%)	1 (0.3%)
Other	3 (2.7%)	3 (2.1%)	0 (0.0%)	3 (1.0%)
Week 24				
Subjects discontinuing treatment	12 (10.6%)	9 (6.2%)	4 (2.7%)	13 (4.5%)
Reasons				
AEs	5 (4.4%)	2 (1.4%)	4 (2.7%)	6 (2.1%)
Unsatisfactory response	3 (2.7%)	2 (1.4%)	0 (0.0%)	2 (0.7%)
Loss to follow-up	1 (0.9%)	1 (0.7%)	0 (0.0%)	1 (0.3)
Other	3 (2.7%)	4 (2.8%)	0 (0.0%)	4 (1.4%)

Searches

A21. **Priority question**: [P170, Section 9.2] Appendix 2: Search strategy for section 5.1 (Identification of studies): The Cochrane Library (specifically CENTRAL) is listed as a resource searched, but there is no search strategy. Please clarify if this database has been searched and provide details of the search strategy if appropriate.

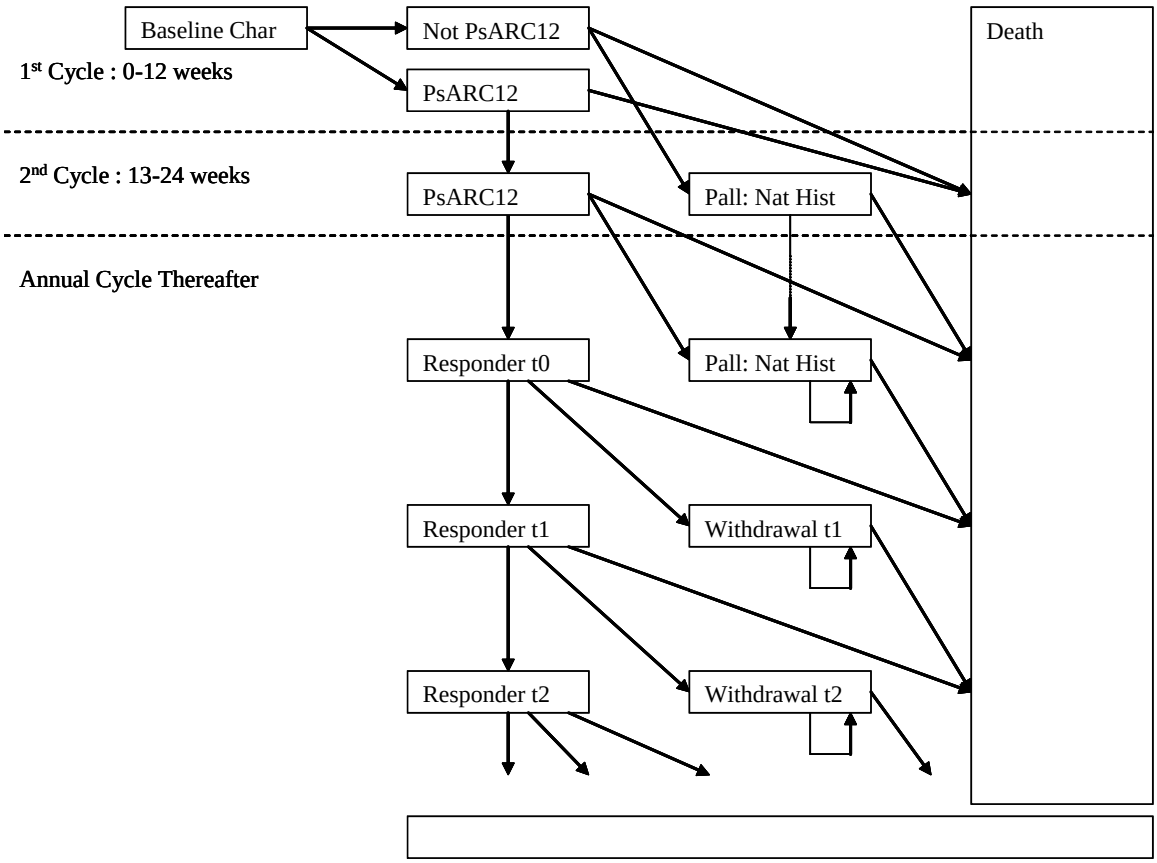
The search strategy used was based on Rodgers et al, 2009 and has been displayed below.

#1 MeSH descriptor Arthritis, Psoriatic, this term only	116
#2 (psoria* NEAR/2 arthrit*) in Clinical Trials	141
#3 (psoria* NEAR/2 arthropath*) in Clinical Trials	8
#4 (#1 OR #2 OR #3)	229
#5 (etanercept or enbrel):ti,ab,kw, from 2008 to 2010 in Clinical Trials	57
#6 (infliximab or remicade):ti,ab,kw, from 2008 to 2010 in Clinical Trials	84
#7 (adalimumab or humira or D2E7 or (D2 adj E7)):ti,ab,kw from 2008 to 2010 in Clinical Trials	39
#8 (golimumab or simponi):ti,ab,kw in Clinical Trials	14
#9 (#5 OR #6 OR #7 OR #8)	238
#10 (#4 AND #9)	22

Section B: Clarification on cost-effectiveness data

B1. [P112, Section 6.2.2] Description of first cycle is missing in Figure B10. Please correct this figure.

The correct figure has been reproduced below.



B2. **Priority question**: [P113, Section 6.2.3] The MS states that Kyle 2005 recommends treatment with biologics for at least 6 months before the continuation decision. The ERG understands that the Kyle 2005 guideline recommends a continuation decision at 12 weeks / 3 months. Could the MS explain further which part of the guideline recommends a decision at 6 months, e.g. provide an exact quotation from the guideline to support this.

This is an error in the MS submission. The Kyle guidelines indeed recommend a continuation decision at 12 weeks / 3 months and the MS submission base case is in line with the 12 weeks continuation rule.

B3. **Priority question**: [P113, Section 6.2.3] The model appears to allow a treatment continuation decision at either 3 or 6 months. The base case should be 3 months. Please clarify that the base case is 6 months and that all sensitivity analyses are relative to this. In the scenario where a decision is made at 6 months, please clarify the data sources and results of the meta-analysis for PsARC responses and HAQ changes at this time. Please conduct sensitivity analyses to a 3month assessment.

The model allows treatment continuation decisions to be made at 3 or 6 months.

However, we would like to confirm that the base case is 3 months. This can be confirmed in the working version of the Excel model wherein patients are classified as responders and non-responders after the first cycle of 12 weeks [Cells E29 and F29 on sheets "Goli", "Infl", "Adal" and "Etan"]. Responders continue with treatment and non-responders are withdrawn. Consequently, all the sensitivity analyses, PsARC response and HAQ changes also relate to 3 month continuation rule.

The 2nd cycle of 3 months (12 – 24 weeks) was included to allow for a possibility of additional treatment effect.

B4. **Priority question**: [P118, Section 6.2.7] The sheet "Therapy costs" in the model refers to Golimumab 50mg or 100mg every 4 weeks. A 4-weekly cycle would not correspond to the number of doses given of Golimumab in the 1st and 2nd cycles (2.8 doses). Please confirm that the dose of Golimumab is 50mg every calendar month.

We would like to confirm that the dose of golimumab is 50 mg every calendar month.

B5. **Priority question**: [P118, Section 6.2.7] The model assumes 50mg per month. The RCT showed that a proportion of patients increased dose to 100mg at 13 weeks to achieve or maintain response. Please provide evidence about what the mean or distribution of dosage would be in the long term in clinical practice. Please conduct a sensitivity analysis with the relevant proportion of the cohort on this higher dose with corresponding costs.

In the RCT, a proportion of patients deemed non-responders were allowed early escape and increased their dose to 100 mg. This was based on the criteria of <10% improvement from baseline in both swollen and tender joint count.

The model however uses PsARC as the response criteria to identify responders. We do not have information on the proportion of PsARC responders who switched to 100 mg dose and therefore are unable to predict the proportion of patients increasing to 100 mg in long term clinical practice. We anticipate that a very small proportion of patients with <10% improvement in both swollen and tender joint count will achieve PsARC criteria in clinical practice and increase their dose to 100 mg. A significant majority of these patients would be deemed as non-responders and would be withdrawn from golimumab treatment.

B6. [P122, Section 6.3.6] Table B 21 shows the baseline PASI is 9.9. Is this the mean in all patients or only those with psoriasis?

Baseline PASI of 9.9 is for all patients (all 3 treatment arms) with psoriasis i.e. subjects with ≥3% body surface area psoriasis skin involvement.

B7. [P122, Section 6.3.6] Does the data used to determine PsARC responder PASI change (only applied to those with >3% BSA) include patients with <3% BSA?

PASI change was not conditional on PsARC response i.e. same for PsARC responder and non-responders. PASI was modelled using data from patients with significant

psoriasis at baseline in trials of TNF-α inhibitors (E.g. ≥3% BSA in golimumab trials; PASI>2.5 in infliximab trials etc.)

B8. **Priority question**: [P123, Section 6.3.6] An additional 4 hours of staff nurse time for administration of golimumab, adalimumab and etanercept has been added to the 1st cycle costs. This is in addition to the outpatient visit taken from reference costs. Please provide the justification for the inclusion of this additional cost and comment on the possibility of double counting the cost for training patients to self-administer.

The 4 hours of additional nurse time in the 1st cycle has been added to account for the self-injection training required for subcutaneous TNF-α inhibitors. This will usually occur along with the 2 outpatient visits. In the first visit, after the prescription of the TNF-α inhibitor the staff nurse will explain the product to the patient and provide a demonstration for the self-injection with a dummy product. The 2nd visit usually is reserved for any questions or clarifications specific to the self-injection as well as general Q&A related to the condition or the product.

B9. [P125, Section 6.3.7] The MS states that PASI would return to baseline and follow natural history thereafter following withdrawal from biologic. Please clarify if the 'natural history' of PASI is 'no change from baseline'?

That is correct. The 'natural history' of PASI is assumed to be 'no change from baseline.'

B10. [P126, Section 6.3.7] The MS states the mean relative change in PASI in patients achieving PASI 25 and no higher improvement was 38.2%. Does this refer to patients who achieved between 25% and 49% improvement in PASI?

Yes. In the model, PASI 25 refers to those who achieved PASI 25 but not PASI 50 (ie a 38.2% improvement is reasonable), PASI 50 is those that achieved PASI 50 but not PASI 75 and so on.

B11. [P130, Section 6.4.3] Table B22 shows the Gray algorithm for HRQOL includes PASI- squared and HAQ squared terms. These do not seem to be significant or have much impact on QOL in Table B24. Please exclude these terms from the regression and present the revised coefficients, the QOL equation. Please conduct a sensitivity analysis with the decision model using the revised Gray algorithm.

The revised Gray algorithm has been displayed below. Table A and Table B are based on combined data from the infliximab (IMPACT 2) and golimumab (GO-REVEAL) trials whereas Table C and Table D are based on golimumab trial (GO-REVEAL) only.

Table A: Using the SF-36 data via Gray algorithm: combined data

Covariate	Mean	Variance-Covariance matrix			
		Intercept	HAQ	PASI	HAQ x PASI

Intercept					
HAQ					
PASI					
HAQ x PASI					

Table B: Using the EQ-5D data: combined data

Covariate	Mean	Variance-Covariance matrix			
		Intercept	HAQ	PASI	HAQ x PASI
Intercept					
HAQ					
PASI					
HAQ x PASI					

Table C: Using the SF-36 data via Gray algorithm: GO study only

Covariate	Mean	Variance-Covariance matrix			
		Intercept	HAQ	PASI	HAQ x PASI
Intercept					
HAQ					
PASI					
HAQ x PASI					

Table D: Using the EQ-5D data: GO study only

Covariate	Mean	Variance-Covariance matrix			
		Intercept	HAQ	PASI	HAQ x PASI
Intercept					
HAQ					
PASI					
HAQ x PASI					

This has been implemented in the revised model through addition of a new worksheet, 'QoL_York MTA 2009.' As a default option, when the QoL basis on the 'Params Used' (c46) is selected as "YORK MTA 2009" it takes values from Table A. To use values from Tables B, C or D, they need to be changed on the 'QoL_York MTA 2009' sheet in ranges J5:K8 and J13:M16.

The use of this revised algorithm changes the base case results. The new base case results combined with the analysis of 'No vial sharing' as requested by ERG have been displayed in the response to question B17.

B12. [P132, Section 6.4.3] Table B25 indicates a non-zero PASI term for HRQOL, although this is for a group who has no psoriasis. Please provide justification for using a non-zero value for those without measurable psoriasis.

This occurs due to the dataset used to estimate the equations. The dataset included PASI values even for patients who do not have measurable psoriasis (BSA>3%). This results in a non-zero PASI term. However, considering the patient group to whom this equation has been applied do not have measurable psoriasis and therefore very small PASI score, it is unlikely to affect the overall results.

B13. [P143, Section 6.5.6] Please confirm the costs as a function of HAQ and PASI are for one year.

We would like to confirm that cost as a function of HAQ and PASI are for one year.

B14. **Priority question**: [P143, Section 6.5.6] Please provide further detail of the cost per PASI data and analysis. Please provide (CIC if necessary):

- The data for each specialist
- The summary of the data by question
- The unit costs used in the analysis of the data (i.e. for inpatient, outpatient, phototherapy, drugs)
- The method of analysis (e.g. simple mean / OLS)
- A measure of variance

The data for each specialists and the summary of data by question have been provided in the accompanying files.

PsA - PASI resource allocation survey - Raw data anonymised: - This table contains the data for each specialist.

PsA – PASI resource allocation survey tables: - This table includes the summary data for each question.

Please note that both these files and the data included are CiC.

B15. **Priority question**: [P151, Section 6.7.7] Table B33 shows the sensitivity analyses as ICERs versus palliative care. Please include another column in Table B33 showing the incremental ICER of golimumab versus the next best alternative for each scenario, or indicate if extendedly dominated

These results include the revised QoL results from question B11.

Variable	Base case	Parameter change	ICER vs Palliative care	ICER vs next best alternative
Time horizon	40 years	5 years 20 years	£50,173 £24,611	£81,519 £31,922
Discount rate	3.5%	0% costs & 0% outcomes 0% costs & 3.5% outcomes 3.5% costs & 0% outcomes	£14,603 £47,546 Dominant	£17,467 £28,280 £15,323
Females	40%	All males All females	£20,352 £19,434	£25,335 £23,995
Age	47 yrs	30 yrs 60 yrs	£18,303 £24,416	£22,362 £31,474
Baseline HAQ score	1.02	+ 50% change - 50% change	£22,005 £19,221	£27,639 £21,547
Baseline PASI score	9.9	+ 50% change - 50% change	£19,915 £20,241	£24,712 £22,960
Placebo HAQ responses	Common	Individual from TNF-α inhibitor trials	£20,056	£26,494
Withdrawal rates	16.5%	11.14%	£20,610	£25,545
Psoriasis Costs	Included	Excluded	£21,459	£26,170
Phototherapy costs	Included	Excluded	£20,994	£25,738
QoL data	Rodgers et al.	Algorithm based on previous NICE appraisal (Bravo Vergel, 2007)	£19,218	£23,687
Golimumab annual acquisition cost	Equivalent to adalimumab	+ 20% change - 20% change	£24,521 £15,466	£47,981 £1,638
HAQ change for	Continued up to 3	No HAQ benefit beyond the first cycle	£22,148	£28,334

responders	cycles			
HAQ change for non-responders	Trial based HAQ benefit in cycle 1	No HAQ benefit for non-responders	£20,003	£24,603
PASI change for non-responders	Trial based PASI benefit in cycle 1	No PASI benefit for non-responders	£20,027	£24,656
Natural history HAQ progression	0.0719	0.1018	£17,482	£21,356
PsA management cost on TNF-α inhibitors	85% of costs for patients on palliative care	+ 15% change - 15% change	£20,595 £19,392	£25,583 £24,063

B16. **Priority question**: [P151, Section 6.7.7] The results of the sensitivity analyses are deterministic. Please provide the probability that golimumab is the most cost-effective at 20,000 and 30,000 per QALY for each sensitivity analysis, relative to all the other strategies (not just palliative care).

These results include the revised QoL results from question B11.

The table below presents the probability of golimumab being cost effective compared to all treatment alternatives including palliative care.

WTP per QALY	Golimumab	Infliximab	Adalimumab	Etanercept	Palliative
£0K per QALY					
£20K per QALY					
£30K per QALY					
£40K per QALY					
£70K per QALY					

The table below presents the probability of golimumab being cost effective compared to all treatment alternatives excluding palliative care.

WTP per QALY	Golimumab	Infliximab	Adalimumab	Etanercept
£0K per QALY				
£20K per QALY				
£30K per QALY				

£40K per QALY				
£70K per QALY				

Section 6.7.7 refers to deterministic sensitivity analyses and therefore we have not presented the probabilistic results for each of the one-way sensitivity analyses. We are unclear whether question B16 (above) refers to conducting a PSA for each of the one-way sensitivity presented in Table B33 of the MS submission. We will provide that information if requested.

B17. [P151, Section 6.7.7] The analysis has assumed vial sharing. Please provide a sensitivity analysis assuming that vial sharing is not permitted.

The results of the base case with no vial sharing permitted and the revised QoL algorithm as per question B11 are presented below.

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus Palliation (QALYs)	ICER (£) incremental vs TNF-α inhibitors (QALYs)
Palliation	£62,224	6.61				
Adalimumab	£86,410	7.89	£24,186	1.28	£18,824	£18,824
Golimumab	£94,151	8.21	£7,740	0.31	£19,993	£24,809
Etanercept	£94,578	8.49	£428	0.29	£17,177	£1,492
Infliximab	£106,620	8.49	£12,042	0.00	£23,578	Dominated

B18. **Priority question**: [P152, Section 6.7.7] NICEs position in the previous MTA of biologics for PsA was that all the biologics have similar effectiveness in terms of PASI, HAQ and PsARC response. Please carry out an additional sensitivity analysis reflecting NICEs position with regard to biologics for PsA in the previous MTA.

These results include the revised QoL results from question B11.

We have conducted the additional analysis which assumes similar effectiveness in terms of PASI, HAQ and PsARC response for all four TNF-α inhibitors. We have used identical values to those used in the previous MTA i.e. PsARC response of 0.713, HAQ change for responders to be -0.63 and HAQ change for non-responders to be -0.19[1] Our model uses a different PASI calculation approach to the MTA and therefore we used the etanercept value for the absolute change from baseline in PASI

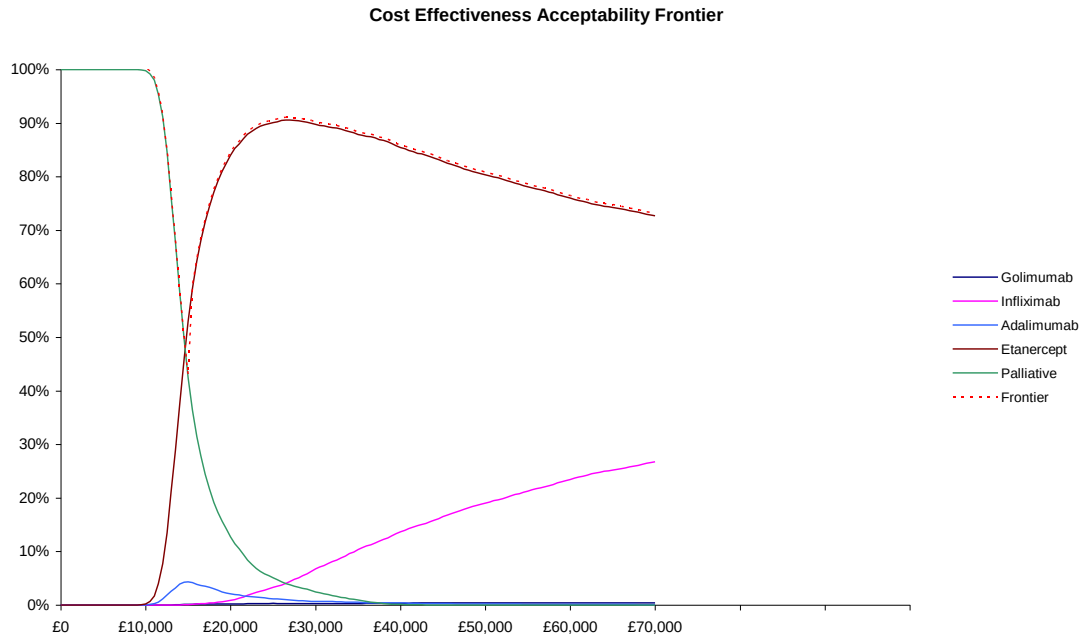
[1] Final evaluation report for the previous MTA. Revisions to the cost effectiveness analysis after the committee meeting of 16th February 2010.; Page 1.

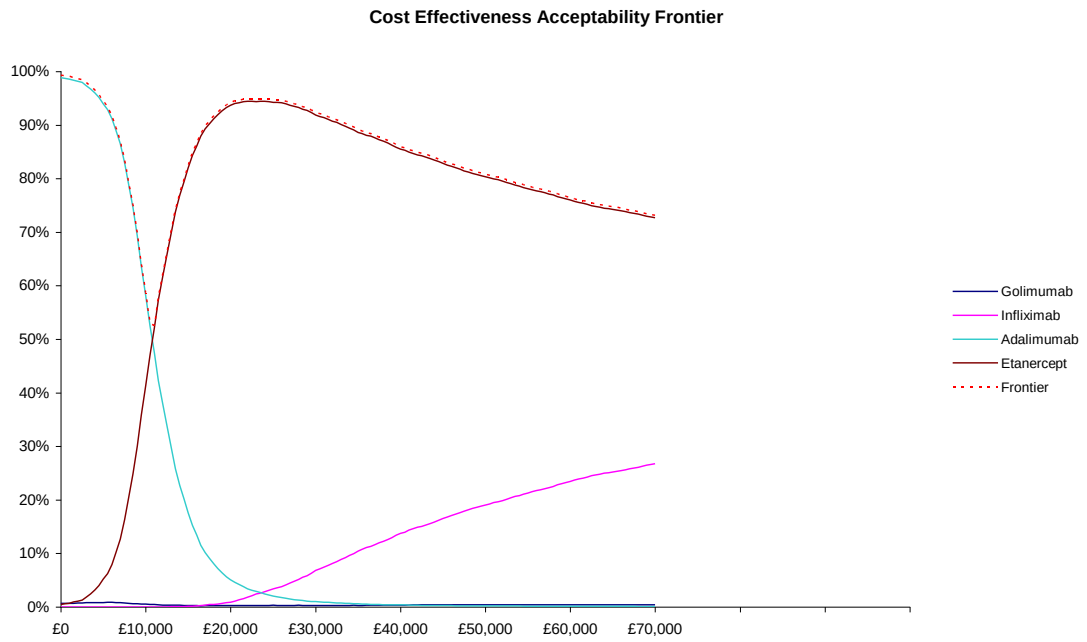
score of -4.5278. This is in line with the previous approach where etanercept values were used to substitute for other TNF-α inhibitors. The results are presented below.

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus Palliation (QALYs)	ICER (£) incremental vs TNF-α inhibitors (QALYs)
Palliation	£62,224	6.61				
Adalimumab OR Golimumab	£92,877	8.59	£30,653	1.98	£15,494	
Etanercept	£92,879	8.59	£2	0	£15,495	-
Infliximab	£104,401	8.59	£11,522	0	£21,319	-

B19. **Priority question**: [P153, Section 6.7.8] The cost effectiveness acceptability curves are shown for each biologic relative to palliative care. Please provide a figure showing the probability that each is the most cost effective compared with all the other strategies.

The cost effectiveness acceptability frontiers with and without inclusion of palliative care have been displayed below.





B20. **Priority question**: [P207, Section 9.14] There are no measures of variance. Please show the standard errors in the table for mean HAQ changes from baseline.

The standard errors for the mean HAQ change from baseline have been provided in the table below.

Study	Treatment	Timelines	Sample size	HAQ change	Std error	Patient group
GO-REVEAL	Placebo					Placebo responders
						Placebo responders
	Golimumab					Golimumab responders
						Golimumab responders
						Golimumab responders

B21. **Priority question**: [Model] When selecting the York_MTA option for QOL values, this returns an error on the New QOL sheet. Please provide a corrected version of the model.

These errors have been corrected and a new version of the model is available with results from the QoL analyses (question B11) included.

Section C: Textual clarifications and additional points

In the version of the MS with the filename “GLM in PsA - NICE STA - Final_CIC marked”, it appears that the responses in the appendices 12 and 13 have been completed but in the version named “GLM in PsA - NICE STA - Final”, they have not. Please clarify whether these are the only differences between the two versions of the MS (aside from CIC marking).

The difference between the two versions is an error. We have now corrected it and “GLM in PsA – NICE STA – Final” has the responses in the appendices 12 and 13 complete. We can confirm that these were the only differences between the two versions of the MS submissions.

References

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Appendix A

Studies included from efficacy search

Antoni CE, Kavanaugh A, Kirkham B, Tutuncu ZN, Burmester G, Schneider U, et al. 2-year data: infliximab maintains clinical response in psoriatic arthritis patients-data from the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT). *Arthritis Rheum* 2005;52 Suppl S:S209.

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Centocor Ltd. A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, a Fully Human Anti-TNFα Monoclonal Antibody, Administered Subcutaneously in Subjects with Active Psoriatic Arthritis. Report Date: 16 OCT 2007.

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Genovese MC, Mease PJ, Thomson GTD, Kivitz AJ, Perdok RJ, Weinberg MA. Adalimumab efficacy in patients with psoriatic arthritis who failed prior DMARD therapy. *Ann Rheum Dis* 2005;64 Suppl III:313.

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