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28th January 2011

Dear Meindert

Re: Golimumab for the treatment of rheumatoid arthritis – Response to request for re-modelling and additional information

The understanding at Schering-Plough Limited, which is now part of Merck Sharp & Dohme Ltd ("MSD"), is that we have been asked to:

1. Provide radiographic outcomes data supporting the recent Type II variation to the product label.
2. Re-present the economic model and results incorporating ACR70 for the DMARD-experienced population
3. Re-present the SF-36 data from GO-FORWARD and a sensitivity analysis in which SF-36 data is included in the economic model using SF-6D and/or mapping approaches to EQ-5D.
4. Present the economic model and clinical and cost-effectiveness results for the TNF inhibitor-experienced population for golimumab compared with tocilizumab with a description of methods.

5. Provide data supporting the level and frequency of dosing of golimumab.
6. Provide any additional long-term outcomes data (HAQ improvement, Maintenance of ACR response) for the DMARD-experienced population.
7. Update on Patient Access Scheme (PAS).
8. Update on recently reported longer term safety data.

1. Radiographic outcomes data from GO-BEFORE (C0524T05) and GO-FORWARD (C0524T06) to support the recent Type II Variation to the SmPC for golimumab

A positive opinion was recently adopted, on 16 December 2010, by the Committee for Medicinal Products for Human Use (CHMP) recommending a variation to the terms of the marketing authorisation for golimumab in Rheumatoid Arthritis (RA). The CHMP adopted a new indication as follows:

"Simponi, in combination with methotrexate (MTX), is indicated for:
The treatment of severe, active and progressive rheumatoid arthritis in adult patients not previously treated with MTX.
Simponi has been shown to reduce the rate of progression of joint damage as measured by X-ray, when given in combination with methotrexate".

The extension of the indication to include the reduction in the rate of progression of structural damage is supported by 2-year radiographic data from the GO-BEFORE clinical study and 2-year data on maintenance of improvement in signs and symptoms of disease, physical function and health-related QoL. Comprehensive 2-year safety data supporting the continued positive benefit risk ratio of golimumab were also presented.

Information re: study and approach to measurement

Study outline

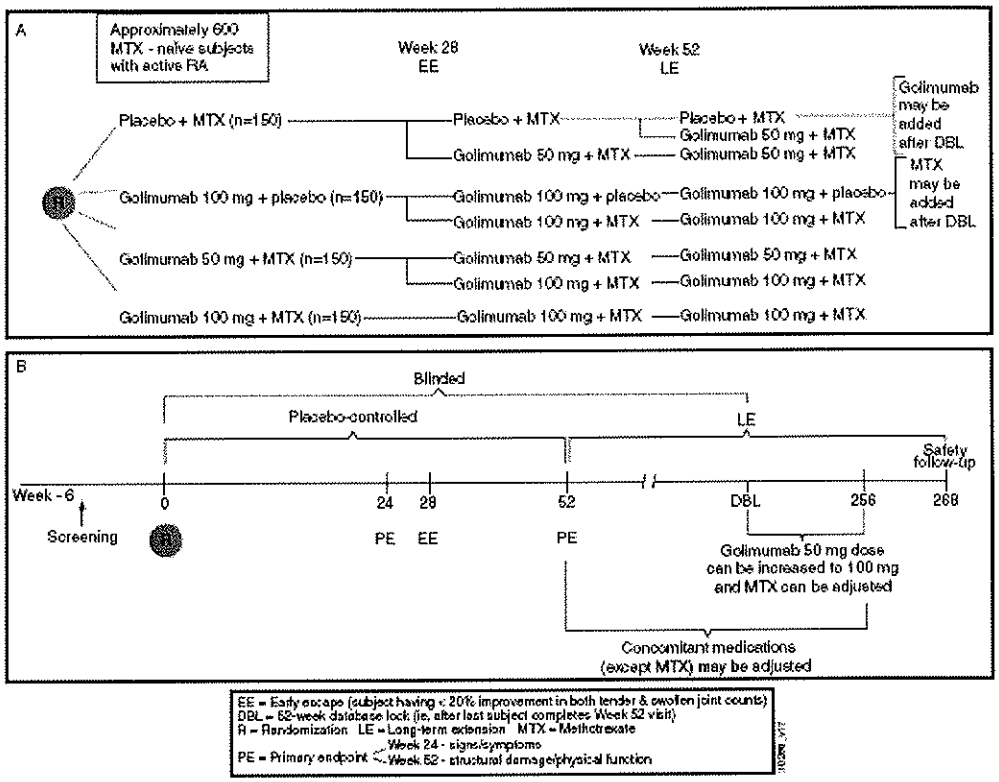
The GO-BEFORE study (C0524T05) is a 256 week, multi-centre, randomised, double-blind, placebo-controlled trial of golimumab in MTX naïve patients with active RA. The primary objectives were to assess the efficacy of golimumab in MTX naïve patients with active RA as measured by:

- Reduction of signs and symptoms at week 24
- Inhibition of progression of structural damage at week 52
- Long term efficacy and safety (unblinded) from week 52 through to week 256 (data up to week 104 included here)

Secondary objectives included assessment of the safety of golimumab, the effect of golimumab on physical function and health related quality of life.

The study schema is presented below in Figure 1. Radiographic data was collected through week 104.

Figure 1. Study schema for GO-BEFORE [Panel A shows study treatments; Panel B shows key time points during the study].



Approach to measurement of radiographic progression

The van der Heijde Modified Sharp score (vdH-S) (van der Heijde et al, 1992, van der Heijde et al, 2005), was used to evaluate reduction of rate of progression of structural damage in the GO-BEFORE study.

The vdH-S score is a validated radiographic measure of structural damage progression in RA widely accepted by regulatory authorities and leading academic and community rheumatologists.

The vdH-S score is the sum of joint erosion score and joint-space narrowing (JSN) score and ranges from 0-448.

Radiographic progression is defined as the change from baseline in total vdH-S score that is greater than the smallest detectable change (SDC). The SDC is defined as the amount of change from baseline for which any score smaller cannot be reliably distinguished from random error in measurement. (Bruynesteyn et al, 2005).

In addition to standard measures of structural damage progression and RA signs and symptoms, improvement in physical function was evaluated in GO-BEFORE. This was assessed with HAQ, and physical component summary (PCS) of SF-36, a validated self-reporting instrument used extensively in a variety of disorders including rheumatologic disorders (Bruce and Fries, 2003; Ware, 2000).

Week 52 Radiographic Analyses.

Efficacy was demonstrated in GO-BEFORE for golimumab + MTX compared with MTX alone in reducing the rate of progression of structural damage as measured by the change from baseline in the vdH-S score at Week 52 (golimumab 50 mg + MTX, $p = 0.015$; golimumab 100 mg + MTX, $p = 0.025$). Consistent treatment effect was observed across all sensitivity analyses performed and results were consistent across the subpopulations analysed in the study, including patients with longer duration of disease. This data is shown in table 1 below.

Table 1. Key Radiographic Data at Week 52 (GO-BEFORE)

	MTX	Golimumab 50 mg +MTX	p-value
Reduction in Rate of Progression of Structural Damage			
Mean change from baseline in vdH-S score			
All subjects at Week 52	1.37 ± 4.555	0.74 ± 5.233	0.015
Subjects at Week 52 with abnormal (>1.0mg/dL) CRP at baseline	2.16 ± 5.642	1.29 ± 6.991	0.010
All subjects (from baseline at Week 28)	1.11 ± 3.875	0.71 ± 3.771	0.065
All subjects (from Week 28 to Week 52)	0.26 ± 1.707	0.04 ± 2.615	0.034
Subjects with change in the total vdH-S score ≤ 0 at Week 52	76 (53.9%)	100 (71.4%)	0.003
Mean change from baseline in vdH-S erosion score (hands and feet)	0.74 ± 2.818	0.48 ± 2.079	0.344
Mean change from baseline in vdH-S JSN score (hands and feet)	0.58 ± 2.258	0.23 ± 1.992	0.044
Prevention of Structural Damage			
Subjects with no new erosions at Week 52 in the joints with 0 score at baseline[a]	76 (53.9%)	100 (71.4%)	0.003
Subjects with no new JSN at Week 52 in the joints with 0 score at baseline [a]	117 (83%)	126 (90%)	0.091

[a] Subjects with no new erosions in the joints with 0 score at baseline. Excludes subjects with a missing score at Week 52

The proportion of patients with no radiographic progression (change from baseline in vdH-S score ≤ 0) was substantial and statistically significant in the golimumab 50 mg + MTX group as compared to the placebo + MTX group.

Similar treatment effects for the golimumab + MTX groups were observed for prevention of joint damage as measured by erosion scores. At Week 52, the proportion of subjects with no newly eroded joints was statistically significantly greater in the golimumab 50 mg + MTX group (p = 0.003) than in the placebo + MTX group.

The radiographic effects observed at week 52 were maintained through week 104.

Two year radiographic data, as well as results from various sensitivity analyses was submitted to the CHMP. The CHMP's overall assessment was reported as *"continue to support a positive effect on progression of structural damage"*.

In summary, golimumab not only provided significant benefit in signs and symptoms of disease but also showed benefit in reducing the rate of progression of structural damage. The data supports the favourable benefit risk profile of golimumab 50 mg in combination with MTX for patients with moderate to severe RA.

GO-FORWARD Data

The effect of golimumab treatment on rate of progression of structural damage was also evaluated as a major secondary endpoint at Week 24 in GO-FORWARD (C0524T06) in patients who had active disease despite MTX therapy. There was minimal progression in structural damage in all treatment groups, including the placebo + MTX group, as indicated by the fact that most subjects had no change in vdH-S score at Week 24 and very few subjects progressed beyond the smallest detectable change threshold. There was also minimal progression in structural damage compared with the progression observed in other trials in a similar RA population treated with MTX (e.g. infliximab ATTRACT study; St Clair et al, 2002). Given the minimal radiographic progression in all treatment groups, it is difficult to evaluate the effect of golimumab + MTX on radiographic progression.

A number of factors may account for the minimal progression rates in GO-FORWARD, including the trial design and subject population. The rate of progression of structural damage as measured by the change in the vdH-S score was not a primary endpoint in GO-FORWARD and, therefore, the sample size determination was not based on the expected difference in x-ray progression between groups. In GO-FORWARD had 89 subjects in MTX + golimumab and 133 in MTX. The placebo-control period was short, with placebo subjects crossing over to golimumab at Week 24. This is supported by evidence from GO-BEFORE where most benefits with respect to radiographic progression were seen from weeks 24-52. Also, for subjects who early escaped at Week 16, radiographic imaging was performed at Week 16, reducing the time for progression of structural damage.

In addition, the baseline disease activity of subjects in GO-FORWARD was less severe compared with earlier infliximab trials, such as ATTRACT in MTX-experienced subjects.

At baseline, the number of tender and swollen joints and the level of inflammation as measured by the median level of CRP were lower than expected. Since activity of disease, including baseline CRP levels, is an important predictor of radiologic progress, it follows that rate of progression, as measured by change in vdH-S-scores, was minimal in the trial.

Golimumab has demonstrated treatment benefit on the signs and symptoms of disease in the MTX-failure RA population as demonstrated in GO-FORWARD both by the short-term control of inflammation and the long-term outcomes at Week 104. Given that control of disease activity is the best predictor of radiologic

response in patients with RA, the lack of separation in treatment arms in GO-FORWARD is likely a result of the low radiographic progression rate and aspects of the trial design, rather than lack of treatment effect.

These results from GO-FORWARD should not contradict the positive radiographic findings of GO-BEFORE, as the primary endpoint of GO-FORWARD was designed to demonstrate efficacy on signs and symptoms rather than radiographic benefit. Given the pathophysiology of RA and mechanism by which structural damage occurs, the GO-BEFORE data is relevant to all RA patient populations, including those for which Simponi is already approved.

Based on the above, the CHMP has adopted a positive opinion recommending the granting of a type II variation to the marketing authorisation for golimumab in combination with MTX for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients when the response to disease modifying anti rheumatic drug (DMARD) therapy including MTX has been inadequate. CHMP concluded that in GO-FORWARD there was no difference in terms of progression of structural joint damage between the group originally treated with placebo + MTX, compared with the approved golimumab 50 mg + MTX group. This could be due to the fact that all placebo + MTX patients crossed over golimumab + MTX treatment by week 16 /24. However, based on the results of GO-BEFORE which demonstrated that golimumab reduced the rate of progression of joint damage as measured by X-ray when given in combination with MTX, the CHMP adopted the claim that golimumab reduced the rate of progression for the broader RA population.

2. Incorporation of ACR 70 data in the economic model.

The ERG was concerned that the submitted model was not internally consistent and therefore the ICERs provided could not be considered valid.

The internal inconsistencies have now been addressed in terms of updated unit costs, anomalies in Markov sheets, and transition probabilities from the Mixed Treatment Comparison (MTC), as follows:

- All analyses presented here are based on a model which incorporated the updated unit costs requested by the ERG during the clarification process.
- Anomalies highlighted in the Markov sheets have now been amended, including those for etanercept (blank cells), infliximab (costs in the death state) and certolizumab (modelling of HAQ decrements). The baseline HAQ scores in the methotrexate (MTX) experienced population has also been amended and returned to 1.41.
- We agree that the model should be based upon the MTC, as per the base case. We have taken into account that those patients achieving a higher response were excluded twice in the formula used to calculate transition probabilities from the MTC. This has been corrected.
- The ERG commented that the rate of HAQ progression on palliative care of 0.09 per year was inconsistent with the rate of 0.06 assumed in the TA130 appraisal. We have revised the base case to account for this and all of the following results are based on a HAQ progression on palliative care of 0.06. (For completeness we have also attached the corresponding results using the original HAQ progression on palliative care of 0.09 in Appendix 1).

The ERG had raised concerns around the selection of data for the MTC and the meta-analysis. For the MTC, the random effects model has been selected. The ACR70 data included in the updated modelling is derived from an MTC which includes the TEMPO trial. These results are now consistent with those which have been included for ACR20 and ACR50. (The MTC is presented in appendix 2 of this report)[1].

These corrected results are presented in table 2 below.

Table 2 – Results based on the MTC

Technologies	Total Costs (£)	Total QALYs	ICER (£) versus baseline (Methotrexate)
Methotrexate	38,320	6.144	-
Etanercept	78,871	7.637	27,157
Golimumab	72,325	7.404	26,996
Infliximab	66,112	7.220	25,825
Adalimumab	70,699	7.413	25,523
Certolizumab	76,641	7.890	21,944

In response to the ACD, all additional analyses were inadvertently derived from a model using a meta-analysis as opposed to the MTC. For transparency and completeness, a corrected version of the base case utilising the meta-analysis has been provided in appendix 3.

As well as the 52 week radiographic data, 2 year data reporting maintenance of improvement in signs and symptoms of disease, physical function, and health-

[1] The MTC submitted in response to a clarification question from the ERG earlier in the submission process was a version that excluded the TEMPO study that was not used in our submission.

related QOL were also submitted in support of the type II variation to the SmPC for golimumab.

3. SF-36 Data

In the GO-FORWARD study health related quality of life data, as measured by the SF-36, was collected at baseline, Weeks 14, 24, 52 and 104. The results presented below, alongside the 24 week data presented to the committee in response to ACD1, provide strong supportive evidence for the long-term efficacy of golimumab 50 mg (Table 3). The improvement in the placebo + MTX arm from Week 52 onwards is consistent with the cross-over of patients to golimumab at Week 24.

Table 3 – Summary change from baseline in SF-36 physical and mental component summary scores Weeks 14 through 104

	Placebo + MTX[a]		Golimumab 50mg + MTX	
	Physical component summary	Mental component summary	Physical component summary	Mental component summary
Week 14				
n	127	127	85	85
Mean ± SD	2.39 ± 7.798	1.63 ± 9.806	8.02 ± 7.170	1.60 ± 11.004
Week 24				
n	125	125	88	88
Mean ± SD	2.54 ± 8.055	0.75 ± 9.676	8.28 ± 8.327	1.83 ± 10.867
Week 52[b]				
n	80	80	70	70
Mean ± SD	8.44 ± 10.418	5.08 ± 10.323	8.89 ± 9.046	3.71 ± 9.365
Week 104[c]				
n	74	74	48	48
Mean ± SD	7.14 ± 10.741	5.46 ± 9.843	10.99 ± 10.129	4.03 ± 9.706

[a]This group includes subjects randomised to placebo + MTX who early escaped/crossed over to 50mg + MTX through the last visit on 50mg + MTX.

[b]Subjects in this group did not discontinue SC study agent prior to Week 24 and did not meet the early escape criteria at Week 16.

[c]By assigned treatment group as of week 52.

One way sensitivity analysis (OWSA) of SF-36 data

The SF-36 results have been updated and a one way sensitivity analysis provided.

SF-36 data from the GO-FORWARD trial has been mapped to SF-6D using the Sheffield algorithm. SF-36 data was not collected in the GO-AFTER study and so ACR70 utilities are assumed equal to the ACR50 utility values. MTX values were estimated by applying the ratio of HAQ scores from the golimumab HAQ scores.

The ERG highlighted that ACR state and utility do not move in the same direction. This is a result of the observed HAQ data from the golimumab trial, as in this trial for the golimumab arm baseline patients had higher HAQ values than the Week 24 non-responders, while in the placebo arm the Week 24 non-responders had higher HAQ values than those at baseline. When the HAQ scores were translated into SF-6D this created the differing directions of ACR response and utility observed by the ERG.

However, this does not invalidate the results and the SF-6D data still acts to fulfil its role as a sensitivity analysis to provide further evidence for the efficacy and cost-effectiveness of golimumab. The ERG is also satisfied that we have provided conclusive evidence that golimumab + MTX has a significant impact on the physical component of health related quality of life for patients for a DMARD-experienced population.

The ERG also commented that a normal distribution for utilities can result in probabilistic sensitivity analysis (PSA) draws of greater than 1. The model has been updated to limit PSA draws that they cannot sample above 1.

A version of the model using a beta distribution has also been uploaded. By comparing the results of these two models it can be seen that the PSA is not materially affected by the choice of utility distribution.

ICERs were derived from the Sheffield algorithm SF-6D mapped estimates and are shown in table 4 (as stated above, these are based on MTC):

Table 4 – ICERs derived from Sheffield algorithm SF-6D mapped estimates*

Technologies	Total Costs (£)	Total QALYs	ICER (£) versus baseline (Methotrexate)
Methotrexate	36,647	6.439	-
Golimumab	70,652	7.554	31,046
Etanercept	77,198	7.769	30,036
Adalimumab	69,026	7.502	30,893
Infliximab	64,439	7.401	29,484
Certolizumab	74,968	7.856	27,413

* Results are presented in tabular format, however this should not be used for ranking, as all technologies have utilities based on the ratio of HAQ scores derived from the SF-36 values collected in the golimumab trial.

4. Presentation of data for anti-TNF experienced patient population.

To provide clarity on the anti-TNF experienced patient population data, the model presented has been updated with a number of applied changes which have been included as one way sensitivity analyses. For comparison the results are presented in table 5 below with all assumptions equal to base case with the HAQ progression in palliative care updated to 0.06. Changes are applied individually in one way sensitivity analyses in subsequent tables.

When adding tocilizumab into the model as a comparator it was necessary to make certain assumptions when deriving a unit cost for this drug.

- The SPC states that tocilizumab should be provided intravenously (IV) at a dose of 8 mg for every kilogram the patient weighs once every four weeks. Patient weight was assumed to be 73 kg when costing infliximab in the MTX experienced population, and for consistency, the same weight of 73 kg was assumed when costing tocilizumab in this population.
- A dosage of 8 mg per kg for a 73 kg patient requires 584 mg of tocilizumab, which can be provided from vials of 400 mg, 200 mg, or 80 mg. Assuming least possible wastage (although some is necessary), each 584 mg treatment with tocilizumab would require one 400 mg vial and one 200 mg vial at a total cost of £768.00.
- The SPC states that tocilizumab should be administered every four weeks. This has also been accounted for, resulting in 7 doses in the first 6 month treatment period and then an average of 6.5 doses per subsequent 6 month period. Final assumptions around costing focus on the levels of monitoring required post 6 months, where the amounts required have again been kept consistent with infliximab as another IV agent.

As per the comments of the ERG, abatacept has also been included as a comparator. Abatacept is also administered by intravenous infusion and as such similar assumptions to those required for tocilizumab were needed.

- Patient weight and monitoring post 6 months have been kept consistent with those of tocilizumab and infliximab (as similar IV agents). This being the case, a patient weight between 60 kgs and 100 kgs (73 kgs) was assumed, meaning that, as per the SPC, the relevant dosage would be 750 mg requiring 3 vials of abatacept at a total cost of £726.51.

- The SPC states that abatacept should be administered in weeks 2 and 4 and then every four weeks, this has also been incorporated, resulting in 7 doses in the first 6 month treatment period and then an average of 6.5 doses per 6 month period.

Both tocilizumab and abatacept have been included with a HAQ progression equal to that of anti TNF agents so as to allow a valid comparison.

The following analysis of the TNF-α experienced population has been undertaken using indirect comparison as there is only 1 trial available per technology and only a small number of technologies are being evaluated.

Table 5 – Results from TNF experienced population per base case

Technologies	Total Costs (£)	Total QALYs	ICER (£) versus baseline (Methotrexate)
Methotrexate	37,134	3.849	-
Rituximab	53,530	4.126	59,238
Abatacept	64,836	4.632	35,382
Tocilizumab	66,070	4.669	35,288
Golimumab	53,519	4.361	32,036

To compare to these base case results, the following section includes a number of OWSAs as requested by the ERG.

Table 6 – OWSA showing rituximab HAQ progression score of 0

Technologies	Total Costs (£)	Total QALYs	ICER (£) versus baseline (Methotrexate)
Methotrexate	37,134	3.849	-
Abatacept	64,836	4.632	35,382
Tocilizumab	66,070	4.669	35,288
Golimumab	53,519	4.361	32,036
Rituximab	53,530	4.514	24,683

Table 7 – OWSA showing rituximab re-administration every 9 months

Technologies	Total Costs (£)	Total QALYs	ICER (£) versus baseline (Methotrexate)
Methotrexate	37,134	3.849	-
Abatacept	64,836	4.632	35,382
Tocilizumab	66,070	4.669	35,288
Golimumab	53,519	4.361	32,036
Rituximab	44,897	4.126	28,047

5. Dose Selection / Frequency

The selected doses and dosage regimens for the Phase III studies in RA, PsA, and AS were golimumab 50 mg and 100 mg subcutaneously (SC) every 4 weeks. These doses were chosen based on the results of non-clinical studies, a phase II dose-ranging study of golimumab in subjects with RA, as well as clinical experience with infliximab.

The phase II RA dose-finding study with golimumab demonstrated clinical efficacy in each of the 4 dose groups (fixed doses of 50 mg and 100 mg, administered SC once fortnightly or once every 4 weeks with MTX). The group

receiving the lowest dosage regimen (golimumab 50 mg every 4 weeks) had ACR 20, ACR 50, and ACR 70 responses that were similar to the responses associated with the 3 higher dose regimens, and no clear dose-response relationship was shown between the four doses.

Furthermore, golimumab 50 mg every 4 weeks suppressed CRP levels to a degree similar to that observed with infliximab maintenance therapy at 3 mg/kg IV infusion 8 weekly, which is both the lowest approved infliximab dose and considered the minimum effective dosage regimen of infliximab in patients with RA.

Thus, these data suggest that golimumab 50 mg every 4 weeks represents the minimum effective dose shown to suppress the inflammatory effects of TNFα. Lower doses would not be expected to provide adequate suppression of CRP levels and would likely result in inferior symptomatic and radiologic outcomes. Higher doses or a shorter frequency did not demonstrate enhanced efficacy in either the Phase IIB studies or in the Phase III studies in RA or PsA therefore the recommended dose is 50 mg once monthly.

In both GO-FORWARD and GO-BEFORE, golimumab 50 mg demonstrated efficacy on multiple clinical endpoints. In each study, the magnitude of treatment effect between the golimumab 50 mg or 100 mg was similar supporting that 50mg is the minimally effective dose for RA.

The dosing recommendation for RA is golimumab 50 mg given as an SC injection monthly (on the same date each month) with MTX, with self-administration as an available option.

6. Maintenance of ACR and HAQ Response in GO-FORWARD

The proportion of golimumab + MTX treated subjects who achieved ACR 20, ACR 50, and ACR 70 responses after Week 52 through Week 104 within each treatment group was generally maintained.

Table 8 – Summary of ACR response Weeks 14 through 104

	Placebo + MTX[a]	Golimumab 50mg+ MTX
Week 14		
n	133	89
ACR 20	44 (33.1%)	49 (55.1%)
ACR 50	13 (9.8%)	31 (34.8%)
ACR 70	5 (3.8%)	12 (13.5%)
Week 24		
n	133	89
ACR 20	37 (27.8%)	53 (59.6%)
ACR 50	18 (13.5%)	33 (37.1%)
ACR 70	7 (5.3%)	18 (20.2%)
Week 52		
n[b]	81	70
ACR 20	58 (71.6%)	58 (82.9%)
ACR 50	37 (45.7%)	40 (57.1%)
ACR 70	20 (24.7%)	22 (31.4%)
Week 104		
n[c]	116	69
ACR 20	50 (67.6%)	40 (83.3%)
ACR 50	30 (40.0%)	33 (68.8%)
ACR 70	21 (28.0%)	24 (50.0%)

[a]This group includes subjects randomised to placebo + MTX who early escaped/crossed over to 50mg + MTX through the last visit on 50mg + MTX.

[b]Subjects in this group did not discontinue SC study agent prior to Week 24 and did not meet the early escape criteria at Week 16.

[c]By assigned treatment group as of week 52.

Table 9 – Summary of the number of subjects who maintained a >= 0.25 improvement in HAQ score from baseline at Weeks 24 through 104

For subjects who achieved at least 0.25 improvement in HAQ score from baseline at Week 24, approximately 87% to 92% of subjects across all treatment groups maintained that improvement at Week 104.

	Placebo + MTX[a]	Golimumab 50mg
Week 24		
n	127	88
HAQ responders	49 (38.6%)	60 (68.2%)
Week 52		
n[b]	81	69
HAQ responders	55 (67.9%)	53 (76.8%)
Week 104		
n[c]	49	60
HAQ responders	43 (91.5%)	52 (86.7%)

[a]This group includes subjects randomised to placebo + MTX who early escaped/crossed over to 50mg + MTX through the last visit on 50mg + MTX.

[b]Subjects in this group did not discontinue SC study agent prior to Week 24 and did not meet the early escape criteria at Week 16.

[c]By assigned treatment group as of week 52.

7. Update on PAS

The PASLU committee met to discuss our PAS for golimumab on 26th January 2011. The final advice document is now being compiled by PASLU and will be sent to us for a final check on 8th February 2011.

8. Safety Data

We have provided data in appendix 5 from an integrated safety summary of all phase III studies of golimumab in patients with RA, PsA and AS. We have also provided rates of discontinuation from study drug related to AEs (appendix 6).

Summary

In summary, MSD is confident that the modelling results within this document address all of the concerns raised by the ERG and the committee.

The radiographic progression data and clinical data such as ACR, HAQ and SF-36 data support the long term efficacy of golimumab in the treatment of patients with rheumatoid arthritis.

The dosing recommendation within the Marketing Authorisation, for the indication of RA is golimumab 50 mg given as an SC injection *monthly* (on the same date each month), with MTX, with self-administration as an available option.

Evidence has been provided, based on the 24, 52 and 104-week data presented in this document, which demonstrates robust efficacy for golimumab 50 mg given once monthly for clinical, functional and radiological arthritis-related endpoints over an extended treatment period through 2 years. These data were submitted for review by EMA as part of a type II variation to the Marketing Authorisation which has received positive CHMP opinion.

Significant treatment benefit was observed across all arthritis efficacy endpoints, including individual components of ACR response. Substantial treatment benefits for golimumab as related to inhibition of structural damage progression maintained through week 104. Golimumab 50 mg also resulted in significant and clinically meaningful improvements in physical function as measured by HAQ and the SF-36 PCS scores.

Should you have any questions regarding the evidence provided here, or require additional information, please do not hesitate to contact me.

Yours Sincerely,

MSD Ltd

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