Executive Summary

Background

With nearly 400,000 patients affected by Rheumatoid Arthritis (RA) within England and Wales, early initiation of therapy with biologic disease-modifying antirheumatic drugs (biologic DMARDs), including tumour necrosis factor α (TNFα) inhibitors is a critical component in the pharmacological management of this chronic, debilitating condition. Clinical evidence suggests that patients with RA respond variably to biologic DMARDs with up to 70% responding within 6 months. Patients with RA will benefit from proven treatment options which address the challenges throughout the treatment pathway in DMARD experienced and biologic DMARD experienced patient populations.

In the last 10 years, the emergence of TNFα inhibitors and more recently the increase in choice of biologic DMARDs have had a considerable effect on the treatment of RA. There is agreement between patient representatives, the BSR, and manufacturers that the positive recommendations from the National Institute for Health and Clinical Excellence (NICE) and the Scottish Medicines Consortium (SMC) have helped to change thousands of lives for the better.

The British Society of Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) published guidelines on the eligibility criteria for the first biologic therapy in 2010. This was the first major update since the first guidelines were produced a decade before in 2000. In these guidelines, the BSR collate and summarise a large quantity of studies to inform their recommendations; namely a reduction in the Disease Activity Score (DAS28 - a measure of the activity of the disease in patients with RA based on 28 defined joints) threshold for initiation of a biologic DMARD from 5.1 to 3.2, citing the following points as drivers for this change in clinical practice:

1. The NICE RA Management Guidelines recommend intensive use of combinations of conventional DMARDs and steroids in early active disease. A DAS28 of 5.1 is too high to identify those patients who are not showing a satisfactory response to such regimens;
2. Patients with persistent DAS28 levels of between 3.2 and 5.1 have outcomes that are not dissimilar to those with persistent levels >5.1;

3. Patients with a DAS <5.1 have a disease activity response to TNFα inhibitor therapies that is as good as, if not better than, patients with a DAS28 >5.1; and
4. An analysis of BSR Biologics Registry (BSRBR) data suggests that patients treated with a DAS28 <5.1 have just as good an improvement in HAQ as those with a DAS28 >5.1, suggesting that this is a cost-effective use of TNFα inhibitor

MSD believes that these guidelines are fully in line with the available evidence and therefore supports their recommendations. We believe a lowering of the DAS28 threshold is an opportunity for thousands more patients to benefit from earlier and more effective treatment. The health economic modelling results support the BSR's conclusion that treating patients with a DAS28 of 3.2 with a TNFα inhibitor is as cost-effective as treating those with a higher DAS28 of 5.1.

The BSR analyses suggest that a reduction in the DAS28 threshold would result in an increased uptake of biologic DMARDs to between 8% and 12% of patients if UK clinical practice aligns to European standards. However, the level of biologic DMARD use could actually decrease by following NICE RA Management guidelines and treating active disease with combinations of conventional DMARDS and steroids closer to symptom onset.

Together with the backing of NICE guidance the BSR and BHPR guidelines could significantly change clinical practice in the UK, opening access to earlier treatment for patients with RA. The economic and clinical case has been made for the lowering of the DAS28 threshold; MSD would request NICE to reflect that in its guidance.

MSD has submitted clinical and cost-effectiveness evidence for the first once-monthly TNFα inhibitor, golimumab (Simponi®) to inform the appraisal of golimumab for the treatment of RA after failure of previous disease-modifying antirheumatic drugs (DMARDs) within the context of this MTA review, which is considering extending the eligible population to those with moderate disease.

Golimumab is the first TNFα inhibitor with randomised, controlled evidence to support a significant clinical response and well tolerated safety profile in DMARD naïve and

DMARD experienced, as well as biologic DMARD experienced patients. Golimumab has been found to have comparable efficacy and safety to the existing biologic DMARDs.

With comparable acquisition costs across the biologic DMARD class, the evidence supports golimumab being a cost-effective treatment alternative within the NICE willingness to accept threshold. The incremental cost effectiveness ratio (ICER) of golimumab compared to previous standard care is similar to ICERs of other biologics which are currently recommended for treatment by NICE.

RA is the most common inflammatory arthritis in England and Wales associated with severe disability, premature mortality and considerable economic implications; total costs of RA in the United Kingdom (UK) are estimated to exceed £1 billion per annum.

In the treatment of RA after failure of two DMARDs (including methotrexate, (MTX)), the National Institute for Health and Clinical Excellence (NICE) has recommended the use of the biologic DMARDs certolizumab (TA186), adalimumab, etanercept, and infliximab (TA130), golimumab (TA225), and tocilizumab (TA247). NICE has also reviewed abatacept for the treatment of RA after the failure of two DMARDs, however NICE did not recommend the use of abatacept for this indication. A rapid review of abatacept is on-going at present.

Randomised controlled trial (RCT) evidence strongly supports a robust clinical and safety profile for golimumab, which improves the signs and symptoms of RA, slowing progression of joint damage and improving physical function.

The Technology

The key features of golimumab are presented in Table 1 as follows:

Table 1: Key Features of Golimumab

Approved name	Golimumab
Brand name	Simponi®
Marketing status	European Commission granted marketing authorisation valid throughout the European Union on 1 October 2009
Pharmacological action	Human immunoglobulin G1κ (IgG1κ) monoclonal antibody produced by murine hybridoma cell line with recombinant deoxyribonucleic acid (DNA) technology. Binds with high affinity

	and specificity to both soluble and transmembrane forms of TNFα, neutralizing the biological activity of TNFα
Formulation	One 0.5 ml pre-filled pen/syringe contains 50 mg golimumab (injected subcutaneously (SC))
Dosing frequency	50 mg given once a month, on the same date each month. No loading dose
Average length of a course of treatment	In accordance with NICE Guidelines, treatment should continue as long as an adequate response (an improvement of ≥1.2 in disease activity score (DAS)) is maintained. Available data suggest that clinical response is usually achieved within 12 to 14 weeks of treatment with golimumab (after 3-4 doses). Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit within this time period
Average interval between courses of treatments	Continuous treatment for at least 12 weeks and then until no response or loss of response

Indications	*Rheumatoid Arthritis (RA):*
	• Golimumab, in combination with methotrexate (MTX), is indicated for:
	  ○ the treatment of moderate to severe, active rheumatoid arthritis in adults when the response to disease-modifying antirheumatic drug (DMARD) therapy including MTX has been inadequate
	  ○ the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with MTX
	• Simponi, in combination with MTX, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function
	Psoriatic arthritis (PsA):
	• Golimumab, alone or in combination with MTX, is indicated for the treatment of active and progressive PsA in adult patients when the response to previous DMARD therapy has been inadequate
	Ankylosing spondylitis (AS):
	• Golimumab is indicated for the treatment of severe, active AS in adult patients who have responded inadequately to conventional therapy

Randomised trials have shown abatacept, adalimumab, certolizumab, etanercept, infliximab, tocilizumab, and golimumab to be effective in the treatment of RA. The advantages that golimumab provides over the other existing treatment options are:

- Golimumab is delivered in a L-histidine buffer (compared to citrate-buffered solution of other biologic DMARDs) and has low injection volume of 0.5 ml thus leading to low incidence of injection-site reactions (ISRs)
- Golimumab's once monthly dosing (12 injections per year) reduces injection frequency in comparison to other SC agents. Injection frequency with etanercept is 52 or 104 injections per year (either once weekly or twice weekly dosing), with adalimumab 26 injections per year, and with abatacept 52 injections per year

Clinical Effectiveness

The safety and efficacy of golimumab has been robustly assessed with two large, randomised, controlled trials.

GO-FORWARD

GO-FORWARD demonstrated that treatment of patients with active RA (despite MTX therapy) with golimumab 50 mg significantly reduced the signs and symptoms of RA and improved physical function.

All primary endpoints were achieved within GO-FORWARD; golimumab 50 mg demonstrated significant benefit in achieving an American College of Rheumatology (ACR)20 response at week 14 (55.1% vs. 33.1%; p=0.001) and median change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) at week 24 (-0.38 vs. -0.13%; p<0.001) compared to placebo.

Long-term data from GO-FORWARD found golimumab 50 mg to be clinically effective over year one with ACR20, ACR50, and ACR70 response rates of 64.0%, 43.8%, and 24.7%, respectively. Patients with active RA despite MTX therapy continued to benefit from treatment with golimumab 50 mg; 90.6% of those patients achieving ACR20 response at week 24 maintained the response at week 52. 61.4% showed DAS28 remission (≤2.6) at week 52 with 36.8% achieving sustained DAS28 remission.

Golimumab 50 mg is generally well-tolerated in combination with MTX with serious adverse events (5.6% vs. 2.3%) and serious infections (2.2% vs. 0.8%) comparable to placebo through week 16. Golimumab 50 mg has a low incidence of ISRs and the majority of those ISRs were mild or moderate, with no serious ISRs.

GO-BEFORE

GO-BEFORE demonstrated that treatment with golimumab 50 mg of patients with active RA who were naïve to MTX therapy, significantly reduced the signs and symptoms of RA and improved physical function.

Using the pre-specified ITT analysis, one primary end point, *i.e.,* an ACR50 response at week 24 in the combined group versus group one(122 [38.4%] of 318 patients and 47 [29.4%] of 160 patients, respectively; P = 0.053), was not met, however results of a post hoc modified ITT analysis of the primary end point resulted in a statistically significant difference between the golimumab group versus placebo (122 [38.5%] of 317 patients and 47 [29.4%] of 160 patients, respectively; P = 0.049). In this modified ITT analysis, ACR50 in patients treated with golimumab 50 mg was statistically superior to that in patients on placebo [P = 0.038].

The co-primary endpoint of change from baseline in total vdH-S score at Week 52 was met. The change from baseline in total vdH-S score for subjects in the combined golimumab + MTX group was statistically significantly less (p = 0.006) compared with the placebo + MTX group. In addition, the change from baseline in total vdH-S score for subjects in both the golimumab 50 mg + MTX was also statistically significantly less (p = 0.015) than the placebo + MTX group.

Cost-Effectiveness

Systematic literature reviews and meta-analyses informed a Markov model which found golimumab 50 mg to be a cost-effective treatment option for patients who demonstrate an inadequate response to DMARDs.

Table 2 presents the basecase results for all comparators within a DMARD experienced RA patient population.

Table 2: Basecase Cost-Effectiveness Results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus Baseline (MTX)	Incremental analysis
Methotrexate	£56,382	6.706	-	-	-	-
Infliximab	£88,326	8.207	£31,944	1.501	£21,278	£21,278
Etanercept	£91,025	8.068	£2,699	-0.139	£25,429	Dominated
Golimumab	£92,130	8.307	£1,105	0.238	£22,331	£4,631
Adalimumab	£93,892	8.512	£1,762	0.205	£20,769	£8,589
Certolizumab	£97,469	8.890	£3,577	0.377	£18,817	£9,476
Tocilizumab	£100,702	8.495	£3,233	-0.395	£24,774	Dominated
Abatacept IV	£105,102	8.100	£4,400	-0.395	£34,953	Dominated
Abatacept SC	£118,036	8.100	£12,934	0.000	£44,232	Dominated

The results indicate that golimumab is a cost-effective treatment alternative compared to standard care. The severe patient subgroup has been displayed in Table 3 below. The similarity between the results for the severe subgroup and the overall moderate to severe population supports the use of golimumab in a population with moderate disease (DAS28 ≥3.2), from an economic perspective.

Table 3: Severe Patient Subgroup Results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus Baseline (MTX)	Incremental analysis
Methotrexate	£56,036	6.425	-	-	-	-
Golimumab	£89,270	8.007	£33,234	1.582	£21,013	N/A

Conclusion

Robust clinical and adverse event (AE) RCT evidence supports the conclusion that patients would substantially benefit from an on-going recommendation of golimumab for the treatment of moderate to severe RA. Indirect comparisons found golimumab to be superior to the previous standard of care and there were no statistically significant differences in efficacy or adverse events to other biologic DMARDs.

As the ICER for golimumab falls under a £30,000 threshold, golimumab can be considered a cost-effective treatment option for patients with moderate to severe RA.

Golimumab is a clinically and cost-effective treatment in first line biologic treatment of rheumatoid arthritis.

Additional Considerations

Ranking by ICER

Attempts have been made in the past to 'rank' technologies where there are multiple drugs with similar efficacy that generate marginally different ICERs when modeled. Given that the data informing the network analyses is from trials of different populations at different times and in different locations this should be regarded as incorrect. At best we believe that the results from such analyses (classically with overlapping credible intervals in all or most endpoints) can support a class effect, as is the case with the network analysis used for this submission.

Abatacept

Neither formulation of abatacept can be considered a cost-effective treatment option based upon the information available to MSD (the calculated ICER in the MSD model using the list price is £34,953 for abatacept IV and £44,232 for abatacept SC). However, there is a Commercial in Confidence Patient Access Scheme (PAS) in place for abatacept, reported on the NICE website as being in the form of a simple discount and it would be reasonable to assume that the scheme would bring abatacept into line with one or more of the other biologic treatments already approved by NICE.

We have undertaken an exploratory analysis using our model to estimate the level of

discount which would be required to provide comparable cost-effectiveness for this product. In the absence of the exact discount, a 'goal seek' analysis was undertaken in the excel model to calculate the change in unit price required to achieve the median of the range of acceptable ICERs resulting from the model for other technologies (ICERS < £30,000 per QALY). For the IV formulation, a discount of 36.42% would be required to achieve comparable cost-effectiveness.

Further, if this discount on the IV formulation is carried through into the analysis for the SC formulation (for the IV loading dose only), a discount of 45.13% on the SC list price would be required achieve comparable cost-effectiveness.