# EXECUTIVE SUMMARY

## Introduction

Clinical evidence suggests that Rheumatoid Arthritis (RA) patients benefit from treatment with tumour necrosis factor-α (TNFα) inhibitors, with up to 70% responding within 6 months. However, this presents the corollary that a significant minority of patients do not achieve low disease activity or clinical remission within this timeframe. Evidence now shows that a significant proportion of patients exposed to a first TNFα inhibitor will respond to subsequent treatment with a second. It therefore follows that many patients would benefit from the option of receiving TNFα inhibitors sequentially.

Schering-Plough Ltd has submitted new clinical and cost-effectiveness evidence for infliximab and other biologic disease-modifying anti-rheumatic drugs (DMARDs) to inform the appraisal of adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNFα inhibitor.

Moreover, Schering-Plough has submitted new evidence regarding the practice of vial optimisation. Market research suggests that 63% of patients receive infliximab which has been prepared using vial optimisation, demonstrating significant real-world uptake of a practice which reduces wastage and thereby increases cost-effectiveness.

In a TNFα inhibitor-experienced patient population, infliximab has been found to be the most cost-effective TNFα inhibitor in a number of treatment sequence scenarios (biologic versus non-biologic DMARDs; biologic + rituximab versus non-biologic DMARDs; and biologic + rituxumab versus rituximab).

## Background

RA is the most common inflammatory arthritis in England and Wales impacting the lives of nearly 400,000 people. RA is a chronic, debilitating condition associated with severe disability, premature mortality and considerable economic implications: total costs of RA in the UK are estimated to exceed £1 billion per annum.

In the treatment of RA, the National Institute for Health and Clinical Excellence (NICE) has recommended the use of the TNFα inhibitors adalimumab, etanercept and infliximab (TA130) and issued restricted and negative guidance for the remaining biologics, rituximab (TA126) and abatacept (TA141), respectively. However, these resulting guidances have not fully addressed the use of biologic DMARDs for RA patients who have had an inadequate response to a TNFα inhibitor.

As the first TNFα inhibitor to receive market authorisation, infliximab is a well-established RA treatment in the UK, administered to nearly 11% of the eligible patient population who have previously failed two non-biologic DMARDs. With an estimated 1,136,000 patients exposed to infliximab worldwide by August 2008 and an estimated cumulative exposure of 4.29 million person-years since first exposure, infliximab is the first TNFα inhibitor to receive MHRA authorisation for the removal of the Black Triangle symbol, indicating a well-established benefit:risk profile.

## Clinical Effectiveness of Infliximab

The clinical evidence base for the sequential use of TNF$\alpha$ inhibitors is continually expanding with several studies reporting findings of similar response with the treatment of a first versus a second biologic:

- Bombardieri et al (2007) reported a 70% ACR20 response rate at week twelve versus 60%; a 0.55 mean HAQ reduction versus 0.48.
- Kristensen et al (2006) reported a 62% ACR20 response rate at month six versus 52%.
- Hjardem (2007) reported 61% of patients switching from one TNF$\alpha$ inhibitor to a second achieved a EULAR good or moderate response.

The safety and efficacy of infliximab after an inadequate response to a non-biologic DMARD have been confirmed in the randomised controlled trials ASPIRE and ATTRACT. Similar evidence is availabe for other TNF$\alpha$ inhibitors. However, evidence in the form of an RCT for the sequential use of TNF$\alpha$ inhibitors had not been available until the completion of GO-AFTER – a prospective, randomised, double-blind, placebo-controlled phase III trial designed to evaluate the efficacy and safety of a TNF$\alpha$ inhibitor, golimumab, in patients with active RA who had previously received and discontinued at least one TNF$\alpha$ inhibitor.

While GO-AFTER evaluates golimumab, which will not be assessed by this appraisal, GO-AFTER provides important new evidence and is relevant to this appraisal for the following reasons:

1. GO-AFTER is the a prospective, randomised, double-blind, placebo-controlled phase III trial which investigates the sequential use of TNF$\alpha$ inhibitors in RA patients.
2. GO-AFTER provides a level of evidence previously unavailable in this area.
3. Network meta-analysis shows that while there are differences between the various TNF$\alpha$ inhibitors, their efficacy is sufficiently similar for the results of GO-AFTER to be considered highly relevant.
4. The existence and consideration of GO-AFTER specifically answers one of the primary weaknesses highlighted in TA130, with regard to sequential use of TNF$\alpha$ inhibitors.

In GO-AFTER, of the patients randomised in the placebo group (n=155) and the 50mg golimumab group (n=153), significantly more patients achieved the primary endpoint of ACR20 at week 14 in the treatment group than the placebo group (35.3% vs 18.1%; $p<0.001$).

Moreover, among the subgroup of patients who discontinued one or more prior TNF$\alpha$ inhibitors due to a lack of efficacy, significantly more subjects achieved an ACR20 response in the golimumab 50mg group than the placebo group (35.7% vs 17.7%; $p=0.006$).

In addition, significantly more patients achieved the secondary endpoints of ACR 50 & 70 at week 14 and ACR 20, 50 & 70 at week 24 in the golimumab 50mg group than the placebo group. At week 24, significantly more patients in the 50mg golimumab group had a clinically important reduction in HAQ-DI than in the placebo group (50% vs 34%, $p=0.0044$).

## Cost Effectiveness of Infliximab

A patient simulation model was built to determine the cost-effective treatment options for patients who have received at least one previous TNF$\alpha$ inhibitor. A total of nine treatment sequences were modeled comprising of:

- *one biologic followed by non-biologic DMARDs;*
- *two biologics (including a TNFα inhibitor) followed by non-biologic DMARDs;*
- *non-biologic DMARDs.*

Results for the analysis are reported below in lifetime as incremental cost per quality-adjusted life year (QALY) gained.

For treatment sequences including one biologic followed by non-biologic DMARDs, infliximab was found to be the most cost-effective TNF$\alpha$ inhibitor (£28,661). The remaining biologics had the following lifetime incremental cost per QALYs gained: rituximab (£17,422-£27,161), adalimumab (£35,138), etanercept (£35,898) and abatacept (£44,795).

For treatment sequences including two biologics (including a TNF $\alpha$ inhibitor) followed by non-biologic DMARDs, a sequence including infliximab followed by rituximab was determined to be the most cost-effective TNF$\alpha$ inhibitor (£30,549-£33,274) ahead of adalimumab + rituximab (£39,084-£41,747) and etanercept + rituximab (£39,673-£42,477).

One-way sensitivity analysis indicated that dosing frequency of rituximab and HAQ progression whilst on treatment were important determinants of the resultant incremental cost effectiveness ratios (ICERs). Specifically for infliximab, patients' weight and vial optimisation also significantly affected the ICERs.

## Discussion

Data from GO-AFTER suggest that although *absolute* response may be worse in those patients receiving a second TNF$\alpha$ inhibitor, the *relative* response rates (compared to non-biologic DMARDs) measured on the odds ratio scale may be comparable or even better amongst those receiving a second TNF$\alpha$ inhibitor.

Switches due to lack of response have a lower absolute probability of response than those withdrawing due to intolerance. However, switches due to secondary failure (failure after initial response) may have a higher absolute probability of response than switches due to primary failure (no initial response).

Whilst infliximab in the current analyses has been determined to be the most cost-effective TNF$\alpha$ inhibitor in an anti-TNF experienced population (versus non-biologic DMARDs and rituximab), infliximab may also be highlighted as the most suitable treatment for patients whom rituximab may not be appropriate (e.g. seronegative patients).

Evidence from a survey of rheumatology specialists makes clear that vial wastage can be avoided reasonably easily in hospitals where large numbers of patients are treated. Vial optimisation can make infliximab a more cost-effective option in the treatment of rheumatoid arthritis patients.

## Conclusion

The identified literature and corresponding analyses support the conclusion that rheumatoid arthritis patients can achieve a good response to a different TNF$\alpha$ inhibitor having received an inadequate response to a previous TNF$\alpha$ inhibitor.

The network meta-analysis (NMA) found that biologic DMARDs represent an efficacious treatment option compared to conventional DMARDs. Furthermore, the NMA reported overlapping confidence intervals for all TNF$\alpha$ inhibitors thus suggesting that there is no statistically significant difference in the efficacy of adalimumab, infliximab and etanercept. In comparison to other biologics, the NMA found that none of the other biologics are superior to any of the TNF$\alpha$ inhibitors.

In an anti-TNF experienced patient population, infliximab was found to be the most cost-effective TNF$\alpha$ inhibitor, particularly where drug wastage can be minimised.

Infliximab is not only a clinical and cost-effective treatment in first line treatment of rheumatoid arthritis but is now shown to provide further benefit to English and W dsh patients when used sequentially.