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Golimumab for Treating Non-Radiographic Axial Spondyloarthritis: A Fast Track Appraisal

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Date completed	Date completed 16 August 2017

Source of funding: This report was commissioned by the NIHR HTA Programme as project number FTA - 15/148/07.

Declared competing interests of the authors

None of the authors have any conflicts of interest to declare.

Acknowledgements

We would like to thank Dr Paul Tappenden, Reader, ScHARR, for providing comments on the draft report and Gillian Rooney, Programme Manager, ScHARR, for providing administrative support and in preparing and formatting the report.

Rider on responsibility for report

This report was commissioned by the NIHR HTA Programme. The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Davis S, Stevens J, Martyn-St James M, Kaltenthaler E, Wong R, Kay,L. Golimumab for Treating Non-Radiographic Axial Spondyloarthritis: A Fast Track Appraisal. School of Health and Related Research (ScHARR), 2017.

Contributions of authors

Sarah Davis acted as project lead for this assessment and critiqued the cost-comparison. Marrissa Martyn-St James and Eva Kaltenthaler critiqued and summarised the clinical effectiveness data reported within the company's submission. John Stevens critiqued and summarised the company's network meta-analysis. Ruth Wong critiqued the company's search strategy. Lesley Kay provided clinical advice to the team. All authors were involved in drafting and commenting on the final report.

CONTENTS

LIST OF TABLES

ABBREVIATIONS AND ACRYONYMS

AE	Adverse event
AG	Assessment Group
AS	Ankylosing Spondilitis
ASDAS-C	Ankylosing Spondylitis Disease Activity Score using CRP level
ASAS	Assessment of SpondyloArthritis international Society
ASAS20	20% improvement in the ASAS score
ASAS40	40% improvement in the ASAS score
ASQoL	Ankylosing spondylitis quality of life
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Activity Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BNF	British National Formulary
CI	Confidence interval
CIC	Commercial in confidence
CRP	C-reactive protein
CrI	Credible interval
CS	Company's submission
CSR	Clinical Study Report
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQ-5D	EuroQol 5 Dimensions
ERG	Evidence Review Group
HAQ-DI	Health Assessment Questionnaire Disability Index
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
MRI	Magnetic resonance imaging

NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
nr-axSpA	Non-Radiographic Axial Spondyloarthritis
NSAIDs	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
OSI	Objective Signs of Inflammation
PAS	Patient Access Scheme
PrI	Prediction interval
QALY	Quality-adjusted life-year
RCT	Randomised controlled trial
SAE	Serious adverse event
SC	Subcutaneous injection
SD	Standard deviation
SE	Standard error
SF-36	36-item Short Form survey
SF-36 MCS	SF-36 Mental Component Score
SF-36 PCS	SF-36 Physical Component Score
SmPC	Summary of Product Characteristics
SpA	Spondyloarthritis
TA	Technology Appraisal
TNF-alpha	Tumour Necrosis Factor – alpha
VAS	Visual Analogue Scale

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The Evidence Review Group (ERG) considers the company's description of the underlying health problem in the company's submission (CS) to be appropriate and relevant to the decision problem set out in the final National Institute for Health and Care Excellence (NICE) scope.[1] The submission comprised Document A. FTA summary for committee, Document B. FTA – cost-comparison[2] and Document B. Appendices.[3] The acronym CS refers to Document B[2] and its appendices[3] in this ERG report. The ERG report also refers to relevant additional material submitted by the company in response to the clarification request from NICE.[4]

The decision problem assesses golimumab for treating adults with severe, active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation (OSI), as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have had an inadequate response to, or are intolerant to non-steroidal anti-inflammatory drugs (NSAIDs). The population addressed in the CS[2] is consistent with the marketing authorisation for golimumab (Summary of Product Characteristics [SmPC] detailed in Appendix C of CS Document B).[3]

The existing NICE technology appraisal of tumour necrosis factor (TNF)-alpha inhibitors for ankylosing spondylitis (AS) and nr-axSpA (TA383) recommends adalimumab, certolizumab pegol and etanercept, within their marketing authorisations, as options for treating severe nr-axSpA in adults whose disease has responded inadequately to, or who cannot tolerate, NSAIDs.[5] The CS[2] compares golimumab 50mg once a month (on the same date each month) to the anti-TNFs currently recommended in TA383 (adalimumab [40mg every other week], certolizumab pegol [400mg at weeks 0, 2 and 4 followed by a maintenance dose of 200mg every other week or 400mg every four weeks] and etanercept [25mg twice weekly, alternatively 50mg once weekly]), which is consistent with the comparators identified in the final NICE scope.[1, 2]

TA383 states that golimumab, adalimumab, certolizumab pegol and etanercept are all TNF-alpha inhibitors with adalimumab, certolizumab pegol and golimumab being monoclonal antibodies and etanercept being a recombinant human TNF-receptor fusion protein.[5] The Committee for TA383 concluded that TNF-alpha inhibitors should be considered as a class with broadly similar if not identical effects.[5] This conclusion appears to have been made for both the AS indication, which included golimumab, and the nr-axSpA indication, which did not include golimumab.

The wording in the marketing authorisation for golimumab is consistent with the wording in the marketing authorisations for the comparator technologies with the small variation that only golimumab and certolizumab pegol use the word "active" in addition to "severe". The ERG's clinical advisor stated

that "active" is generally understood to mean a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of 4 or more. They also advised that golimumab and the comparator technologies would be considered alternatives in the same patients at the same point in the treatment pathway.

1.2 Summary of clinical effectiveness evidence submitted by the company

The key clinical effectiveness evidence in the CS[2] for golimumab was based on one randomised controlled trial (RCT): the GO-AHEAD trial.[6] This RCT investigated subcutaneous (SC) golimumab 50mg every 4 weeks versus placebo in patients ages ≥18 years to ≤45years who had active nr-axSpA according to the Assessment of SpondyloArthritis international Society (ASAS) criteria for ≤5 years since symptom onset (Company's clarification response,[4] A10), high disease activity, and an inadequate response to or intolerance of NSAIDs. The inclusion criterion of ≤5 years since symptom onset was based on the fact that long-standing disease is more likely to have radiographic changes not consistent with diagnosis of nr-axSpA (Company's clarification response,[4] question A10) and the inclusion criteria of age ≤45 years at enrolment was selected because it is the ASAS criteria for axial spondyloarthritis (Company's clarification response,[4] question A10).

Patients were recruited from 52 centres in 13 countries (Czech Republic, Denmark, Finland, Germany, Greece, Ireland, Italy, Russia, Slovakia, Spain, Turkey, UK, and US, see CS, p.30).[2] Ninety-eight patients were randomised (97 treated) to the golimumab arm and 100 patients were randomised to the placebo arm, of which 4/97 (4%) and 5/100 (5%) respectively were from the UK (Company's clarification response,[4] question A13). Ninety-three (95%) and 97 (97%) patients respectively completed the 16-week follow-up. GO-AHEAD[6] was a two-part study. After 16 weeks, placebo patients switched to golimumab for a pre-planned 44-week, open-label extension to evaluate long-term treatment effectiveness and safety. In response to the clarification letter (Company's clarification response,[4] question A1), the company stated that assessment of clinical response at 16 weeks was consistent with patients receiving a fourth dose of treatment at 12 weeks and the monthly schedule of study visits. The company also stated in the clarification letter[4] (question A1) that performing the assessment at week 16, at a time of trough (i.e. lowest) levels of golimumab, was conservative relative to assessment at week 14 when levels would have been higher.

In the double-blind phase of the GO-AHEAD[6] study, for the primary endpoint of 20% improvement in the Assessment of SpondyloArthritis International Society score (ASAS20) at 16 weeks, the between-group difference was statistically significant in favour of golimumab compared with placebo (p<0.0001). A statistically significant difference in favour of golimumab was also observed in the OSI population (MRI positive sacroiliac [SI] or CRP >upper limit of normal [ULN]) (p<0.001).

Assessment of ASAS20 response by subgroups was also undertaken (n=158 [golimumab n=78, placebo n=80], CS,[2] p.39). Subgroups demonstrating statistically significant responses favouring golimumab over placebo were: sex male, age ≤30, age >30, disease duration >median, HLA-B27+, MRI SI+, CRP >ULN, and MRI SI+ or CRP >ULN. Between-group differences were not statistically significant for subgroups: sex female, disease duration ≤ median, HLA-B27-, MRI SI-, CRP ≤ULN, and MRI SI- and CRP ≤ULN.[2]

In response to the clarification letter (Company's clarification response,[4] question A22), subgroup analyses for weight, BASDAI score, use of NSAIDS, and geographic region were provided by the company for ASA20. A statistically significant difference in favour of golimumab was observed for: weight >76Kg (p=0.0181), weight ≤ 76Kg (p=0.0003), BASDAI > Median (p<0.0001), NSAIDs No (p=0.0349), NSAIDs Yes (p=0.0004), Eastern Europe (p<0.0001), and Western Europe and US (p=0.0450).

For the secondary endpoint ASAS40 (40% improvement in ASAS), the score at 16 weeks was statistically significant in favour of golimumab compared with placebo (p<0.0001). Results in the OSI population were similar (p<0.0001). Similar to the findings for ASAS20, the subgroup analysis of patients who were MRI SI- with CRP ≤ULN was non-significant (p=0.2636).[6]

For the secondary endpoints BASDAI50, ASAS partial remission (ASAS PR, a value of 2 [on a 0 to 10 scale] or less in each of the following domains: patient global, pain, function [Bath Ankylosing Spondylitis Functional Activity Index - BASFI], and inflammation [mean of BASDAI questions 5 and 6]), and SPARCC MRI SI joint score, results were also statistically significant at week 16 in favour of golimumab (BASDAI50, p<0.0001; ASAS PR, p<0.05 and SPARCC MRI SI, p<0.0001). Results in the OSI population were similar.

For the other secondary endpoints of: Ankylosing Spondylitis Disease Activity Score using CRP level (ASDAS-C), BASDAI, BASFI, Bath Ankylosing Spondylitis Metrology Index (BASMI), Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), total back pain Visual Analogue Scale (VAS), CRP levels, Ankylosing spondylitis quality of life (ASQoL), EuroQol 5 Dimensions (EQ-5D), 36-item Short Form survey Mental Component Score (SF-36 MCS) and SF-36 Physical Component Score (SF-36 PCS), these results were also statistically significant at week 16 in favour of golimumab. Results were similar in the OSI population (Company's clarification response,[4] question A3).

Network meta-analyses (NMAs) were performed to simultaneously compare the relative efficacy of golimumab with the comparators adalimumab, certolizumab pegol and etanercept in patients with nr-axSpA who were inadequate responders to or intolerant of NSAIDs for ASAS20, ASAS40, BASDAI50,

change from baseline in BASFI and change from baseline in BASDAI and BASMI, adverse events (AEs), serious AEs (SAEs), and infections. The outcome time point was 12 weeks for all studies except for safety data and change from baseline BASMI from GO-AHEAD,[6] which was only reported at 16 weeks (CS, p.54).[2] In response to the clarification letter (Company's clarification response,[4] question A5) the company stated that they were unable to rerun the NMA for the SF-36 MCS and PCS outcomes including the GO-AHEAD[6] trial data at the time of responding to the clarification request.

The comparator studies in the NMA were as follows. ABILITY-1[7] evaluated adalimumab 40mg every other week versus placebo in 185 (94 placebo and 91 adalimumab) adult patients with nr-axSpA. The primary endpoint was the percentage of patients achieving ASAS40 at week 12. Haibel *et al.*[8] also evaluated adalimumab 40mg every other week versus placebo in 46 (24 placebo and 22 adalimumab) adult patients with nr-axSpA. The primary endpoint was also the percentage of patients achieving ASAS40 at week 12. The RAPID-axSpA[9] study evaluated certolizumab pegol 200mg every other week or 400mg every four weeks versus placebo in 325 (107 placebo, 111 CPZ 200mg and 107 CPZ 400mg) adult patients with nr-axSpA. The primary endpoint was the percentage of patients achieving ASAS20 at week 12. The EMBARK[10] study evaluated etanercept 50mg every other week versus placebo in 215 (109 placebo and 106 etanercept) adult patients with nr-axSpA. The primary endpoint was the percentage of patients achieving ASAS40 at week 12.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The literature searches in the AG report for TA383 were conducted in July 2014. Searches in the company submission were conducted in April 2017. The GO-AHEAD[6] study was identified in the searches for TA383 but it was excluded because golimumab was excluded from the scope of TA383 for this indication. The ERG considers the searches for clinical effectiveness evidence reported in the CS[2] to be adequate, and believes that the included RCT of golimumab to be relevant to the decision problem.

The eligibility criteria applied in the selection of evidence for clinical effectiveness were considered by the ERG to be reasonable and consistent with the decision problem outlined in the final NICE scope. The studies included in the NMA are consistent with those considered in the AG report for TA383 except that the GO-AHEAD[6] study has been added to the NMA and the infliximab study by Barkham *et al*.[11] has been removed, which is consistent with the scope of this FTA.[1, 12] The quality of the included RCTs was assessed using well-established and recognised criteria and the methodological quality of the GO-AHEAD[6] study and comparator RCTs was considered to be good. The GO-AHEAD[6] study is of a similar size (n=198) compared with the pivotal trials informing the licenses for the comparator therapies (n= 147 to 215) with one smaller additional study for adalimumab (n=46).

The ERG notes baseline differences in the populations across the comparator RCTs compared with the population in the GO-AHEAD[6] study (Table 1). However, the CS[2] (p.67-68) reports that differences in baseline characteristics and disease indicators were explored, where possible, in five sensitivity analyses (<5 years disease duration, 16 week endpoints for efficacy, >ULN CRP, the OSI population, and removal of the Haibel *et al*.[8] trial) and that these showed that the between-study differences in baseline characteristics, had no significant impact upon the final efficacy results for golimumab.

Limited details were provided in the CS[2] on the exact methods used to conduct the sensitivity analyses exploring the impact of potential treatment effect modifiers (disease duration, CRP levels and OSI status), but based on the NMA input data reported in the CS (CS Document B,[3] Appendix K), the ERG believes that these sensitivity analyses were conducted by removing relevant subgroups of patients in individual studies to provide more comparable populations across the included studies.[2, 3] In the sensitivity analysis examining disease duration, the subgroup with disease duration <5years from the ABILITLY-1[7] study appears to have replaced the base case data for ABILTIY-1[7], but base case data were used for the other studies. In the sensitivity analysis examining CRP levels, data from the CRP >ULN subgroup of GO-AHEAD[6] have been included in the NMA with the base case data from the comparator studies. The ERG noted that there appeared to be an error in the data inputs for the ASAS20 outcome in the sensitivity analysis examining CRP levels, as the table of data inputs (CS Document B,[3] Appendix K, Table 121) showed ASAS40 data for the comparator trials. The ERG explored this error by reproducing the company analysis using the ASAS20 data and concluded that the inputs were most likely correct in the analysis conducted by the company (i.e., they used the correct ASAS20 data) but were incorrectly reported in Table 121. In the sensitivity on OSI, the OSI population was used instead of the base case data for the GO-AHEAD[6] study, but base case data were used for the comparator studies. This was due to a lack of available OSI population data for the comparators in the published studies (CS clarification response,[4] A20).

Mean age ranged from 32 years[10] to 38 years,[6] with the mean age reported in the GO-AHEAD[6] and EMBARK[10] studies being approximately five to seven years lower than the other studies. The proportion of patients who were male ranged from 45% [6] to 60%.[10] The proportion of patients who were white was not reported by Haibel *et al.*[8] or the RAPID-axSpA study.[9] Studies in adalimumab and certolizumab pegol included patients with longer disease duration (up to 24 years[8] and up to 41.5 years,[9] respectively). The ABILITY-1[7] study reported a disease duration of approximately 10 years, whereas the GO-AHEAD[6] study reported a median disease duration of 0.5 years. The proportions of patients who were MRI and/or CRP positive ranged from 48% for adalimumab[6] to 88% for etanercept[10] but were not reported for certolizumab pegol.[9] The proportion of patients who were HLA-B27 positive was reasonably comparable across studies (78%,[6] 67%,[8] 71%,[10] 75%[9]). All studies reporting the prior

treatments of patients indicated that patients were biologic-naïve, except for RAPID-axSpA[9] where 10.9% of patients were not biologic naïve.

Table 1. Patient characteristics across the studies included in the NMA

Study and treatment	N	Mean age	% male	% white	Disease duration, years	MRI/CRP + %	HLA-B27+ %	Biologic naïve
GO-AHEAD[6] golimumab	198	31	57%	100%	Median 0.5 (range 0-5)	66%	82%	Yes
ABILITY-1[7] adalimumab	185	38	45%	98%	Mean 3	48%	78%	NR
EMBARK[10] etanercept	215	32	60%	79%	Mean 2.5 (range 3-5)	88%	71%	Yes
Haibel[8] adalimumab	46	37	47%	NR	Mean 7.5 (range 1-24)	65% MRI+	67%	Yes
RAPID[9] certolizumab pegol	147	37.4	48.30%	NR	Median 5.5 (range 0.3-41.5)	NR	74.80%	131/147 (89.1%)

The ERG considers the 16-week follow-up in the GO-AHEAD[6] to be acceptable (Company's clarification response,[4] question A1). The ERG considers that the primary endpoints and selected analyses for clinical efficacy were appropriate. The ERG notes that the efficacy outcomes of ASAS20, ASAS40, ASAS partial remission, and change from baseline in: BASFI, BASMI, BASDAI and MASES are measured and reported in the same way across studies that are included in the NMA; pain is reported in a similar/comparable way across studies; and peripheral symptoms (enthesitis) are measured and reported across studies. The ERG considers that no study evaluates extra-articular manifestations (one of the outcomes in the NICE scope[1]). The ERG notes that the measurement and reporting of AEs of treatment and health-related quality of life outcomes (HRQoL) are also similar but are not available for certolizumab pegol. The ERG notes that the CS[2] describes outcomes that are directly related to the outcomes that influence costs and quality-adjusted life-years (QALYs) in the AG economic model for TA383 i.e., BASDAI50 response at 12 weeks, mean changes in BASDAI and BASFI over 12 weeks.[2, 12] The ERG also considers that the proportion of discontinuations as a consequence of AEs is similar to those for other TNF-alpha inhibitors for nr-axSpA, as shown in the Assessment report for TA 383, Appendix 8.[12]

The NMA analysed continuous outcomes using an identity link function and binary outcomes using a logit link function. No feedback loops were created by the studies that were included in the NMA. Consequently, it is not possible to assess potential inconsistency in the evidence base; unbiased estimates of relative treatment effect in an NMA rely on the assumption that there is not an imbalance in treatment effect modifiers between studies comparing different pairs of treatments. The company stated that they used the Cochrane Collaboration tool which assesses the risk of bias in each study and conducted sensitivity analyses to investigate the impact of the distribution of treatment effect modifiers on the results (Company's clarification response,[4] question A6). The ERG recognises the difficulty in comparing the distribution of treatment effect modifiers across studies comparing different pairs of treatments when there is no (or limited) replication of studies comparing different pairs of treatments. However, the ERG does not believe that the approach taken by the company mitigates any potential biases.

The CS[2] used a fixed effect model to analyse the data on the basis that "the network did not contain enough evidence in order to accurately estimate a random effects model …" This ignores the point that a fundamental feature of a Bayesian analysis, as used in the CS, is the use of external evidence, including expert opinion. Reference prior distributions for variance parameters are not non-informative when data are sparse (i.e., few studies) and consideration needs to be given to defining a plausible prior distribution for the heterogeneity parameter. A fixed effect analysis assumes either that interest is in whether the treatments had an effect in the available studies and/or it is believed that there is no variability in treatment effects between studies beyond sampling variation. Both of these scenarios are unlikely to be

relevant in this case; the consequences for the current analyses are that they are likely to underestimate genuine uncertainty.

The base case fixed effect NMAs in the CS[2] presented results in terms of the effects of golimumab versus placebo and all other active treatments. Treatments were not ranked according the probability of treatment rankings (i.e., the probability of being the best, 2nd best, 3rd best, 4th best, 5th best and worst performing treatment) or surface under the cumulative ranking (SUCRA) plots.[13]

The base case fixed effect NMAs in the CS[2] found some differences in favour of golimumab versus some, but not all, of the comparator anti-TNFs for change in BASFI, change in BASDAI and change in BASMI (i.e., 95% credible interval (CrI) excluding the null values). In some cases the estimated treatment effect was of a size considered to be clinically meaningful (>1.0 for BASDAI and >0.7 for BASFI; MCID based on AG report page 69) but the 95% CrI included values that would not be considered clinically meaningful.

The ERG re-analysed the primary outcome used in the GO-AHEAD[6] study (i.e., ASAS20) using a more plausible prior distribution for the heterogeneity parameter. As expected, the results were more uncertain, although the 95% CrI for the random effects odds ratio (OR) of golimumab 50mg versus placebo and the 95% prediction interval (PrI) for the effect of golimumab 50mg in a new study both excluded the null value (Table 2).

Table 2. ASAS20 – Posterior ORs relative to placebo

	Mean	SD	2.5% percentile	Median	97.5% percentile
Company Results					
Golimumab 50mg	3.63	1.19	2.03	3.63	6.62
Random Effects: Prior SD ~ HN(0, 0.32^2)					
Golimumab 50mg	4.03	2.09	1.50	3.65	8.91
Adalimumab 40mg	3.41	1.52	1.54	3.11	7.10
Etanercept 50mg	2.16	1.10	0.83	1.95	4.67
Certolizumab pegol 200mg	2.50	1.56	0.76	2.15	6.24
Certolizumab pegol 400mg	2.97	1.88	0.91	2.57	7.43
Between-study SD	0.27	0.19	0.01	0.23	0.72
Prediction distribution[a]					
Golimumab 50mg	4.28	3.53	1.17	3.64	11.15
Adalimumab 40mg	3.64	3.02	1.22	3.09	9.47
Etanercept 50mg	2.30	2.14	0.64	1.96	5.99
Certolizumab pegol 200mg	2.65	2.47	0.62	2.15	7.57
Certolizumab pegol 400mg	3.16	3.03	0.75	2.57	8.98

[a] Predictive distribution for the effect of treatment in a new study

There is uncertainty about the relative effects of treatments (i.e. ORs) and the extent to which these vary according to patient characteristics (i.e. treatment effect modifiers). The uncertainty about the relative effects of treatments affects uncertainty about the absolute effects of treatments; Table 36 of the CS (Document B Appendix I)[3] presents the company's estimates of absolute effects, although the uncertainty is likely to be greater based on the results in Table 2. The ERG's clinical advisor believes the claim of clinical similarity between the treatments to be biologically plausible.

1.4 Summary of safety evidence submitted by the company

The CS[2] reports that the OSI population in the GO AHEAD[6] study was analysed for overall AEs (p.71). With respect to whether or not the entire randomised population was included, the company's clarification response[4] (question A4) stated that the AEs presented in Table 20 of the CS[2] (p.72) included all randomised subjects who had taken at least one dose of study medication and included both the OSI and non-OSI populations. The company reported that golimumab was well tolerated and that the incidence of SAEs and other significant AEs was comparable between patients treated with golimumab and those treated with placebo (CS,[2] p.71). In response to clarification question A12,[4] it was reported that of the three discontinuations in the placebo group, one was due to AEs and of the four discontinuations in the golimumab group, one was due to AEs.

Overall, the incidence of the most frequently reported clinical AEs was lower in the golimumab group than in the placebo group apart from skin and subcutaneous tissue AEs (10.3% for golimumab vs 6.0% for placebo, see CS,[2] p.71). No new safety signals were identified in the treatment of nr-axSpA during the GO AHEAD[6] study. The CS[2] concludes that the safety profile in this study is consistent with that for golimumab in other conditions (AS and other rheumatic diseases) and similar to other TNF alpha inhibitors (CS,[2] p.71).

The ERG considers that golimumab appears to have a good safety profile. However, the evidence for the nr-axSpA population comes from one study only.[6] At the data cut-off date (May 2014) for the GO-AHEAD[6] study no deaths, serious opportunistic infections, active TB, malignancies or serious systemic hypersensitivity had been reported (CS Appendix C,[3] p.113).

The CS[2] reports that the safety profile of golimumab is considered to be well established with the most commonly reported AE reported in RCTs being upper respiratory infection (CS Appendix C,[3] p.112). The most serious AEs that have been reported for golimumab include serious infections (including sepsis, pneumonia, TB, invasive fungal and opportunistic infections), demyelinating disorders,

lymphoma, HBV reactivation, CHF, autoimmune processes (lupus-like syndrome) and haematologic reactions (CS Appendix C,[3] p.112).

Further information on AEs for Part 2 of the GO AHEAD[6] study is provided in the 60-week Clinical Study Report (CSR).[14] Adverse events were reported by 54 (55.7%) of the 97 subjects who received golimumab 50mg in Parts 1 and 2. This trend was similar to that described for golimumab 50mg and placebo treatment groups in Parts 1 and for golimumab 50/golimumab 50mg and placebo/golimumab 50mg treatment groups in Part 2 (CSR,[14] p.203). A total of five SAEs were reported in five subjects in Part 2: two in the golimumab 50mg / golimumab 50mg group and three in the placebo/golimumab 50mg group. Two SAEs (bacterial infection in the golimumab 50mg / golimumab 50mg group and migraine in placebo/golimumab 50mg group) were considered to be drug-related by the investigators (CSR,[14] p.197).

The AG report for TA383[15] summarised that from open-label studies there did not appear to be important differences in AEs across TNF-alpha inhibitors, although the included data were limited because of small sample sizes and non-RCT design across these studies (p.93). The report also summarised that anti-TNFs as a group are associated with significantly higher rates of serious infections, TB reactivation, non-melanoma skin cancer, total AEs, and withdrawals due to AEs, when compared with control treatments (p.93).[15]

In the GO-AHEAD[6] study, all patients received the 50mg dose of golimumab. The CS Appendix C,[3] (p.115, Table 20), provides information on AEs associated with the 100mg dose of golimumab (data from the GO-RAISE study in 356 adult patients with active AS – citation not reported in CS). From the evidence for this study reported in the CS Appendix C,[3] there appears to be a higher percentage of subjects with one or more SAE in 100mg group compared to the 50mg group. There is therefore the potential for a higher AE profile for nr-axSpA patients requiring the 100mg dosage.

1.5 Summary of cost effectiveness submitted evidence by the company

The CS[2] presents acquisition costs for golimumab and each comparator anti-TNF therapy in the first and subsequent years of treatment for patients remaining on treatment (Tables 22 and 23 of CS Document B).[2] The acquisition cost for golimumab is the same as for adalimumab in both the first year of treatment and in subsequent years of treatment (£9,155.64). The acquisition costs of certolizumab pegol in the first year (£5,720), is lower due to the Patient Access Scheme (PAS) which provides the first 10 vials at zero cost but the cost of certolizumab pegol in subsequent years (£9,295) is higher than for golimumab. The cost of etanercept in the CS[2] is higher in both the first and subsequent years (£9,295 for both).

The CS describes the resource use and costs associated with the anti-TNF comparator treatments (Section B.2.2 of the CS Document B[3]) including drug administration, treatment initiation and monitoring, management of AEs and long-term disease management costs.[2] The company have used the same data sources as cited in the AG report for TA383 but have updated them to use the most recent reference costs, or they have inflated published costs from the AG report for TA383.[12] However, the company's cost-comparison analysis assumes that all resource use and costs other than drug acquisition costs are identical across golimumab and the comparator anti-TNF technologies (Section B.4.2.4. of CS Document B).[2] Therefore, none of the estimates described in Section B.2.2. affect the company's cost-comparison analysis.

1.6 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG's clinical advisor believed that healthcare resource costs associated with administration, monitoring and treating AEs would be similar to existing biologics currently recommended as assumed in the company's cost-comparison. The unit costs applied in the cost-comparison are not important as the same resource use has been assumed for all anti-TNF inhibitors. Therefore, any over- or under-estimation of unit costs would apply equally to all comparators and would not affect the relative cost of golimumab versus comparator technologies.

The assumption in the CS that only acquisition costs differ between golimumab and the comparator anti-TNFs is consistent with the Assessment Group's (AG's) assumption in TA383 where differences in the incremental cost-effectiveness ratios (ICERs) versus usual care for the various anti-TNF inhibitors were driven only by differences in the acquisition, administration and monitoring costs (Section 7.6, p.205 of AG report).[12] In the AG model for TA383, monitoring costs were identical for all comparators and administration costs differed only for infliximab, which is not considered here, so the only difference in costs remaining for the treatments considered in the CS would be acquisition costs (Table 92 of AG report, p.203).[12]

The ERG notes that the AG's assumption is dependent on each of the anti-TNFs having similar clinical effectiveness outcomes within the economic model (Section 7.1 of AG report).[12] Specifically, the AG model assumes no difference between the anti-TNFs in the following efficacy outcomes (Table 83 of AG report):[12]

- Treatment response measured by BASDAI50 at 12 weeks
- Mean change in BASDAI at 12 weeks for responders and non-responder
- Mean change in BASFI at 12 weeks for responders and non-responder
- Rate of serious infections and TB reactivation
- Long-term disease progression (measured by BASFI, progression to radiographic disease and MSASSS change)

- Mortality
- Treatment discontinuation

In the AG model, utilities are related to BASDAI and BASFI and disease costs are related to BASFI (Section 7.1 of AG report).[12] The assumption of equivalent efficacy for anti-TNFs on the measures listed above is what results in identical disease costs and QALY gains in the AG model. Therefore, the validity of the cost-comparison modelling is dependent on golimumab having clinical outcomes similar to those achieved for the anti-TNF comparators.

One aspect of the cost-comparison which was not addressed in the CS is the fact that patients who have a bodyweight greater than 100kg who do not receive an adequate clinical response after 12-14 weeks (3-4 doses) of golimumab have the option to switch to a higher dose, which is provided at the same cost under the existing golimumab PAS (Table 2 of CS Document B).[2] Discontinuation is recommended if no response is achieved after 3-4 doses at the higher dose.[2] The SmPC for golimumab states that there is an increased risk of certain serious adverse drug reactions with the 100mg dose compared with the 50mg dose (SmPC in Appendix C of CS Document B).[3] It should be noted that the comparison of clinical effectiveness in the CS is based on the GO-AHEAD[6] study in which patients in the intervention arm only received the 50mg dose.[2, 6] Therefore, the option to allow inadequate responders with a bodyweight over 100kg to increase their dose can only increase the number of patients who respond to golimumab relative to the other anti-TNF comparators. Patients who have had an inadequate response to one of the comparator anti-TNFs given first-line, would be offered a switch to a second anti-TNF under TA383.[5] Therefore, the option of a dose increase for golimumab in patients with a body weight over 100kg is not expected to adversely impact the cost-comparison provided patients have a similar or greater chance of achieving an adequate response compared to switching to a second anti-TNF and provided the impact of any increase in AEs is small. The ERG's clinical advisor noted that the higher dose would normally only be tried in patients who have experienced a partial response to golimumab at the standard dose. Furthermore, according to Table 1 of the European Public Assessment Report (EPAR) (Appendix C of CS Document B[3]), only 6 of 92 patients (6.5%) in the golimumab arm of GO-AHEAD[6] (population included in the analysis of serum golimumab concentrations at week 16) had a body weight >100kg.[3] Therefore, any impact of dose increases for golimumab on the average cost-effectiveness of golimumab versus other anti-TNFs is likely to be small.

The ERG is satisfied that the acquisition cost for golimumab in both the first and subsequent years of treatment is similar to at least one of the comparator formulations currently recommended in TA383, but it is not lower than all of the comparator formulations currently recommended in both the first and subsequent years. In particular, the ERG notes that the CS does not present acquisition costs for biosimilar formulations of the comparator anti-TNFs. The cost of etanercept in the CS is based on the

British National Formulary (BNF) list price for the original branded formulation (Enbrel, Pfizer Ltd).[2] The cost for etanercept based on the BNF list price for biosimilar etanercept (Benepali, Biogen Idec Ltd) is 8% lower (£656 vs £715).[16] It should also be noted that there is a biosimilar licensed for adalimumab (Amgevita, Amgen) for which a list price is not yet available.[16] The ERG was unable to conduct a systematic review on the uptake of biosimilar anti-TNF inhibitors for this indication in the time available. However, *ad hoc* searches by the ERG identified one study on the uptake of biosimilar infliximab and biosimilar insulin glargine in the UK which reported that the proportion of prescribing for these two medicines using biosimilar formulations had increased from approximately 6% in 2015 to approximately 37% in 2016 (figures estimated by ERG from graphical data).[17] The British Society for Rheumatology's position statement on biosimilars supports the inclusion of biosimilars as a treatment option for patients initiating a new biologic therapy but states that switching patients currently receiving a reference product to a biosimilar should be done on a case-by-case basis. According to the ERG's clinical advisor, the uptake of biosimilars is currently variable across National Health Service (NHS) trusts and therefore golimumab may be cost-neutral or cost-saving relative to current practice in some areas of England.

In TA383, adalimumab, etanercept and certolizumab pegol were all recommended despite there being differences in the acquisition costs across the various anti-TNF formulations.[5] These differences in acquisition costs, for the branded formulations at least, are unchanged since TA383 as the list prices presented in the CS for the branded versions of the comparator anti-TNFs match current BNF prices.[16] The recommendations in TA383 state, "*The choice of treatment should be made after discussion between the clinician and the patient about the advantages and disadvantages of the treatments available. This may include considering associated conditions such as extra-articular manifestations. If more than 1 treatment is suitable, the least expensive (taking into account administration costs and patient access schemes) should be chosen*".[5] The ERG's clinical advisor commented that the choice of agent used might also depend on other comorbidities e.g. etanercept would be a less likely choice in a patient with concomitant acute anterior uveitis or Crohn's disease. The ERG considers that whilst biosimilar etanercept is lower cost than golimumab, and there is some uncertainty regarding the uptake of biosimilars, there is a low risk that recommending golimumab will lead to a substantial increase in NHS costs provided the recommendations for golimumab contain similar instructions as given in TA383 to ensure that the lowest cost anti-TNF is used in practice.

In terms of budget impact, the worst-case scenario would be that patients who would otherwise receive biosimilar etanercept receive golimumab instead. The resource impact template for TA383 assumes that 30% of those with nr-axSpA will be receiving etanercept in future practice and the price used in the resource impact template is for branded etanercept.[15] Under the assumptions used in the resource impact template, the budget impact of TA383 is predicted to be £60.3 million per annum when uptake reaches

its maximum in 2022/23. If the price of biosimilar etanercept is used in the resource impact template instead of branded etanercept, the resource impact of TA383 is predicted to be £58.8 million when uptake reaches its maximum in 2022/23. If all those predicted to receive etanercept are assumed to switch to golimumab, then the resource impact of TA383 in 2022/23 increases to £60.0 million. Therefore, the resource impact of golimumab is predicted to be an extra cost of £1.2 million per annum under a worst-case scenario. It is also feasible that it could result in savings relative to current budget impact predictions if it is used in patients who would have otherwise received branded etanercept or certolizumab pegol.

1.7 ERG commentary on the robustness of evidence submitted by the company

1.7.1 Strengths

The ERG considers the data on clinical effectiveness in the CS to be well-reported and the included studies are of good quality. The AE profile appears to be broadly similar to those for the NICE recommended comparators.[15]

The company's cost-comparison has used assumptions that are consistent with those made in the AG model for TA383.

1.7.2 Weaknesses and areas of uncertainty

The use of a fixed-effect assumption in the NMA presented in the CS is likely to have underestimated uncertainty around the estimates of both absolute and relative treatment effects.

There is uncertainty regarding the current and future uptake of biosimilar etanercept and biosimilar adalimumab, and golimumab would not be cost-saving relative to these products. However, the ERG considers that there is a low risk that recommending golimumab will lead to a substantial increase in NHS costs provided the recommendations for golimumab contain similar instructions as given in TA383 to ensure that the lowest cost anti-TNF is used in practice.

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