Slides for committee, projector and public (no confidential information)

Committee presentation

Golimumab for treating non-radiographic axial spondyloarthritis

1st Appraisal Committee meeting

Committee A

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ERG: School of Health Related Research, University of Sheffield

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Key issues

- The company has made a case for this appraisal to follow the FTA process (cost comparison analysis) based on the similar clinical effectiveness of golimumab compared with each of the technologies recommended in TA383 (adalimumab, etanercept, certolizumab pegol).
- Is the committee satisfied with the clinical evidence for benefit and safety from the pivotal trial?
- Does the committee accept the design and reliability of the network meta-analysis?
- Does the committee consider that the list price is in line with other agents with the same indication?
- Are the lifetime costs and QALYs likely to be similar to those treatments already approved?

The technologies

	Golimumab (intervention)	Adalimumab, etanercept, certolizumab pegol (comparators)
Mode of action	TNF-alpha inhibitor	
Marketing authorisation	Severe, active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs.	**Adalimumab** and **etanercept:** severe axial spondyloarthritis without radiographic evidence of axial spondyloarthritis but with objective signs of inflammation by elevated CRP and/or MRI, who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs. **Certolizumab pegol** includes 'active'.
Administration subcutaneous, dose	50 mg or 100 mg (for patients weighing >100kg) once a month.	**Adalimumab**: 40 mg every other week **Certolizumab pegol**: 400 mg (2 injections of 200 mg each) wk 0, 2, 4; Maintenance regimen: 200 mg every other week or 400 mg every 4 weeks **Etanercept**: 25 mg twice or 50 mg once weekly.

Definition of terms

- ASAS 20 - 20% improvement in assessment in ankylosing spondylitis
- BASDAI - Bath ankylosing spondylitis disease activity index
- BASFI - Bath ankylosing spondylitis functional activity index
- BASMI - Bath ankylosing spondylitis metrology index
- BASDAI 50 - 50% improvement in bath ankylosing spondylitis disease activity index

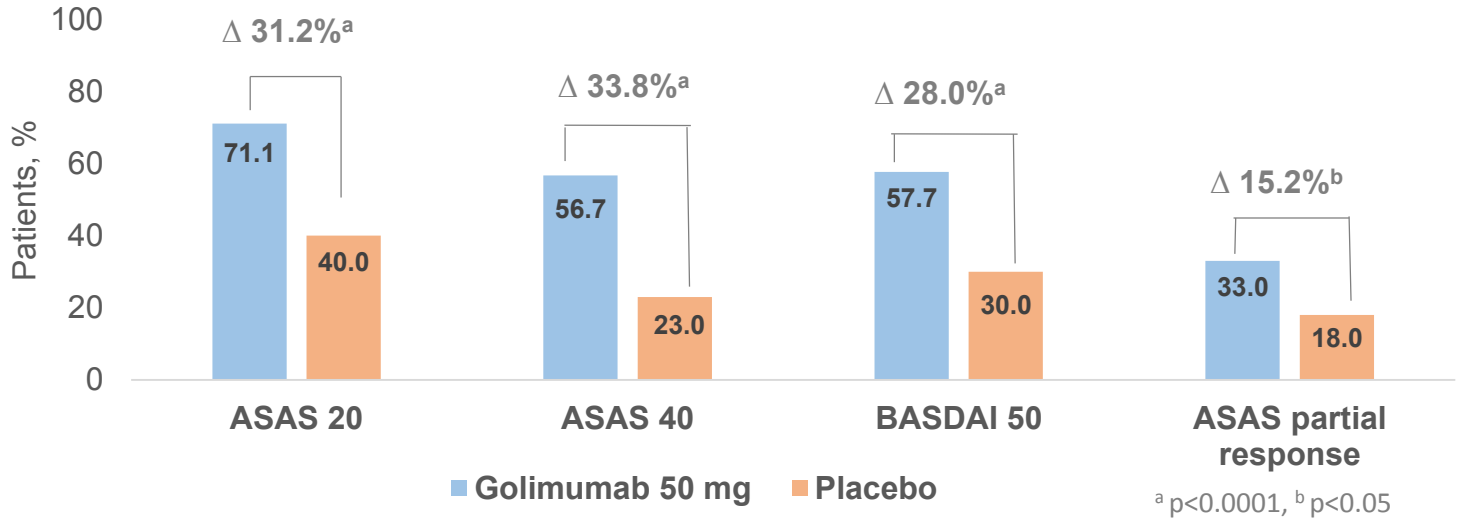
Key drivers of the cost-effectiveness of the comparators (TA383)

Clinical outcomes	• BASDAI50, baseline BASDAI and BASFI scores, change in BASDAI, change in BASFI, re-bound following discontinuation of TNF-alpha inhibitor
Key clinical drivers	• BASDAI50 response, and change in BASDAI and BASFI
Clinical uncertainties	• Given the lack of difference between the clinical effectiveness of TNF inhibitors: committee considered as a class. • No data on the efficacy of a 2nd or 3rd TNF inhibitor in non-radiographic spondyloarthritis, although efficacy likely to reduce • In the AG model BADAI50 responders had lower baseline BASDAI and BASFI scores than non-responders. The committee considered that people with mild disease required numerically smaller improvement to achieve BASDAI50, but absolute numerical improvements were relevant for all degrees of severity
Resource use assumptions	• The committee agreed with AG assumptions on drug initiation, monitoring, administration, acquisition costs.
Resource use uncertainties	• Sequential use of TNF inhibitors not modelled (no data)

Company's clinical effectiveness evidence

- GO-AHEAD randomised 198 patients to either golimumab 50 mg or placebo.
- Patient characteristics:
  - age ≥18 years to ≤45years with high disease activity
  - with active non radiographic axylospondyloarthritis according to ASAS criteria for ≤5 years
  - inadequate response to or intolerance of NSAIDs.
- **Primary outcomes:** ASAS20 response at Week 16
- **Secondary outcomes:** ASAS40, BASDAI50, ASAS PR, ASDAS-C, BASDAI, BASFI, BASMI, MASES, total back pain (VAS), CRP levels, ASQoL, EQ-5D, SF-36 MCS and SF-36 PCS (abbreviations in the notes)
- During clarification the ERG queried why response was assessed at 16 weeks when in clinical practice response for adalimumab, etanercept and certolizumab pegol is assessed at 12 weeks (TA383)
- The company considered 16 week assessment to be conservative because response is being measured just before the 5th dose of golimumab is administered (systemic levels of golimumab are lower than at 14 weeks)

Results of GO-AHEAD trial
Full analysis set



- The primary outcome in the GO-AHEAD trial was ASAS20 response.
- Outcomes which inputted to the cost and QALYs of the TA383 model were BASDAI50 response, and change in baseline BASDAI and BASFI.
- Golimumab was associated with statistically significant improvement in all outcomes compared to placebo.
- A statistically significant improvement was also seen in the population with objective signs of improvement (MRI or elevated CRP at baseline)

Source: CS figures 3 and 4

Discontinuations and adverse events
Company submission

Study arm	Golimumab (n=97)	Placebo (n=100)
All-cause discontinuations	4 (4.1)	3 (3)
Discontinuations due to AEs	1 (NR)	1 (NR)
Discontinuations due to lack of efficacy	0	0
Adverse events, n (%)		
Treatment-emergent AE	40 (41.2)	47 (47.0)
Treatment-related AE	13 (13.4)	17 (17.0)
Any SAE	1 (1.0)	2 (2.0)
Female partner reported fetal death	1 (1.0)	0
Infections	24 (25)	23 (23)
Serious infections	0	0
Active tuberculosis	0	0
Malignancies	0	0
Serious systemic hypersensitivity	0	0
Injection site reactions	0	3 (3)
Deaths	0	0

Source: CS table 20

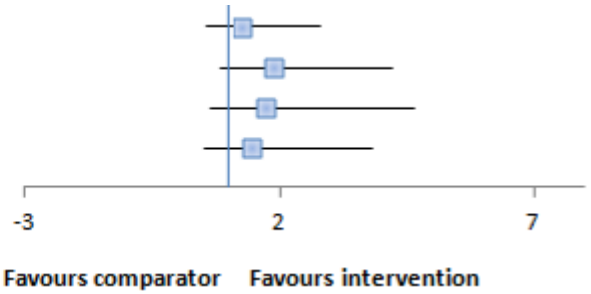
Network meta-analysis (NMA)

- A NMA was conducted to compare the clinical effectiveness of golimumab with adalimumab, etanercept and certolizumab pegol.
- The company used the same trials as the NMA in TA383 (excluding infliximab which does not have a marketing authorisation for this indication).
- In the GO-AHEAD study outcomes were assessed at 16 weeks
- Outcomes in the NMA were assessed at 12 weeks for all studies except for safety data and change from baseline BASMI from GO-AHEAD (reported at 16 weeks).
- NMA for:
  - binary outcomes (ASAS20, ASAS40, BASDAI50),
  - continuous efficacy outcomes: change from baseline in BASFI, BASDAI and BASMI,
  - adverse events, serious adverse events and infections.
- NMA for the SF-36 MCS and physical component score outcomes not done.

Comparison of health benefits and safety (1)
Company NMA results

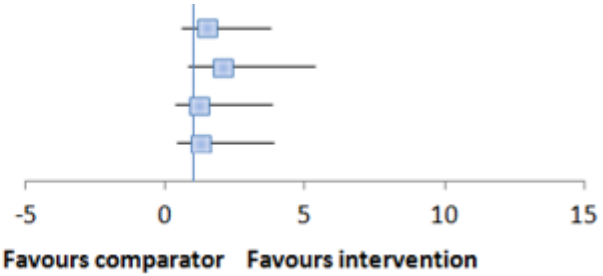
ASAS 20 base case

GLM vs. ADA	1.24	[0.56, 2.79]
GLM vs. ETN	1.86	[0.83, 4.19]
GLM vs. CZP 200mg	1.68	[0.61, 4.63]
GLM vs. CZP 400mg	1.42	[0.52, 3.81]



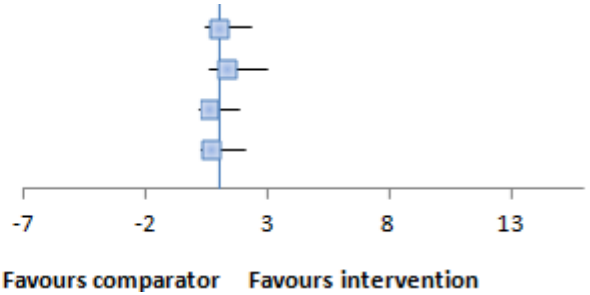
ASAS 40 base case

GLM vs. ADA	1.48	[0.59, 3.73]
GLM vs. ETN	2.06	[0.80, 5.33]
GLM vs. CZP 200mg	1.20	[0.36, 3.80]
GLM vs. CZP 400mg	1.23	[0.38, 3.89]



BASDAI50 base case

GLM vs. ADA	0.97	[0.41, 2.32]
GLM vs. ETN	1.29	[0.55, 2.98]
GLM vs. CZP 200mg	0.58	[0.18, 1.80]
GLM vs. CZP 400mg	0.66	[0.21, 2.01]



Golimumab compared to:

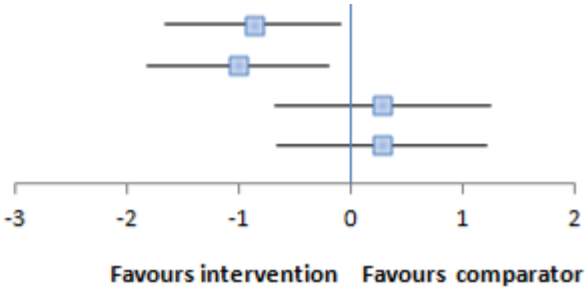
- placebo - statistically significant results
- active treatments – not statistically significant results

Source: CS figures 20, 21, 22

Comparison of health benefits and safety (2)
Company NMA results

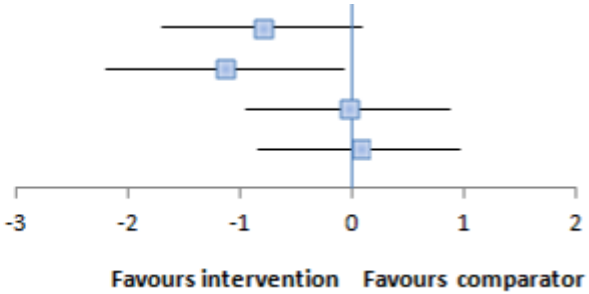
Δ BASFI

GLM vs. ADA	-0.89	[-1.68, -0.10]
GLM vs. ETN	-1.03	[-1.85, -0.22]
GLM vs. CZP 200mg	0.26	[-0.70, 1.23]
GLM vs. CZP 400mg	0.26	[-0.68, 1.21]



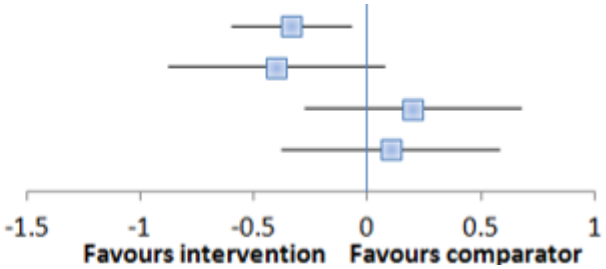
ΔBASDAI

GLM vs. ADA	-0.82	[-1.71, 0.07]
GLM vs. ETN	-1.15	[-2.21, -0.08]
GLM vs. CZP 200mg	-0.05	[-0.96, 0.86]
GLM vs. CZP 400mg	0.05	[-0.85, 0.94]



ΔBASMI

GLM vs. ADA	-0.34	[-0.60, -0.07]
GLM vs. ETN	-0.40	[-0.88, 0.08]
GLM vs. CZP 200mg	0.20	[-0.28, 0.68]
GLM vs. CZP 400mg	0.10	[-0.38, 0.58]



Golimumab superior to:

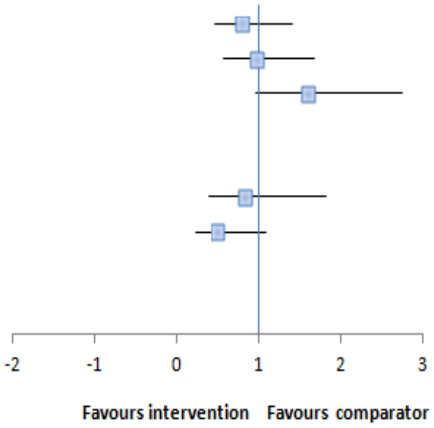
- etanercept and adalimumab for Δ BASFI,
- etanercept for Δ BASDAI
- adalimumab for Δ BASMI

Source: CS figures 23, 24, 25

Comparison of health benefits and safety (3)
Company NMA results

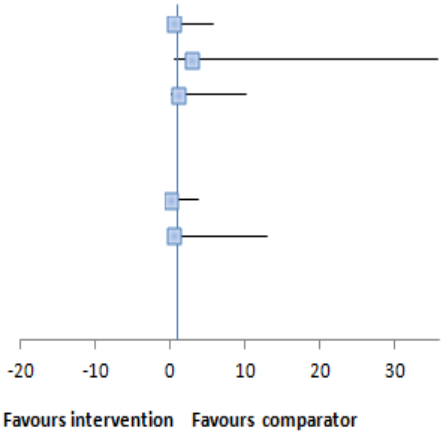
Adverse events

Comparison	Median OR	[95% CrI]
GLM vs. PBO	0.79	[0.45, 1.40]
ADA vs. PBO	0.96	[0.55, 1.67]
ETN vs. PBO	1.60	[0.94, 2.73]
CZP 200mg vs. PBO		
CZP 400mg vs. PBO		
GLM vs. ADA	0.83	[0.37, 1.81]
GLM vs. ETN	0.49	[0.23, 1.07]
GLM vs. CZP 200mg		
GLM vs. CZP 400mg		



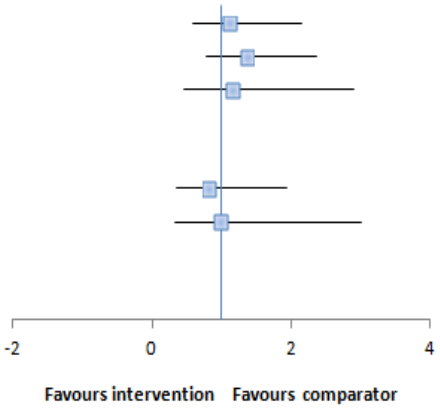
Serious adverse events

Comparison	Median OR	[95% CrI]
GLM vs. PBO	0.42	[0.01, 5.57]
ADA vs. PBO	2.86	[0.42, 35.56]
ETN vs. PBO	1.02	[0.10, 10.09]
CZP 200mg vs. PBO		
CZP 400mg vs. PBO		
GLM vs. ADA	0.14	[0.00, 3.71]
GLM vs. ETN	0.40	[0.01, 12.77]
GLM vs. CZP 200mg		
GLM vs. CZP 400mg		



Infections

Comparison	Median OR	[95% CrI]
GLM vs. PBO	1.10	[0.57, 2.14]
ADA vs. PBO	1.35	[0.78, 2.36]
ETN vs. PBO	1.14	[0.45, 2.89]
CZP 200mg vs. PBO		
CZP 400mg vs. PBO		
GLM vs. ADA	0.82	[0.34, 1.93]
GLM vs. ETN	0.97	[0.31, 3.00]
GLM vs. CZP 200mg		
GLM vs. CZP 400mg		



Source: CS figures 26, 27, 28

ERG clinical effectiveness review

- 16-week follow-up in GO-AHEAD is acceptable
- Differences in baseline characteristics and disease indicators were explored in 5 sensitivity analyses and had no significant impact on final efficacy results for golimumab.
- Primary endpoints and selected analyses for clinical efficacy were appropriate
- 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
- Outcomes (BASDAI50 response at 12 weeks, mean changes in BASDAI and BASFI over 12 weeks) described in the company submission are directly related to the outcomes that influence costs and QALYs in the AG economic model for TA383.
- Pain is reported in a similar/comparable way across studies;
- Peripheral symptoms (enthesitis) are measured and reported across studies

Network meta-analysis

ERG comments - strengths

- Trials for the comparators in the NMA are the same as used in TA383.
- Population similar and comparable across the trials:
  - Age (>30-<40 years) and % of male (45-60%)
  - Disease duration for golimumab similar to etanercept (<5 years) trials but shorter than in adalimumab (up to 24 years) and certolizumab pegol trials (41.5 years).
  - Proportion of patients MRI and/or CRP positive reasonably comparable for golimumab, adalimumab and etanercept (NR for certolizumab pegol).
  - Proportion of patients HBA-L27 +ve reasonably comparable (67-82%).
  - All trials indicated that patients were biologic-naïve, except for RAPID-axSpA (certolizumab pegol study) where 10.9% of patients were not biologic naïve.

Network meta-analysis

ERG comments - limitations

- The company's fixed effect NMA model assumed that there was no variability in treatment effects between studies beyond sampling variation; ERG argues that this assumption is likely to be inappropriate, since heterogeneity is expected.
- The results from a fixed effect model should therefore be interpreted with caution as the uncertainty in treatment effects was underestimated.
- A random effects model was used by the ERG to allow for heterogeneity in treatment effects between studies. This resulted in similar point estimates but wider credible intervals.
- ERG's clinical advisor considers the claim of clinical similarity between the treatments to be biologically plausible.
- The ERG compared the 12 week outcomes data from the golimumb trial (used in the NMA) with the 16-week outcome data (published trial data) and considered the results to be comparable.
- Company were unable to run NMA for SF-36 MCS and PCS at time of clarification response

Company submission: cost comparison

Technologies	Acquisition costs (£)	Total costs (£)
Golimumab 50 mg and 100 mg once monthly	762.97	9,155.64
Adalimumab 40 mg once every two weeks	352.14	9,155.64
Etanercept 50 mg once weekly	178.75	9,295
Etanercept 25 mg twice weekly	89.38	9,295.52
Certolizumab pegol[a] 400 mg at weeks 0, 2 and 4, then 400 mg once every 4 weeks	715	5,720[b] 9,925[c]
Certolizumab pegol[a] 400 mg at weeks 0, 2 and 4, then 200 mg once every 2 weeks	357.50	5,720[b] 9,925[c]
1 year time horizon applied, no discount [a]Certolizumab pegol has a complex patient access scheme providing the first 10 doses as free stock (equivalent to the first 12 weeks) [b]year 1 only, [c]year 2 and thereafter, excluding initiation PAS		

Source: CS, table 22

- No differences in the initiation, administration and monitoring costs of golimumab and the comparators
- Resource use costs excluded from the cost comparison analysis

ERG review: cost comparison

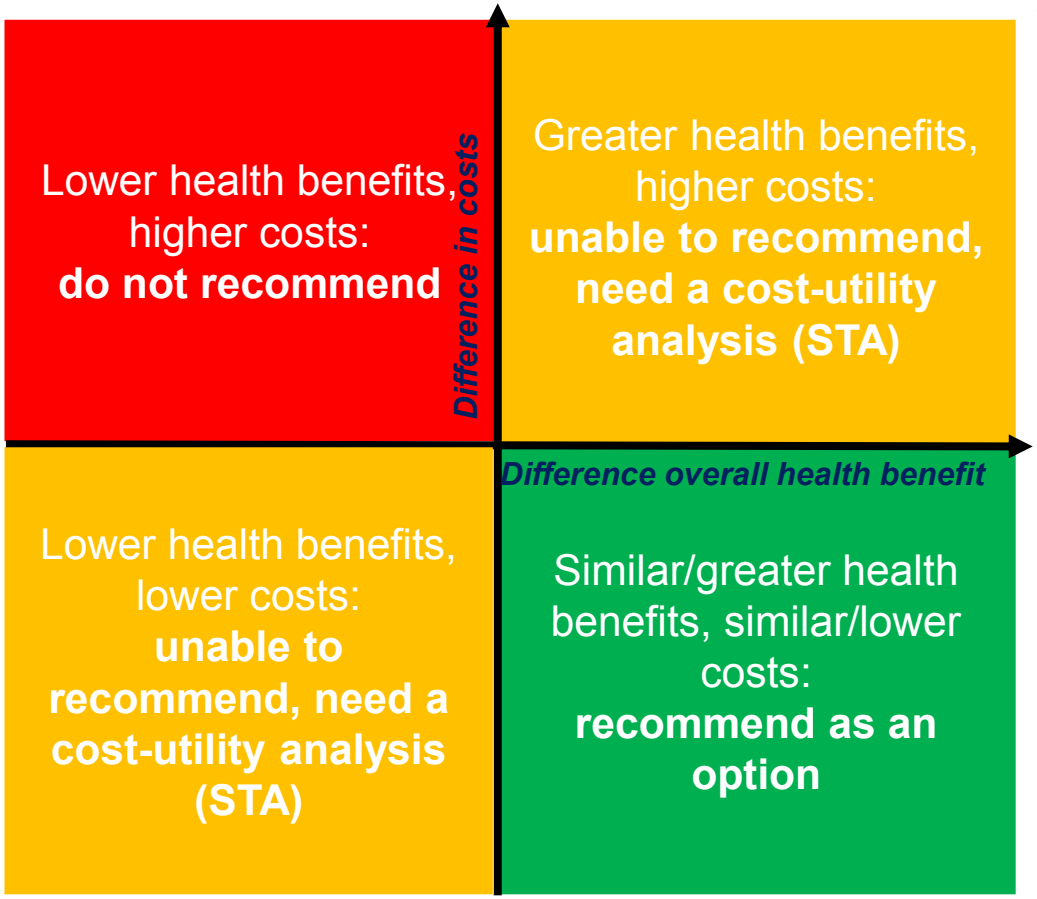
- Administration, monitoring and costs for treating AEs is similar to comparators.
- Dose increase for golimumab (50 mg to 100 mg) in patients with a body weight >100 kg would not adversely impact the cost-comparison if:
  - patients have a similar or greater chance of having an adequate response compared to switching to a second anti-TNF
  - the impact of any increase in AEs is small.
- Acquisition cost for golimumab in both the 1st and subsequent years of treatment is similar to at least one of the comparators, but it is not lower than all of the comparators in both the 1st and subsequent years.
- Acquisition costs for comparator biosimilars were not presented. Etanercept BNF list price for biosimilar is 8% lower (£656 vs £715). List price for adalimumab biosimilar not yet available.
- ERG's clinical advisor: uptake of biosimilars is variable across NHS trusts; golimumab may be cost-neutral or cost-saving relative to current practice in some areas of England.
- Low risk that recommending golimumab will lead to a substantial increase in NHS costs if the recommendations for golimumab contain similar instructions as in TA383 to ensure that the lowest cost anti-TNF is used in practice.

Additional considerations
Patient and clinical expert submissions

National Ankylosing Spondylitis Society submission based on a survey of 2000 people with AS noted that an additional treatment would be welcomed given the fewer treatment options available for nrAS compared with AS.

- Golimumab:
  - once every 4 week dosing, providing choice and more flexibility for patients which is not available from the current subcutaneous anti-TNF inhibitors.
  - Once monthly doing was considered to be important by the NASS
  - will potentially treat and improve both ulcerative colitis (which can be an extra-articular manifestation of axial spondyloarthritis) and axial spondyloarthritis as it is indicated in both conditions.
  - is well tolerated and comparable to the existing anti-TNF agent therapies
  - will be a good additional option for people with non radiographic axial spondyloarthritis.

Potential committee recommendations and rationale



What is the committee view on:

- The clinical efficacy and safety of golimumab vs. placebo?
- The design and reliability of the NMA for the purposes of decision making?
- The similarity of the acquisition cost of golimumab compared with other recommended treatments?
- Whether the lifetime costs and benefits are likely to be similar to other recommended treatments?
- Whether in light of the above it is reasonable to recommend golimumab in the same way as TA383?