NICE National Institute for Health and Care Excellence

Fast Track Appraisal

Golimumab for treating non-radiographic axial spondyloarthritis [ID903]

Committee Papers

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NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

FAST TRACK APPRAISAL

Golimumab for treating non-radiographic axial spondyloarthritis [ID903]

Contents:

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Technical briefing

Golimumab for treating non-radiographic axial spondyloarthritis

This slide set is the technical briefing for this appraisal. It has been prepared by the technical team and it is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the appraisal committee meeting and is expected reading for committee members. The submissions made by the company, consultees and nominated experts as well as the ERG report are available for committee members, and are optional reading.

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The technologies (1)

	Golimumab (intervention)	Comparators: adalimumab, etanercept, certolizumab pegol (TA383)
Mechanism 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 word ‘active’

The technologies (2)

	Golimumab (intervention)	Comparators: adalimumab, etanercept, certolizumab pegol (TA383)
Administration and dose (all drugs administered subcutaneously)	50 mg or 100 mg (for patients weighting >100kg) once a month	Adalimumab: 40 mg every other week Certolizumab pegol: 400 mg (given as 2 injections of 200 mg each) at weeks 0, 2 and 4; Maintenance regimen: 200 mg every other week or 400 mg every 4 weeks Etanercept: 25 mg twice weekly or 50 mg once weekly
Monitoring	Quarterly	
Annual cost per course of treatment	£9155.54 (including PAS) in year 1 and subsequent years	Adalimumab: £352.14 for a 40 mg pre-filled pen or pre-filled syringe, or a 40 mg/0.8 ml vial Certolizumab pegol: £10,368 (or with the patient access scheme, £6793) Etanercept: £9,296

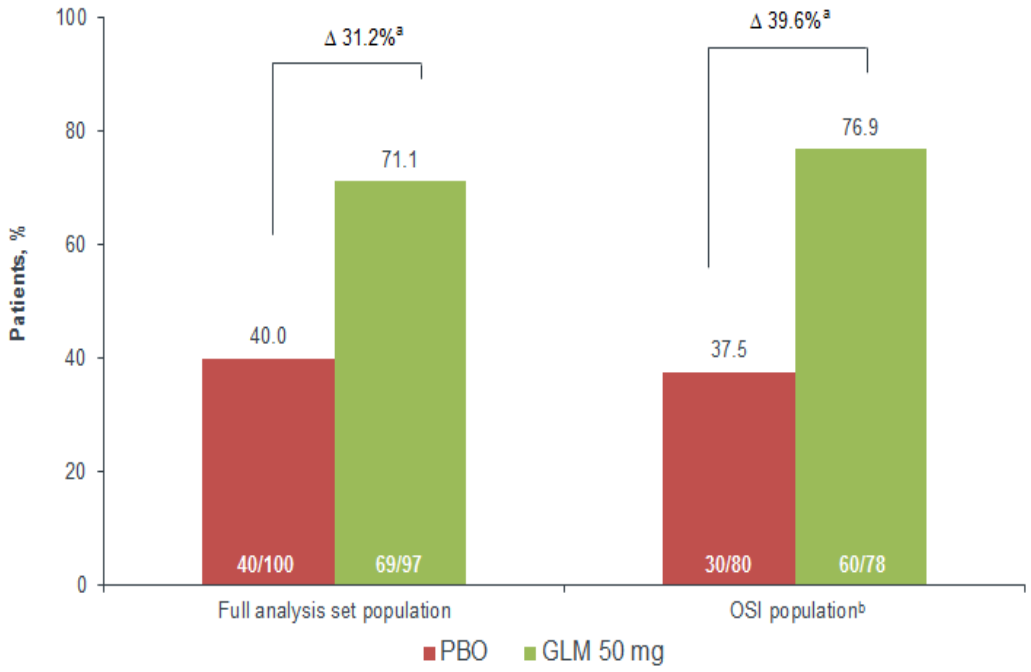
Key drivers of the cost-effectiveness of the comparators (TA383)

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 the committee considered them as a class. • No registry data on the efficacy of a 2nd or 3rd TNF inhibitor in non-radiographic spondyloarthritis, although clinical experts considered the efficacy is likely to reduce with each subsequent treatment. • In the AG model responders had lower baseline BASDAI and BASFI scores than non-responders which the committee did not think was plausible
Resource use assumptions	• The committee agreed with the AG used assumptions: drug initiation, monitoring, administration, acquisition costs.
Resource use uncertainties	• Sequential use of TNF inhibitors was not modelled because of lack of data

Company's clinical effectiveness evidence

- GO-AHEAD – randomised controlled trial that assessed golimumab 50 mg versus placebo in patients:
  - 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)
- 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
- Outcome time point 12 weeks for all studies except for safety data and change from baseline BASMI from GO-AHEAD (reported at 16 weeks).
- Company clarified that 16 week assessment was conservative (systemic levels of golimumab are lower than at 14 weeks).

ASAS20 response at Week 16 (primary outcome)



- 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.

OSI population: signs of inflammation by MRI or elevated CRP at baseline

Source: CS figure 3

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
Cholelithiasis	0	1 (1.0)
Back pain	0	1 (1.0)
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)
Company & ERG

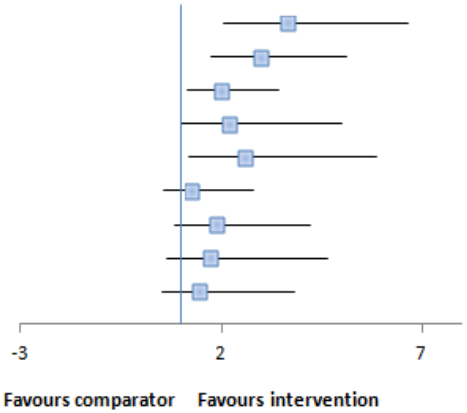
- Trials for the comparators in the NMA are the same as those in TA383. The GO-AHEAD trial was added and infliximab (which does not have a MA for nrAS) removed and the population was similar and comparable across the trials:
  - Age (>30-<40 years)
  - % of male (45-60%)
  - disease duration for golimumab 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 who were MRI and/or CRP positive was reasonably comparable for golimumab, adalimumab and etanercept but was not reported for certolizumab pegol
  - Proportion of patients who were HBA-L27 positive was reasonably comparable across trials (67-82%).
  - All trials reporting the prior treatments of patients indicated that patients were biologic-naïve, except certolizumab pegol (10.9%).

Similarity of health benefits and safety (1)

Company NMA results

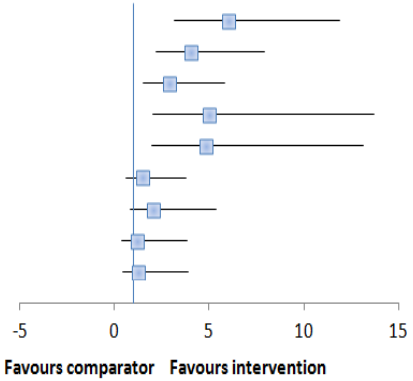
ASAS 20 base case

Comparison	Median OR	[95% CrI]
GLM vs. PBO	3.63	[2.03, 6.62]
ADA vs. PBO	2.93	[1.70, 5.10]
ETN vs. PBO	1.96	[1.14, 3.41]
CZP 200mg vs. PBO	2.16	[0.96, 4.97]
CZP 400mg vs. PBO	2.57	[1.17, 5.83]
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]



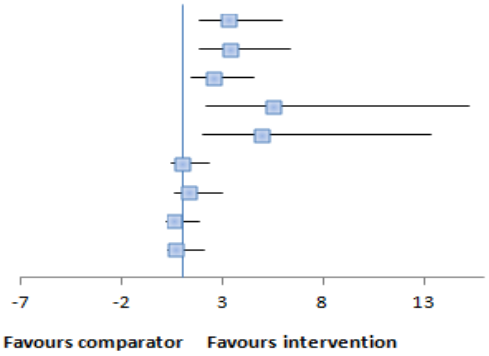
ASAS 40 base case

Comparison	Median OR	[95% CrI]
GLM vs. PBO	5.99	[3.15, 11.87]
ADA vs. PBO	4.06	[2.17, 7.90]
ETN vs. PBO	2.91	[1.51, 5.82]
CZP 200mg vs. PBO	5.01	[1.97, 13.70]
CZP 400mg vs. PBO	4.86	[1.95, 13.09]
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

Comparison	Median OR	[95% CrI]
GLM vs. PBO	3.23	[1.78, 5.95]
ADA vs. PBO	3.31	[1.79, 6.33]
ETN vs. PBO	2.51	[1.40, 4.54]
CZP 200mg vs. PBO	5.51	[2.16, 15.23]
CZP 400mg vs. PBO	4.87	[1.96, 13.29]
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

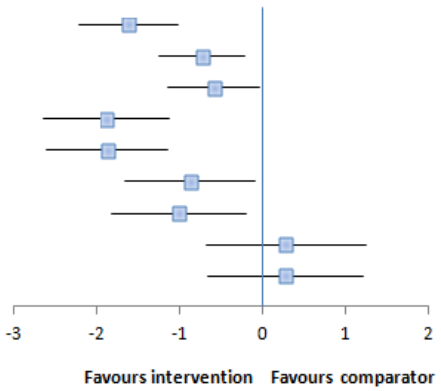
Source: CS figures 20, 21, 22

Similarity of health benefits and safety (2)

Company NMA results

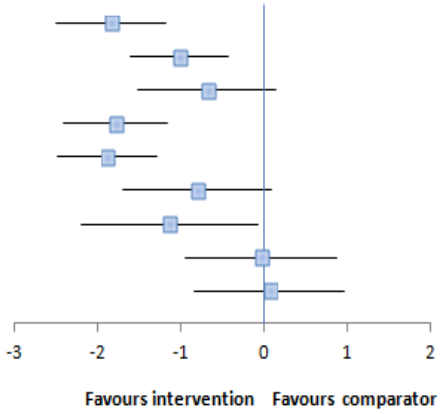
Δ BASFI

Comparison	Median DIFF	[95% CrI]
GLM vs. PBO	-1.64	[-2.24, -1.03]
ADA vs. PBO	-0.75	[-1.27, -0.23]
ETN vs. PBO	-0.60	[-1.15, -0.05]
CZP 200mg vs. PBO	-1.90	[-2.65, -1.14]
CZP 400mg vs. PBO	-1.89	[-2.63, -1.16]
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]



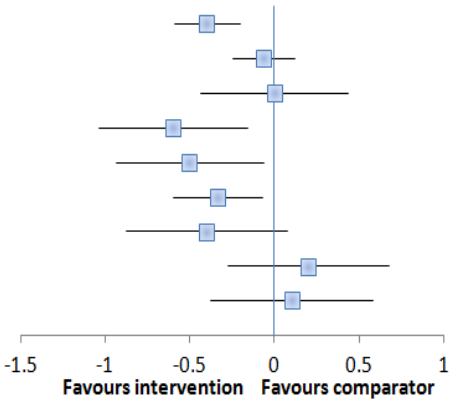
ΔBASDAI

Comparison	Median DIFF	[95% CrI]
GLM vs. PBO	-1.85	[-2.51, -1.19]
ADA vs. PBO	-1.03	[-1.63, -0.44]
ETN vs. PBO	-0.70	[-1.53, 0.13]
CZP 200mg vs. PBO	-1.80	[-2.42, -1.17]
CZP 400mg vs. PBO	-1.90	[-2.51, -1.29]
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

Comparison	Median DIFF	[95% CrI]
GLM vs. PBO	-0.40	[-0.59, -0.21]
ADA vs. PBO	-0.06	[-0.25, 0.12]
ETN vs. PBO	0.00	[-0.44, 0.44]
CZP 200mg vs. PBO	-0.60	[-1.04, -0.16]
CZP 400mg vs. PBO	-0.50	[-0.94, -0.06]
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

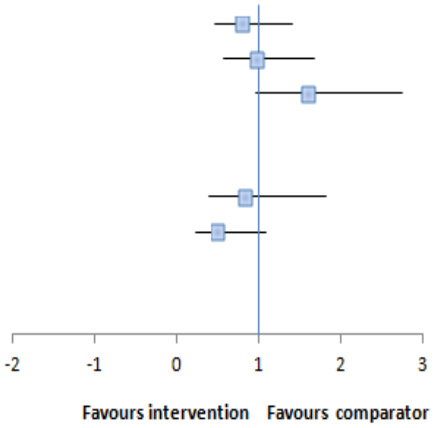
Source: CS figures 23, 24, 25

Similarity of health benefits and safety (3)

Company NMA results

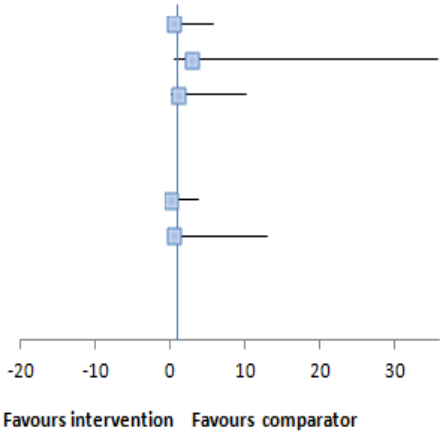
Adverse events

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		



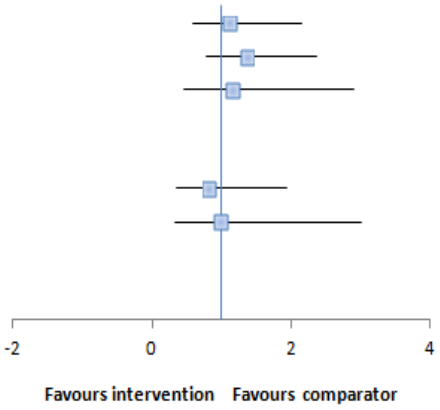
Serious adverse events

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

- Differences in baseline characteristics and disease indicators were explored in 5 sensitivity analyses and showed that it had no significant impact on final efficacy results for golimumab.
- Primary endpoints and selected analyses for clinical efficacy were appropriate
- 16-week follow-up in the GO-AHEAD is acceptable
- 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

Company submission: cost comparison

Technologies	Acquisition costs (£)	TOTAL COSTS (£)
Golimumab 50 mg and 100 mg once daily	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 400 mg at weeks 0, 2 and 4, then 400 mg once every 4 weeks	715	5,720 9,925*
Certolizumab pegol 400 mg at weeks 0, 2 and 4, then 200 mg once every 2 weeks	357.50	5,720 9,925*
1 year time horizon applied, no discount *(year 2 and thereafter, excluding initiation PAS)		

- 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 comparator, 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

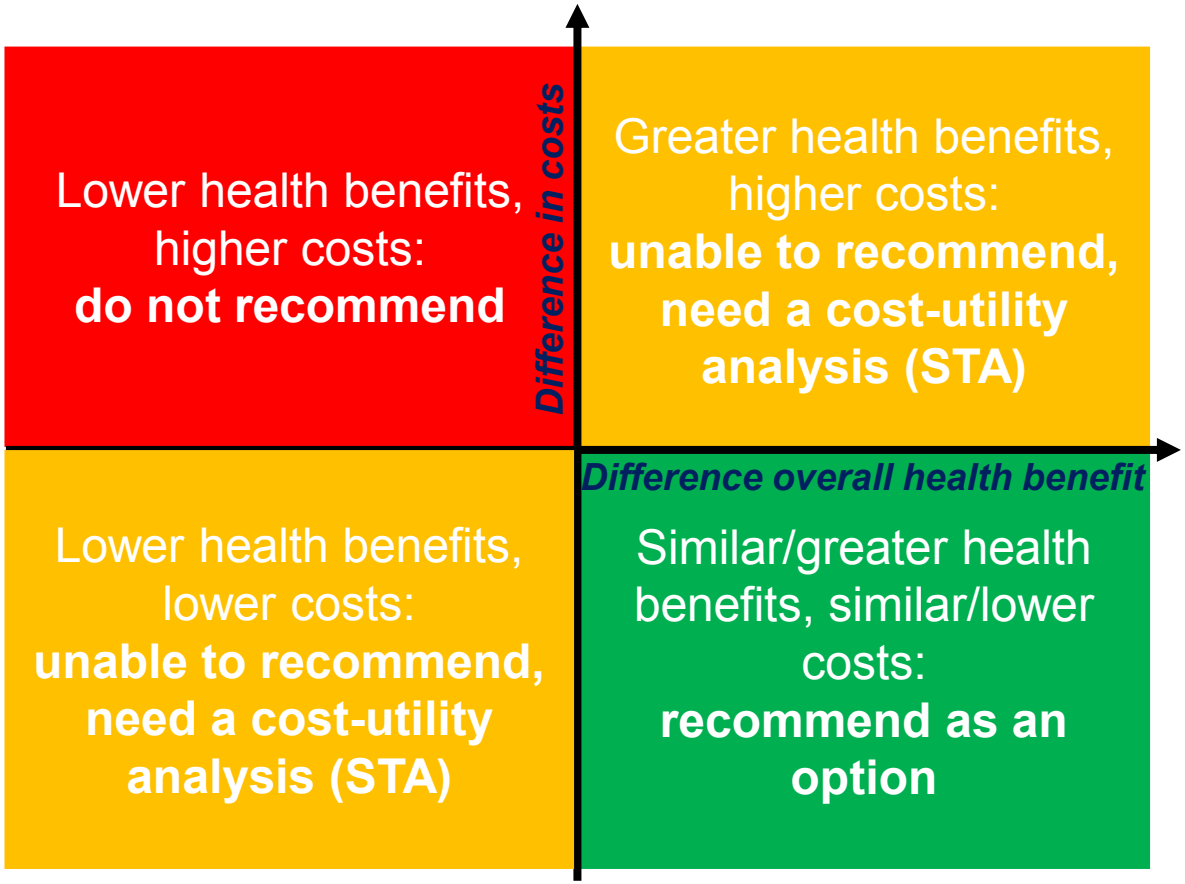
- Golimumab:
  - allows for once every 4 week dosing, providing choice and more flexibility for patients which is not available from the current subcutaneous anti-TNF inhibitors.
  - will potentially treat and improve both ulcerative colitis (which can be an extra-articular manifestation of axial spondyloarthritis) 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.

Technical team recommendation and rationale

Criteria for cost comparison case are met

- TA383 noted that the clinical effectiveness of the TNF inhibitors was so similar that they should be considered as a class.
- The company's indirect treatment comparison shows clinical similarity in the efficacy of golimumab with comparator TNF inhibitors for ASAS20, ASAS40 and BASDAI between golimumab and NICE recommended comparators in TA383 (adalimumab, etanercept, certolizumab pegol).
- The main resource use associated with golimumab and comparators is drug acquisition (no difference in administration and monitoring).
- When the PAS for golimumab and certolizumab is taking into account over the long term (year 1 onwards) golimumab is cost neutral or cost saving compared with comparators and would not introduce any additional burden to the NHS.

Potential recommendations: cost comparison



Key issues:

- Is it appropriate to assume that the response to golimumab at 16 weeks will be similar or no worse than at 12 weeks.
- In people over 100 kg who at 12 weeks receive 100 mg golimumab; is it reasonable to assume that the response and AE's will be similar/no worse than to other TNF inhibitors.
- Is there any rationale not to recommend golimumab as the other TNF inhibitors in TA383?

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Fast track appraisal: cost-comparison case

Golimumab for treating non-radiographic axial spondyloarthritis [ID903] [NoACIC]

Company evidence submission summary for committee

MSD confirm that all information in the submission summary is an accurate summary or replication of evidence in the main submission and accompanying appendices and that wherever possible a cross reference to the original source is provided.

9th June 2017

File name	Version	Contains confidential information	Date
		None	9th June 2017

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Tables and figures

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Submission summary

A.1 The technology

Table 1 - Technology being appraised – (Section B.1.2, Table 2 - page 11)

UK approved name and brand name	Golimumab (SIMPONI®)
Mechanism of action	Golimumab is a human monoclonal antibody that forms high affinity, stable complexes with both soluble and transmembrane bioactive forms of human TNF-alpha, which prevents the binding of tumour necrosis factor (TNF)-alpha to its receptors. TNF-alpha is an important mediator of articular inflammation and it is implicated in the pathophysiology of several chronic inflammatory diseases such as rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis, where elevated TNF-alpha levels in the blood, synovium, and joints are detected.
Marketing authorisation/CE mark status	The European Medicines Agency granted a marketing authorisation for golimumab for the treatment of non-radiographic axial spondyloarthritis (nr-axial SpA) on 22nd June 2015 (MSD 2017).
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The indication to which this submission relates is: the treatment of adults with severe, active nr-axial SpA with objective signs of inflammation (OSI) 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 non-steroidal anti-inflammatory drugs (NSAIDs). Other indication for which golimumab is licensed, are: *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 anti-rheumatic drugs (DMARD) therapy including MTX has been inadequate. • the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with MTX. Golimumab, 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 *Juvenile idiopathic arthritis* Polyarticular juvenile idiopathic arthritis (pJIA) Golimumab in combination with MTX is indicated for the

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	treatment of polyarticular juvenile idiopathic arthritis in children with a body weight of at least 40 kg, who have responded inadequately to previous therapy with MTX. *Psoriatic arthritis (PsA)* Golimumab, alone or in combination with MTX, is indicated for the treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate. Golimumab has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease and to improve physical function. *Axial Spondyloarthritis (AS)* Golimumab is indicated for the treatment of severe, active ankylosing spondylitis in adults who have responded inadequately to conventional therapy. *Ulcerative colitis (UC)* Golimumab is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.
Method of administration and dosage	Golimumab is administered subcutaneously (SC) once a month. Golimumab is available at the following doses in a pre-filled pen or pre-filled syringe: 50mg or 100mg Available data suggest that clinical response is usually achieved within 12 to 14 weeks of treatment (after 3-4 doses). Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit within this time period. For patients with bodyweight greater than 100 kg who do not achieve an adequate clinical response after 3 or 4 doses, increasing the dose of golimumab to 100 mg once a month may be considered, taking into account the increased risk of certain serious adverse drug reactions with the 100 mg dose compared with the 50 mg dose. Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit after receiving 3 to 4 additional doses of 100 mg.
Additional tests or investigations	N/A
List price and average cost of a course of treatment	List price (BNF 2016): • SIMPONI® 50mg: £762.97 • SIMPONI® 100mg: £1525.94 (Excluding PAS) Annual cost of a course of treatment, assuming a dose of 50mg or 100mg:

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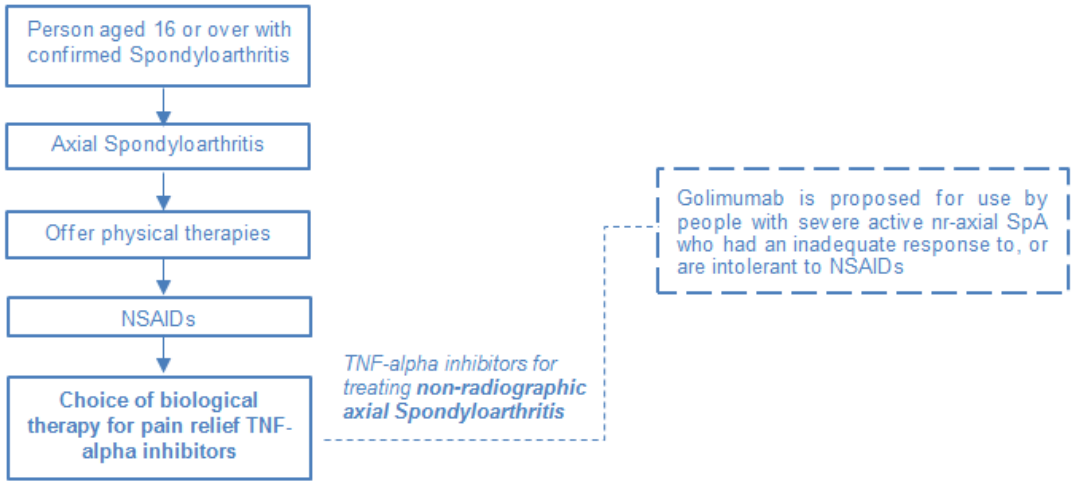
	• In year 1: £9155.54 (including PAS) • In subsequent years: £9155.54 (including PAS)
Patient access scheme (if applicable)	There is a Department of Health approved patient access scheme providing the 100 mg dose of golimumab at the same cost as the 50 mg dose of £762.97. This is a simple discount scheme providing discount at the point of invoice avoiding any administrative burden for the NHS

Abbreviations: TNF, tumour necrosis factor; nr-axial SpA, non radiographic axial spondyloarthritis; CRP, C reactive protein; MRI, magnetic resonance imaging; NSAIDs; non-steroidal anti-inflammatory drugs; MTX, methotrexate; DMARDs, disease modifying anti-rheumatic drugs; NHS, National Health Service; BNF, British National Formulary

A.2 Clinical pathway of care (Section B.1.3 page 13)

There have been no changes in the clinical pathway of care since NICE appraised the comparators in TA383.

Figure 1 Proposed position of golimumab within the clinical pathway of managing spondyloarthritis in adults (Section B.1.3, Figure 1 – page 13)



A.3 Equality considerations

MSD has not identified any equality issues.

A.4 Key drivers of the cost effectiveness of the comparator(s)

A.4.1. Clinical outcomes and measures

Key clinical outcomes and measures from competitor submission

In 2016 NICE published the Multiple Technology Appraisal (MTA), TA383 (NICE 2016), which assess the clinical effectiveness, safety, and cost-effectiveness of the TNF-alpha

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inhibitors adalimumab, certolizumab and etanercept for the indication of AS and nr-axial SpA, within the NHS. Nr-axial SpA is the focus of this submission.

The NICE committee identified five key clinical outcomes and measures that drove the cost-effectiveness analysis in TA383 (NICE 2016). These key outcomes and assumptions were:

- BASDAI50
- Baseline BASDAI and BASFI scores
- Change in BASDAI
- Change in BASFI
- Re-bound following discontinuation of TNF-alpha inhibitor

In the base case BASDAI 50 responders had lower baseline BASDAI and BASFI scores than responders, implying that patients with severe disease did not benefit as much as patients with less severe disease. Additionally it was necessary to assume how patients physical functioning progressed (BASFI) whilst they were receiving TNF-alpha inhibitors and how patients rebound following discontinuation of treatment.

The sensitivity analyses conducted to assess the impact of the five key clinical outcomes and the assumptions made are summarised in Table 2 below.

Table 2 Sensitivity analysis conducted in TA383 (NICE 2016) (Section B.2.1, Table 3 – page 16)

Parameter/Assumption	Base-case assumption	Sensitivity analysis
Different baselines assumed for responders and non-responders, and change in BASDAI/BASFI scores.	Separate baselines and changes in BASDAI/BASFI conditioned on responses estimated via extended synthesis model.	Separate baselines based on pooled estimates provided by manufacturers. Changes in BASDAI/BASFI conditioned on responses estimated via extended synthesis model.
BASFI progression.	Treatment effect applied from year 4 onwards.	No effect of TNF-alpha inhibiters on BASFI progression.
BASFI progression.	Treatment effect applied from year 4 onwards.	Treatment effect of TNF-alpha inhibitors applied from the start of the model.
Rebound following discontinuation of treatment.	Rebound equal to gain	Rebound equal to convention care
BASDAI50	Characterised efficacy achievement	No sensitivity analysis conducted.

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Abbreviations: BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; TNF, tumour necrosis factor

The impact of the outcomes and TA383 committee's preferred assumptions are summarised in Table 3 below. All results assume BASFI rebound equal to gain as this was the NICE committee's a preferred assumption. .

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Table 3 - Clinical outcomes and measures appraised in TA383 (rebound equal to gain) (Section B.2.1, Table 4 – page 17)

	Outcome	Measurement scale	Used in cost-effectiveness model?	Impact on ICER*	Committee's preferred assumptions	Uncertainties
TA383 (NICE 2016)	BASFI rebound equal to gain	BASFI	Yes	Rebound to conventional care significantly increased the ICERs between £3,561 and £4,979	Rebound equal to gain	-
	Change in BASFI	BASFI (no effect of TNF-alpha inhibitors on BASFI progression)	Yes	The ICER for Adalimumab marginally increased by £318, yet for the other comparators the ICER declined by £396 to £955	TNF-alpha inhibitors have an effect on BASFI progression	-
		BASFI (Treatment effect of TNF-alpha inhibitors applied from the start of the model)	Yes	ICERS increased between £265 to £1,522	TNF-alpha inhibitor effect on progression is applied at the start of the model.	-
	Change in BASDAI	Different baseline scores assumed for responders and non-responders, and change in BASDAI/BASFI scores	Yes	The ICERs significantly reduced between £1,429 and £2,765	No evidence to suggest that people with moderate disease were less likely to have a clinically meaningful benefit from TNF-alpha inhibitor use.	-

Abbreviations: ICER, Incremental Cost-Effectiveness Ratio; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; TNF, tumour necrosis factor

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The committee concluded that:

- Having discontinued from TNF-alpha inhibitors, rebounding to baseline was the most plausible assumption for progression of BASFI.
- Whilst receiving TNF-alpha inhibitor therapy BASFI continued to deteriorate, but at a slower rate than if conventional care (natural history) had been used alone.
- The positive effect of TNF-alpha inhibitors on disease progression was felt immediately.
- No evidence to suggest patients with severe disease were less likely to achieve a clinical benefit than those with less severe disease.

A.4.2. Resource use assumptions

The NICE committee agreed with assessment group assumptions on resource use and unit costs.
Summarised below are the healthcare resource use and unit costs associated with drug acquisition, drug administration and monitoring, long-term disease management and adverse events.
All costs were updated to 2015/16 prices using the latest unit costs or inflated using the HCHS inflation index (Curtis 2016).

Drug acquisition costs
Table 4 below summarises the licenced doses of the TNF-alpha inhibitors assessed in TA383, whilst Table 5 presents the drug acquisition costs.

Table 4 - TNF-alpha inhibitor comparators licensed dosage (Section B.2.2, Table 5 – page 18)

Drug	Licensed dosage
Adalimumab (Abbvie 2017)	• 40mg administered every other week via SC injection
Certolizumab pegol (UCB 2016)	• 400mg administered at weeks 0, 2, and 4, and every 4 weeks thereafter. • 400mg administered at weeks 0, 2, and 4, and then 200mg

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Drug	Licensed dosage
	given every two weeks thereafter.
Etanercept (Pfizer 2017)	• 50mg administered once weekly • 25mg administered twice weekly

Table 5 - Drug acquisition costs (Section B.2.2, Table 6 – page 19)

Comparator	Strength	Unit cost (per pre-filled syringe/pen)	Dosage	Annual cost	Reference
Adalimumab	40mg	£352.14	Every two weeks by subcutaneous injection (SC)	£9,155.64	BNF 2017
Certolizumab pegol	400mg	£715	Every four weeks by SC	£9,295.00 (£5,720 with PAS*)	BNF 2017
	200mg	£357.50	Every two weeks by SC	£9,295.00 (£5,720 with PAS*)	BNF 2017
Etanercept	50mg	£178.75	Once a week by SC	£9,295.00	BNF 2017
	25mg	£89.38	Twice a week by SC	£9,295.52	BNF 2017

Abbreviations: BNF, British National Formulary; PAS, Patient Access Scheme, * Certolizumab pegol has a complex PAS where the first 10 doses, approximately the first 12 weeks, are provided as free stock

Drug administration

For the cost of administration training, the cost of an hour of patient related nurse time of £108 (Curtis 2016), (Specialist Nurse, Band 6, face to face contact [£44 per working hour]) was assumed for all subcutaneous TNF-alpha inhibitors in TA383. It was assumed that drug administration did not differ between TNF-alpha inhibitors.

The NICE committee assumed that after the initial training, patients would be able to self-administer the subcutaneous injection

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Initiation and monitoring costs

The initiation and monitoring assumptions were originally sourced from the NICE TA199 (NICE 2010) York Model for psoriatic arthritis, and conformed to the guidelines from the British Society of Rheumatology (BSR 2016), on patient eligibility for the use of biologic treatment.

The initiation period was aligned to the SmPCs of adalimumab, certolizumab and etanercept (Abbvie 2017) (UCB 2016) (Pfizer 2017), which states that a clinical response is usually achieved within 12 weeks of therapy. As such, from this point it was considered that patients were in the maintenance period of health care. Resource use is presented below in Table 6 as quarterly monitoring.

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Table 6 - Initiation and monitoring resource use and costs (Section B.2.2, Table 7 – page 21)

Item	Resource use		Costs		Cost reference
	Initiation period (12 weeks)	Quarterly monitoring	Initiation period (12 weeks)	Quarterly monitoring	
Full Blood Count (FBC)	2	1	£6.08	£3.04	TA383 (NICE 2016), inflated using the HCHS inflation index (Curtis 2016)
Erythrocyte sedimentation rate (ESR)	2	1	£6.04	£3.02	TA383 (NICE 2016), inflated using the HCHS inflation index (Curtis 2016)
Liver Function Test (LFT)	2	1	£1.54	£0.77	TA383 (NICE 2016), inflated using the HCHS inflation index (Curtis 2016)
Urea and Electrolytes (U&E)	2	1	£2.82	£1.41	TA383 (NICE 2016), inflated using the HCHS inflation index (Curtis 2016)
Chest X-ray	1	0.25	£26.78	£6.70	TA383 (NICE 2016), inflated using the HCHS inflation index (Curtis 2016)
Tuberculosis (TB) Heaf test	1	0	£8.92	£0	TA383 (NICE 2016), inflated using the HCHS inflation index (Curtis 2016)
Antinuclear antibody (ANA)	1	0	£4.75	£0	TA383 (NICE 2016), inflated using the HCHS inflation index (Curtis 2016)
Double-stranded (ds) DNA test	1	0	£4.75	£0	TA383 (NICE 2016), inflated using the HCHS inflation index (Curtis 2016)
Specialist visit	2	0.5	£274 .00	£68.50	NHS Reference costs 2015/16
MRI cost	1	0	£145.14	£0	NHS Reference costs 2015/16
C reactive protein (CRP) test	1	0	£6.77	£0	TA383 (NICE 2016), inflated using the HCHS inflation index (Curtis 2016), originally sourced from Henriksson 2010
		Total	£595.59	£83.44	

Abbreviations: TA, technology appraisal; HCHS, Health Care and Hospital Services; PSSRU, Personal and Social Services Resource Use; NHS, National Health Service

A total cost of £595.59 was attributed to the induction period tests and a cost of £83.44 to monitoring the patient and disease progression every quarter thereafter.

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Table 7 below summarises the drug acquisition, administration and monitoring costs for each of the TNF-alpha inhibitors.

Table 7 - Summary of drug acquisition, administration and monitoring costs (Section B.2.2, Table 8 – page 23)

	Initiation period (3 months)*			Annual costs (after initial period)			Total costs	
Treatment/dosage	**Acquisition drug cost**	**Administration cost**	**Monitoring cost**	**Acquisition drug cost**	**Administration cost**	**Monitoring cost**	**Initial period**	**Subsequent annual cost**
Adalimumab / (40mg every other week) (BNF 2016)	£2,112.84	£108	£595.59	£7,042.80	£0	£83.44	£2,816.43	£8,534.84
Certolizumab / 200mg every two weeks (BNF 2016)	£2,145†	£108	£595.59	£7,150	£0	£83.44	£2,848.59	£8,663.44
Certolizumab / 200mg every two weeks (PAS applied) (BNF 2016)	£0	£108	£595.59	£7,150	£0	£83.44	£703.59	£8,663.44
Etanercept / 50mg once per week (BNF 2016)	£2,145	£108	£595.59	£7,150	£0	£83.44	£2,848.59	£8,663.94
Etanercept / 25mg twice per week	£2,145.12	£108	£595.59	£7,150.4	£0	£83.44	£2,848.71	£8,663.44

Abbreviations: BNF, British National Formulary; PAS, Patient Access Scheme;
*It has been assumed that the induction period is a 3 month period (12 weeks). †Excluding loading doses for certolizumab pegol. Including the loading dose would increase the initiation period acquisition cost to £3,575.

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Long-term disease management costs

The NICE committee (NICE 2016) assumed that patients who remain on TNF-alpha inhibitor treatment incur disease management costs over the long-term. The committee also decided that only BASFI should be employed as the major predictor of costs as it reflects long-term disease progression, whilst BASDAI appears to fluctuate but not increase over time.
The committee concluded that the Outcomes in Ankylosing Spondylitis International Study (OASIS) (Boonen et al. 2003,) data as the most reliable source, which was applied in the regression equation developed by AbbVie,

$$NHS\ cost = £1{,}439.18\ x\ EXP\ (0.213\ x\ BASFI)$$

Note: The cost element of the equation has been adjusted to 2015/16 prices using the HCHS Pay and Prices Index (Curtis 2016).

Adverse reaction unit costs and resource use

In TA383, only the costs of serious infections and TB reactivation were included in the economic evaluation. The costs of serious infection were sourced from the Pfizer submission, and TB reactivation costs were originally based on the Cochran review of adverse events. Both were based on a weighted average of the relevant Health Care Resource Groups (HRG) codes. As the HRG codes have changed both of the serious infection and TB costs have been inflated using the PSSRU 2016 HCHS inflation index and are presented below.

- Cost of serious infection: £1,489.60
    - Old HRG codes: WA03C/DZ23G/LA04M/PA16B/DZ22J/DZ21U
- Cost of TB reactivation: £3,276.20
    - Old HRG codes: DZ14C/DZ14D/DZ14E

A.5 Decision problem and NICE reference case

This submission covers the golimumab (Simponi) full marketing authorisation for this indication: treatment of adults with severe, active non-radiographic axial spondyloarthritis (nr-axial SpA) with objective signs of inflammation (OSI) 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 non-steroidal anti-inflammatory drugs (NSAIDs) (MSD 2017).

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Table 8 - The decision problem – (Section B.1.1, Table 1 - page 9)

	Final scope issued by NICE (February 2017)	**Decision problem addressed in the company submission** (June 2017)	**Rationale if different from the final NICE scope**
Population	People with severe active non-radiographic axial spondyloarthritis with objective signs of inflammation, whose disease has responded inadequately to, or who are intolerant to, non-steroidal anti-inflammatory drugs	People (18 years and older) with severe active non-radiographic axial spondyloarthritis with objective signs of inflammation, whose disease has responded inadequately to, or who are intolerant to, non-steroidal anti-inflammatory drugs	Not applicable
Intervention	Golimumab	Golimumab	Not applicable
Comparator(s)	Adalimumab Certolizumab pegol Etanercept	Adalimumab Certolizumab pegol Etanercept	Not applicable
Outcomes	• disease activity • functional capacity • disease progression • pain • peripheral symptoms (including enthesitis, peripheral arthritis and dactylitis) • symptoms of extra-articular manifestations (including uveitis, inflammatory bowel disease and psoriasis) • adverse effects of treatment • health-related quality of life	• disease activity • functional capacity • disease progression • pain • peripheral symptoms (including enthesitis, peripheral arthritis and dactylitis) • symptoms of extra-articular manifestations (including uveitis, inflammatory bowel disease and psoriasis) • adverse effects of treatment • health-related quality of life	Not applicable

Abbreviations: TA, technology appraisal; SmPC, Summary of Product Characteristic

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A.6 Clinical effectiveness evidence

The efficacy of golimumab has been evaluated in a Phase 3, multicentre, randomised, parallel-group, double-blind, placebo-controlled study of the treatment of patients with active nr-axial SpA, GO-AHEAD (NCT01453725/GO-AHEAD 2011/ Sieper et al 2015). A comprehensive summary of the GO-AHEAD trial is presented **Table 9** below.

Table 9 - Clinical effectiveness evidence (Section B.3.2, Table 10 - page 26)

Study	**GO-AHEAD (NCT01453725/GO-AHEAD 2011/ Sieper et al 2015)**
Study design	A two part phase 3, multicentre, randomised, parallel-group, double-blind, placebo-controlled trial with a 16-week double-blind phase and a 44-week open-label extension
Population	Patients ages ≥18 years to ≤45 years who had active nr-axial SpA according to the Assessment of SpondyloArthritis international Society (ASAS) criteria for ≤5 years since diagnosis, high disease activity, and an inadequate response to or intolerance of NSAIDs.
Intervention(s)	Golimumab (N=98) • Part 1: SC injection of golimumab 50mg at baseline (week 0) and then at week 4, 8, and 12 (16 weeks of treatment) • Part 2: All patients (N=189; from golimumab Part 1 and placebo Part 1 patients) received golimumab 50 mg SC at Week 16 and every 4 weeks thereafter, with the final dose administered at Week 48. After this, patients were to be followed for safety for 12 weeks (44 weeks open label study)
Comparator(s)	Placebo (N=100) • Part 1: SC injection of placebo every 4 weeks at baseline (week 0) and then at week 4, 8, and 12 (16 weeks of treatment). • Patients continuing to the OLE switched to golimumab 50 mg (PBO/GLM, n=96)
Reported outcomes specified in the decision problem	Disease activity outcomes • ASAS 20 • ASAS 40 • BASDAI 50 • Change in BASDAI Functional capacity • Change in BASFI Pain • Total back pain, 10-cm VAS Peripheral symptoms • MASES Symptoms of extra-articular manifestations

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	• Uveitis • IBD • Psoriasis HRQoL outcomes, including: • ASQoL • SF-36 [mental and physical component scores] • EQ-5D [index score and VAS] Adverse effects • Treatment-emergent and treatment-related AEs • Serious AEs • Infections • Injection site reactions • Malignancies • Deaths
Superiority, equivalence or non-inferiority trial?	Superiority trial
Reference to section in submission	Section B.3.2 (Table 10)

Abbreviations: AEs, adverse events; ASAS, Assessment of Spondyloarthritis International Society; ASQoL, Ankylosing Spondylitis Quality of Life; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; EPAR, European public assessment report; EQ-5D, EuroQol 5-dimensions questionnaire; GLM, golimumab; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; mg, milligram; nr-axial SpA, non-radiographic axial Spondyloarthritis; NSAID, non-steroidal anti-inflammatory drugs; OLE, open-label extension; PBO, placebo; SF-36, 36-Item Short Form Survey; VAS, visual analogue scale

A.7 Key results of the clinical effectiveness evidence

The key clinical outcomes taken from the GO-AHEAD trial, that reflect the outcomes included in TA383 include:

- BASDAI50
- ASAS20
- ASAS40
- Change in BASDAI
- Change in BASFI
- Change in BASMI

BASDAI50 (Section B.3.6.2 – page 41)

BASDAI50 is a key marker of disease activity and response to treatment, whereby it represents a 50% improvement from baseline, of the BASDAI score. Statistically significant differences between golimumab and placebo were observed for BASDAI50 (golimumab 57.7% versus placebo 30.0%, difference versus placebo [95%CI] = 28.0% [14.4%, 40.6%], p<0.0001).

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ASAS20 (Section B.3.6.1 – page 38)

In the full analysis set (FAS) the percentage of patients achieving ASAS20 response at 16 weeks in the golimumab group was significantly higher than in the placebo group (golimumab 71.1% versus placebo 40.0%; difference versus placebo [95%CI] = 31.2% [17.5%, 43.6%], p<0.0001) (Figure 3, Section B.3.6.1 – page 38). Analysis of ASAS20 response in the OSI population demonstrated a greater difference in response between golimumab and placebo-treated patients (golimumab 76.9% versus placebo 37.5%; difference versus placebo [95%CI] = 39.6% [24.6%, 52.6%], p<0.0001) (Figure 3, Section B.3.6.1 – page 38).

ASAS40 (Section B.3.6.2 – page 41)

In the FAS, the percentage of patients achieving ASAS40 response at 16 weeks in the golimumab group was significantly higher than in the placebo group (golimumab 56.7% versus placebo 23.0%, difference versus placebo [95%CI] = 33.8% [20.4%, 46.1%], p<0.0001) (Figure 4, Section B.3.6.2 – page 40). The treatment group difference for this secondary endpoint was similar to that observed for the primary endpoint of ASAS20. A similar ASAS40 response was observed in the OSI population (Figure 5, Section B.3.6.2 – page 41).

Change in BASDAI, BASFI and BASMI from baseline score (Section B.3.6.3 – page 42)

The mean change from baseline in all scores at Week 16 in the golimumab group was significantly greater than in the placebo group as shown in Table 15 (Section B.3.6.3 – page 44) of the full submission.

Table 10 - Summary of efficacy outcomes (Table 15 Section B.3.6 page 44)

Study arm	Intervention group (GLM 50 mg) n=97	Comparator group (PBO) n=100	Difference (95% CI)	Statistical analyses
Disease activity				
BASDAI, mean (SD) Change from baseline	*n=93* 3.82 (0.25)	*n=96* -1.81 (0.24)	-2.00 (-2.68, -1.35)	P<0.0001
Functional capacity				
BASFI, mean (SD) Change from baseline	*n=93* 2.63 (0.23)	*n=97* -0.91 (0.22)	-1.73 (-2.33, -1.13)	P<0.0001
Spinal mobility				
BASMI, mean (SD) Change from baseline	*n=94* -0.48 (0.07)	*n=100* -0.08 (0.07)	-0.39 (-0.58, -	P<0.0001

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Study arm	Intervention group (GLM 50 mg) n=97	Comparator group (PBO) n=100	Difference (95% CI)	Statistical analyses
			0.20)	

Abbreviations: GLM, golimumab; PBO, placebo; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index

A.8 Evidence synthesis

Trials included within the NMA and identified through SLR are presented in Table 11 (Section B.3.9.1 Table 16 – page 53) and further explained in Appendix D and Section B.3.1.

Table 11 - Summary of the trials used to carry out the indirect or mixed treatment comparison (Section B.3.9.1 - Table 16)

Trial identifier	Golimumab	Adalimumab	Etanercept	Certolizumab pegol
GO-AHEAD (Sieper et al., 2015)	✓			
Haibel, 2008		✓		
ABILITY-1(Sieper et al., 2012)		✓		
Dougados, 2014			✓	
RAPID-axSpA (Landewé et al. 2013)				✓

Efficacy

For binary efficacy outcomes, results show that golimumab vs placebo had the largest median odds ratio for ASAS20 and ASAS40 outcomes (Figure 20 - 21, Section B.3.9.3 – page 56); however, the CrIs crossed one for active treatment comparisons (not statistically significant). Certolizumab pegol 400 mg and certolizumab pegol 200 mg had the largest median odds ratios for BASDAI50 (Figure 22, Section B.3.9.3 – page 57), respectively. However, as in the case above, the CrIs crossed one for active treatment comparisons.

For continuous outcomes certolizumab pegol 200mg and certolizumab pegol 400mg had the largest effect sizes for change from baseline in BASFI (Figure 23, Section B.3.9.3 – page 57), change from baseline in BASDAI (Figure 24, Section B.3.9.3 – page 58) and change from baseline in BASMI (Figure 25, Section B.3.9.3 – page 58). However, the CrIs for certolizumab pegol 200mg and 400mg crossed zero when compared with golimumab. Golimumab was superior to etanercept and adalimumab for change from baseline in BASFI (Figure 23, Section B.3.9.3 – page 57), superior to etanercept for change from baseline in

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BASDAI (Figure 24, Section B.3.9.3 – page 58) and finally superior to adalimumab for change from baseline in BASMI (Figure 25, Section B.3.9.3 – page 58).

Safety

In TA383 the assessment Group, who were considering ankylosing spondylitis and nr-axial SpA, concluded based on the number, size and short duration of trials not to develop a network meta-analysis of adverse events. The AG opted to use the Cochrane Review by Corbett et al. (2016) in which TNF-alpha inhibitors were instead assessed both as a class and individually.

Certolizumab pegol was the only treatment considered in this appraisal that showed statistically significant incidence of AEs in the Cochran review.Compared to placebo patients receiving certolizumab pegol had a significantly higher likelihood of experiencing a serious infection (OR – 4.75, 1.52-18.45).

With the exception of certolizumab pegol (no data on nr-axial SpA) the MSD NMA and the Cochran NMA are consistent on the common outcomes of AEs, SAEs and infections (no significant difference).

The sensitivity analysis conducted on the NMA confirmed that the base case results for the NMA were robust and that golimumab is at least as efficacious and safe as its comparators.

A.9 Overview of the cost-comparison analysis

Table 12 - Assumptions applied in the cost-comparison analysis

Costs and assumptions	Source	Justification
Time Horizon – one year	Guide to the methods of technology appraisal 2013 (NICE)	This is a long enough time period to reflect the differences between the technologies being appraised
Drug acquisition cost – based on list price and publically available PAS prices.	BNF 2017	The drug acquisition costs presented are based on publically available list prices. The PAS schemes for golimumab and certolizumab pegol are not confidential, and have been applied in the cost comparison analysis. .A simple PAS is provided for golimumab where the 100mg presentation is provided at the same price as the 50mg presentation at the point of invoice. Certolizumab pegol has a complex PAS, providing the first 10 doses of certolizumab pegol as free stock (equivalent to the first 12 weeks).

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Costs and assumptions	Source	Justification
Administration and monitoring resource use – not included	TA383	As assumed in TA383 (NICE, 2016), there are no differences in the health care resource uses associated with the initiation, administration and monitoring of golimumab and the comparators, and as a result the resource use costs have been excluded from this analysis.

Abbreviations: NICE, National institute of health and care excellence; PAS, Patient access scheme; BNF, British national formulary; TA, technology appraisal

Table 13 - Acquisition costs of the intervention and comparator technologies (Section B.4.1, Table 21 – page 78)

	Golimumab	Adalimumab	Certolizumab pegol	Etanercept
Pharmaceutical formulation	50mg or 100mg	40mg	400mg or 200mg	50mg or 25mg
(Anticipated) care setting	Secondary care	Secondary care	Secondary care	Secondary care
Acquisition cost (excluding VAT) *	£762.97 list price**	£352.14 list price	£715 list price or £357.50 list price	£178.75 list price or £89.38 list price
Method of administration	SC injection	SC injection	SC injection	SC injection
Doses	1	1	2 or 1	2 or 1
Dosing frequency	Every month	Every 2 weeks	Every 4 weeks or every 2 weeks	Once weekly or twice weekly
Dose adjustments	N/A	N/A	N/A	N/A
Average length of a course of treatment	Long term	Long term	Long term	Long term
Average cost - (first year only)	£9,155.64 first year	£9,155.64 first year	£5,720 first year ++	£9,295 first year
Average cost – (subsequent years)	£9,155.64 per annum	£9,155.64 per annum	£9,295.00 per annum	£9,295.00 per annum
(Anticipated) average interval between courses of treatment	N/A	N/A	N/A	N/A
(Anticipated) number of repeat courses of treatment	On-going	On-going	On-going	On-going

Abbreviations: SC, subcutaneous; N/A, not applicable

** A PAS has been agreed with the PASLU, which provides the 100mg presentation of golimumab at the same price of the 50mg presentation at the point of invoice, when used by the NHS in any licensed indication.

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[++] A PAS is agreed with PASLU, whereby the first 12 weeks of certolizumab pegol, equivalent to 10 vials, are provided free of charge

A.10 Base-case results

Presented in Table 14 and 15 below are the base case analyses including and excluding the initiation PAS for certolizumab pegol. Certolizumab pegol is provided as free stock for the first 10 vials (equivalent to the first 12 weeks), and as a result is the most cost-effective treatment with the lowest acquisition cost, followed by golimumab and adalimumab, and finally etanercept.

In the alternative base case scenario, when the initiation PAS is excluded and we consider the drug acquisition cost for the second year and beyond, golimumab and adalimumab are the most cost-effective with a cost of £9,155.64, followed by certolizumab pegol and etanercept with a cost of £9,295.00.

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Table 14 - Base-case results – initiation year (including the initiation PAS for certolizumab pegol) – Section B.4.3, Table 22 - page 81

Technologies	Dose	Acquisition costs (£)	Resource costs (£)	Adverse event costs (£)	Other costs (£)	Annual cost (£)	Total costs (£)	Difference to golimumab
Golimumab	50mg once monthly	762.97	N/A	N/A	N/A	9,155.64	9,155.64	N/A
	100mg once monthly *	762.97	N/A	N/A	N/A	9,155.64	9,155.64	N/A
Adalimumab	40mg once every two weeks	352.14	N/A	N/A	N/A	9,155.64	9,155.64	£0 (Golimumab is cost neutral)
Certolizumab pegol	400mg at weeks 0, 2 and 4, then 400mg once every 4 weeks++	715	N/A	N/A	N/A	5,720	5,720	-£3,435.64 (Certolizumab pegol is cost saving)
	400mg at weeks 0, 2 and 4, then 200mg once every 2 weeks++	357.50	N/A	N/A	N/A	5,720	5,720	-£3,435.64 (Certolizumab pegol is cost saving)
Etanercept	50mg once weekly	178.75	N/A	N/A	N/A	9,295	9,295	£139.36 (Golimumab is cost saving)
	25mg twice weekly	89.38	N/A	N/A	N/A	9,295.52	9,295.52	£139.88 (Golimumab is cost saving)

Abbreviations: N/A, not applicable

*A PAS has been agreed with the department of health that flat prices the cost of the 100mg administration to that of the 50mg administration, at the point of invoice. ++ A PAS is agreed with PASLU, whereby the first 10 vials of certolizumab pegol, equivalent to the first 12 weeks, are provided free of charge

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Table 15 - Base case results - year 2 and thereafter (excluding the initiation PAS for certolizumab pegol) – B.4.3, Table 23 - Page 83

Technologies	Dose	Acquisition costs (£)	Resource costs (£)	Adverse event costs (£)	Other costs (£)	Annual cost (£)	Total costs (£)	Difference to golimumab
Golimumab	50mg once monthly	762.97	N/A	N/A	N/A	9,155.64	9,155.64	N/A
	100mg once monthly *	762.97	N/A	N/A	N/A	9,155.64	9,155.64	N/A
Adalimumab	40mg once every two weeks	352.14	N/A	N/A	N/A	9,155.64	9,155.64	£0 (Golimumab is cost neutral)
Certolizumab pegol	400mg at weeks 0, 2 and 4, then 400mg once every 4 weeks	715	N/A	N/A	N/A	9,295	9,295	£139.36 (Golimumab is cost saving)
	400mg at weeks 0, 2 and 4, then 200mg once every 2 weeks	357.50	N/A	N/A	N/A	9,295	9,295	£139.36 (Golimumab is cost saving)
Etanercept	50mg once weekly	178.75	N/A	N/A	N/A	9,295	9,295	£139.36 (Golimumab is cost saving)
	25mg twice weekly	89.38	N/A	N/A	N/A	9,295.52	9,295.52	£139.88 (Golimumab is cost saving)

Abbreviations: N/A, not applicable

*A PAS has been agreed with the department of health that flat prices the cost of the 100mg administration to that of the 50mg administration, at the point of invoice.

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A.11 Key sensitivity and subgroup analyses

No sensitivity analysis was conducted as the cost comparison analysis is based on drug acquisition cost alone (list price and publically available patent access schemes), and as mentioned in Section B.3.7 (Page 48) no clinically relevant subgroups were identified.

A.12 Interpretation and conclusions of the evidence

The cost comparison analysis for the initiation year, accounting for the certolizumab pegol 12 week PAS, showed golimumab to be jointly the second most cost-effective treatment. Post initiation (year 2 and thereafter, Table 15) analysis demonstrated that golimumab is a long term cost neutral alternative therapy to adalimumab, and a cost saving alternative to both certolizumab pegol and etanercept. The total annual cost of treatment with golimumab is £139.36 less per patient than for certolizumab pegol and etanercept.

The economic analysis can be considered robust, as it is based on the TA383 committee assumptions for common resource use for subcutaneous injection administration training, and conservatively assumes equal efficacy (despite significant findings favouring golimumab on BASDAI and BASFI in the NMA (Section B.3.9.3, page 55).

Golimumab also has benefits that are not accounted for in the cost comparison analysis that should be acknowledged. Golimumab has the longest dosing interval at one month which is particularly helpful for active people, has a self-injectable pen that is specifically designed for those who feel discomfort with self-injection, and those who have limited mobility in the hands. The MSD homecare programme can deliver golimumab directly to patients' homes each month, at a convenient time, and provide support to help patients manage treatment expectations and concordance. Additionally the homecare programme reduces the administrative burden for healthcare professionals.

The findings of the cost comparison analysis are generalisable to adults in England and Wales with severe, active non-radiographic axial spondyloarthritis with objective signs of inflammation who have responded inadequately to, or are intolerant to, non-steroidal anti-inflammatory drugs.

In summary, it can be concluded that the introduction of golimumab will result in a cost-saving or cost-neutral therapy for the NHS in England and Wales, supporting its implementation as a valuable treatment alternative for patients with nr-axial SpA.

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Fast track appraisal: cost-comparison case

Golimumab for treating non-radiographic axial spondyloarthritis ID903

Dear Gethin

The Evidence Review Group, School of Health and Related Research (ScHARR), and the technical team at NICE have looked at the submission received on **12 June 2017** from Merck Sharpe and Dohme. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **19 July 2017** Your response and any supporting documents should be uploaded to NICE Docs/Appraisals [embed https://appraisals.nice.org.uk/request/30604 on 'NICE Docs/Appraisals'].

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Irina Voicechovskaja, Technical Lead (Irina.voicechovskaja@nice.org.uk). Any procedural questions should be addressed to the Project Team, at TACommA@nice.org.uk.
Yours sincerely

Eleanor Donegan
Technical Advisor – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

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Section A: Clarification on effectiveness data

A1. **Priority question:** Document B, page 12, Table 2. It is stated that "Available data suggest that clinical response is usually achieved within 12 to 14 weeks of treatment (after 3-4 doses)." Please clarify why treatment was continued for, and efficacy assessed at, 16 week when clinical response to golimumab is usually achieved within 12-14 weeks with continued therapy reconsidered at this time point.

A2. **Priority question**: Several efficacy analyses report treatment effects on the probability scale. This is an uncommon scale to use when adjusting for covariates because it can lead to predicted probabilities that lie outside the range [0, 1]. Please perform an analysis on the logit scale with a linear predictor adjusting for sacroiliitis (active inflammation) on MRI of the sacroiliac joint (yes/no), CRP level (≤ ULN/ > ULN [0.9mg/dL]) at baseline and other covariates that were pre-specified in the protocol. Please perform an analysis that assesses the interaction between the pre-specified covariates and treatment.

A3. **Priority question:** Please provide a summary of the efficacy outcomes at 16 weeks for the OSI subgroup similar to that presented in Table 15 of Document B for the full analysis set (FAS).

A4. **Priority question**: Document B, section B.3.10.1, Page 71: It is stated, "The OSI population was analysed for overall AEs. The OSI population for safety endpoint analyses were derived from the APaT population. The APaT population consisted of all patients who received at least one dose of trial medication." However, the numbers of patients in the OSI population (n=158 [golimumab n=78, placebo n=80]) as stated on page 32) are different to those in Table 20. Please clarify if AEs are presented only for the OSI population and if so what the rationale for only including the OSI population in the safety analysis.

A5. **Priority question**: The data for SF-36 across all relevant trials are presented in Table 29 of Document B Appendix D (page 166) but NMA results are not presented in Document B. Please provide the NMA results for SF-36 MCS and PCS, as was presented in TA383, but with the addition of the GO-AHEAD trial.

A6. **Priority question:** In Document B Appendix D (page 158) it states "Some differences in baseline characteristics and baseline disease indicators were observed across the included studies." Treatment effects will be biased when there is an imbalance in treatment effect modifiers in studies comparing different pairs of treatments. Please comment on whether the distribution of treatment effect modifiers between studies comparing different pairs of treatments is likely to bias the estimates of treatment effect.

A7. **Priority question**: Document B, Appendix D (page 159), table 23 states that the study duration was 16 weeks for the RAPID-axSpA study but Landewé *et al.*

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((Landewe et al., 2013, (reference 25 of Document B)) present graphical data at multiple time points and patients in the placebo arm were able to switch to active treatment at either 12 or 14 weeks. Please clarify whether the data incorporated in the NMA for certolizumab pegol RAPID-axSpA study was from 12 or 16 weeks as this is not specified in Table 21 of the Appendices to Document B (page 157).

A8. Document A, page 15: It is stated that the indication for use in the decision problem is for the "treatment of adults with severe, active non-radiographic axial spondyloarthritis (nr-axial SpA) with objective signs of inflammation (OSI) 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 non-steroidal anti-inflammatory drugs (NSAIDs)". Please clarify whether there are accepted definitions for 'severe' and 'active' and whether these definitions were part of the trial inclusion criteria.

A9. Document B, page 26, Table 10: Please confirm how high disease activity was measured.

A10. Document B, page 26, Table 10: Please supply a rationale for inclusion criterion of disease duration <5 years and whether this is time since diagnosis or time since symptom onset.

A11. Document B, page 26, Table 10: Please supply rationale for the inclusion criteria of age ≤45 years and clarify if this is age at diagnosis or age at time of enrolment into the trial.

A12. Document B, page 29, Figure 2: Please state reasons for treatment discontinuation.

A13. Document B: section B.3.3.1.3, Page 30: Please provide the number n/N (%) of patients who were from the UK by treatment group.

A14. Document B, Table 12, page 35: It is stated that a placebo response rate of 25% "based on estimates from pivotal anti-TNF trials in AS" was used to justify the sample size. Please comment on why this differed from the placebo response rate of 40% observed in the GO-AHEAD study (as reported on page 38 of Document B).

A15. Document B, section B.3.3.1.1, page 28: Patients were stratified based on whether they had evidence of sacroiliitis (active inflammation) on MRI of the sacroiliac joint (yes/no) and CRP level (≤ ULN/ > ULN [0.9mg/dL]). Please clarify whether the stratification factors used in the randomisation are considered to be prognostic variables or treatment effect modifiers.

A16. Analysis of covariance is generally preferred over change from baseline. Please provide results of analysis of covariance where change from baseline has been

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performed and assess whether there is evidence of a covariate by treatment interaction.

A17. Document B, Page 32, section 3.3.1.6: It is stated "All result at week 60 and 16 were compared. The results show no statistically difference between the outcomes at both time points" Please supply the results for the outcomes at week 60 that were compared with week 16, along with the methods for comparison.

A18. Document B, Figure 13, please confirm is this any adverse event?

A19. Document B, Figure 15, please confirm is this a severe infection or any opportunistic infection?

A20. Document B, Page 67: Please clarify whether the data for other anti-TNFs included in sensitivity analysis 4 were restricted to patients with OSI and if not please explain why this was not done.

A21. Document B, Appendix D (text above Table 11 of page 137), as well as the number of reviewers involved in study selection, please confirm how many reviewers were involved in data extraction and quality assessment.

A22. Document B, Appendix C.2 EPAR report (page 102). It is stated that pre-specified subgroups were gender, age (>30 years and <=30 years), weight (<=median, 76 kg, >median, 76 kg), BASDAI score (<=median, 6.35 cm >median, 6.35 cm), HLA-B27 status, use of NSAIDS, region (Western Europe and US, Eastern Europe), MRI (positive, negative) and CRP status (≤ULN, >ULN [0.9 mg/dL]). Please provide the subgroup analysis for weight, BASDAI score, use of NSAIDS, and geographic region in a format similar to Table 14 of Document B. Please also comment on other potential reasons for heterogeneity in response between patients and describe any published meta-analyses which explore heterogeneity in treatment response for anti-TNFs in this disease area.

Section B: Clarification on cost-effectiveness data

NB: No questions for this section

Section C: Textual clarifications and additional points

C1. Please double check references against PDFs provided in Appendix N. We appear to be missing PDFs for following 7 references: 16, 24, 25 (the PDF provided is for the CSR and not for Landewé 2013) 30, 33, 35, 37.

MSD Response to Clarification Questions on Fast track appraisal: cost-comparison case - Golimumab for treating non-radiographic axial spondyloarthritis ID903

Section A: Clarification on effectiveness data

A1. **Priority question:** Document B, page 12, Table 2. It is stated that "Available data suggest that clinical response is usually achieved within 12 to 14 weeks of treatment (after 3-4 doses)." Please clarify why treatment was continued for, and efficacy assessed at, 16 week when clinical response to golimumab is usually achieved within 12-14 weeks with continued therapy reconsidered at this time point.

Response

Clinical response in the GO-AHEAD trial was evaluated after 4 doses. The 4th dose was administered at Week 12, with the evaluation of response being assessed 4 weeks later (week 16), and prior to the 5th administration of golimumab. This was consistent with the monthly visits and a conservative approach to timing the assessment of efficacy, because this assessment was performed at a time of trough (i.e. lowest) levels of golimumab instead of week 14 when levels would have been higher

A2. **Priority question**: Several efficacy analyses report treatment effects on the probability scale. This is an uncommon scale to use when adjusting for covariates because it can lead to predicted probabilities that lie outside the range [0, 1]. Please perform an analysis on the logit scale with a linear predictor adjusting for sacroiliitis (active inflammation) on MRI of the sacroiliac joint (yes/no), CRP level (≤ ULN/ > ULN [0.9mg/dL]) at baseline and other covariates that were pre-specified in the protocol. Please perform an analysis that assesses the interaction between the pre-specified covariates and treatment.

Response

Analysis using a logit scale with adjustment has not been conducted as the applied Miettinen and Nurminen method is a valid analysis approach for the comparisons of two proportions. This allows for the adjustment of stratifying variables and produces good coverage of confidence intervals for the difference between two proportions. The results of the analyses using this method have been peer reviewed and published in the Journal of Arthritis and Rheumatology in 2015 (Sieper et al., 2015).

The binary outcomes were analysed using the stratified Miettinen and Nurminen method with baseline evidence of sacroiliitis on MRI (yes/no) and screening CRP level (≤ ULN/ > ULN [0.9mg/dL]) as stratification factors. Subgroup analyses by the two stratification factors based on Miettinen and Nurminen method were also performed which are informative in terms of the interaction between the baseline evidence of sacroiliitis on MRI (yes/no) and screening CRP level and treatment

A3. **Priority question:** Please provide a summary of the efficacy outcomes at 16 weeks for the OSI subgroup similar to that presented in Table 15 of Document B for the full analysis set (FAS).

Response

The summary of the efficacy outcomes at 16 weeks for the OSI population is included below in Table 1.

Table 1: Summary of efficacy outcomes at 16 weeks among the OSI (Curtis et. al., 2014)

Study arm	Intervention group (GLM 50 mg) n=	Comparator group (PBO) n=	Difference (95% CI)	P-value*
Disease activity				
ASAS 20, n (%)	60 /78 (76.9)	30 /80 (37.5)	39.6 (24.6, 52.6)	<0.0001
ASAS 40, n (%)	47 /78 (60.3)	18 /80 (22.5)	37.9 (23.0, 51.2)	<0.0001
ASAS partial remission, n (%)	27 /78 (34.6)	15 /80 (18.8)	16.1 (2.5, 29.6)	0.0204
BASDAI 50, n (%)	46 /78 (59.0)	23 /80 (28.8)	30.5 (15.4, 44.3)	<0.0001
BASDAI, mean (SD) Week 16 Change from baseline	N=76 2.866 (2.5365) -3.692 (0.2811)	N=77 4.739 (2.7731) -1.511 (0.2770)	-2.181 (-2.959, -1.404)	<0.0001
ASDAS, mean (SD) Week 16 Change from baseline	N=71 1.859 (1.0474) -1.828 (0.1373)	N=71 2.895 (1.2602) -0.639 (0.1358)	-1.189 (-1.561, -0.816)	<0.0001
Functional capacity				
BASFI, mean (SD) Week 16 Change from baseline	N=76 2.425 (2.5224) -2.775 (0.2530)	N=78 3.977 (2.8035) -0.872 (0.2491)	-1.903 (-2.582, -1.224)	<0.0001
Spinal mobility				

Study arm	Intervention group (GLM 50 mg) n=	Comparator group (PBO) n=	Difference (95% CI)	P-value*
BASMI, mean (SD) Week 16 Change from baseline	N=77 1.89 (1.172) -0.48 (0.080)	N=80 2.43 (1.407) -0.06 (0.078)	-0.42 (-0.64, -0.21)	0.0002
Pain				
Total back pain, 10-cm VAS, mean (SD) Week 16 Change from baseline	N=76 2.68 (2.800) -4.24 (0.335)	N=78 4.86 (3.179) -1.86 (0.330)	-2.37 (-3.29, -1.46)	<0.0001
Peripheral symptoms				
MASES, mean (SD) Week 16 Change from baseline	N=75 1.5 (2.79) -1.4 (0.28)	N=77 2.2 (3.06) -0.8 (0.28)	-0.6 (-1.3, 0.1)	0.0872
Health-related quality of life				
ASQoL, mean (SD) Week 16 Change from baseline	N=77 5.6 (5.23) -5.1 (0.54)	N=80 8.6 (5.05) -1.8 (0.53)	-3.4 (-4.8, -2.0)	<0.0001
EQ-5D Index, mean (SD) Week 16 Change from baseline	N=77 0.68 (0.288) 0.27 (0.034)	N=80 0.53 (0.323) 0.11 (0.033)	0.16 (0.07, 0.24)	0.0004
EQ-5D VAS, cm, mean (SD) Week 16 Change from baseline	N=77 6.70 (2.461) 1.98 (0.258)	N=80 5.53 (2.299) 0.51 (0.254)	1.47 (0.80, 2.15)	<0.0001

Study arm	Intervention group (GLM 50 mg) n=	Comparator group (PBO) n=	Difference (95% CI)	P-value*
SF-36 Physical, mean (SD) Week 16 Change from baseline	N=74 43.63 (10.188) 10.38 (0.933)	N=78 38.43 (9.879) 3.68 (0.913)	6.70 (4.17, 9.22)	<0.0001
SF-36 Mental, mean (SD) Week 16 Change from baseline	N=74 46.83 (11.558) 5.55 (1.251)	N=78 42.87 (11.968) 1.03 (1.227)	4.52 (1.28, 7.76)	0.0065

*The statistical tests were conducted at the α= 0.05 (2-sided) level

Abbreviations: GLM, golimumab; PBO, placebo; ASAS, Assessment of Ankylosing Spondylitis; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CRP, C-reactive protein; VAS, visual analogue scale; MASES, Maastricht Ankylosing Spondylitis Enthisetis Score; ASQoL, Ankylosing Spondyloarthirtis Quality of Life; EQ-5D, EuroQoL 5 dimension; SF-36, sort form 36

A4. **Priority question**: Document B, section B.3.10.1, Page 71: It is stated, "The OSI population was analysed for overall AEs. The OSI population for safety endpoint analyses were derived from the APaT population. The APaT population consisted of all patients who received at least one dose of trial medication." However, the numbers of patients in the OSI population (n=158 [golimumab n=78, placebo n=80]) as stated on page 32) are different to those in Table 20. Please clarify if AEs are presented only for the OSI population and if so what the rationale for only including the OSI population in the safety analysis.

Response

The adverse events presented in Table 20 are for the APaT population, consisting of all randomized subjects who received at least one dose of study treatment, this includes:

- OSI population (target population): subjects with Baseline evidence of sacroiliitis on MRI and/or screening CRP level > upper limit of normal and derived from the APaT population
- Non-OSI population (non-target): subjects without Baseline evidence of sacroiliitis on MRI and screening C-reactive protein (CRP) within normal limits and was derived from the APaT population

A5. **Priority question**: The data for SF-36 across all relevant trials are presented in Table 29 of Document B Appendix D (page 166) but NMA results are not presented in Document B. Please provide the NMA results for SF-36 MCS and PCS, as was presented in TA383, but with the addition of the GO-AHEAD trial.

Response

As was noted on page 60 of the Document B, when the NMA was produced the objective was to develop the data to populate a decision analytic model and as a result the general health related quality of life measures of SF-36 PCS and MCS were omitted. Unfortunately we are unable to rerun the NMA including the GO-AHEAD trial data at this time.

A6. **Priority question:** In Document B Appendix D (page 158) it states "Some differences in baseline characteristics and baseline disease indicators were observed across the included studies." Treatment effects will be biased when there is an imbalance in treatment effect modifiers in studies comparing different pairs of treatments. Please comment on whether the distribution of treatment effect modifiers between studies comparing different pairs of treatments is likely to bias the estimates of treatment effect.

Response

The Cochrane Collaboration tool was used (see Appendix D, page 170) to assess the risk of bias for each study included in the systematic literature review and the network meta-analysis. The application of the tool allowed the evaluation of the randomisation process applied to the RCTs, and the likelihood of having differences in baseline characteristics that may bias the estimates of treatment effect. Overall, each study showed a low risk of bias.

Additionally the differences detected in the baseline characteristics and indicators, based on data availability, were analysed by performing sensitivity analyses (see Document B, page 66-67). These analyses showed that the between trial differences in baseline characteristics, had no significant impact upon the final efficacy results for golimumab.

Based on the Cochrane Tool and the sensitivity analysis, it is not believed that the distribution of treatment effect modifiers seen in the studies comparing different pairs of treatments, biases the estimates of treatment effect.

A7. Priority question: Document B, Appendix D (page 159), table 23 states that the study duration was 16 weeks for the RAPID-axSpA study but Landewé et al. ((Landewe et al., 2013, (reference 25 of Document B)) present graphical data at multiple time points and patients in the placebo arm were able to switch to active treatment at either 12 or 14 weeks. Please clarify whether the data incorporated in the NMA for certolizumab pegol RAPID-axSpA study was from 12 or 16 weeks as this is not specified in Table 21 of the Appendices to Document B (page 157).

Response

The data incorporated in the NMA for certolizumab pegol from the RAPID-axSpA (Landewe et al., 2013) study was at the 12 week time point.

A8. Document A, page 15: It is stated that the indication for use in the decision problem is for the "treatment of adults with severe, active non-radiographic axial spondyloarthritis (nr-axial SpA) with objective signs of inflammation (OSI) 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 non-steroidal anti-inflammatory drugs (NSAIDs)". Please clarify whether there are accepted definitions for 'severe' and 'active' and whether these definitions were part of the trial inclusion criteria.

Response

The ASAS definition for "active" disease in non-radiographic axial spondyloarthritis patients outlines that the active manifestation of the disease is through objective signs of inflammation (elevated CRP levels and images of sacroiliitis by MRI), with a specification of active as follows: >4 weeks with a BASDAI score >4 (score range: 0-10). This "active" definition was part of the inclusion criteria of the GO-AHEAD trial.

Although there is not an accepted definition for "severe", the inclusion criteria required high disease activity at both Screening and Baseline, at levels of Total Back Pain score and BASDAI score that are consistent with 'severe' disease that require treatment with anti-TNF therapy.

A9. Document B, page 26, Table 10: Please confirm how high disease activity was measured.

Response

The inclusion criteria for the GO-AHEAD trial for SpA disease activity states that each participant must show high disease activity at Screening and Baseline. As noted in Question 8, high disease activity was measured as both a total back pain evaluation of ≥40mm, and a BASDAI score of ≥40mm on a 0-100mm VAS.

A10. Document B, page 26, Table 10: Please supply a rationale for inclusion criterion of disease duration <5 years and whether this is time since diagnosis or time since symptom onset.

Response

The inclusion criterion of <5 years since symptom onset is based on the fact that long-standing disease is more likely to have radiographic changes not consistent with diagnosis of nr-axSpA. Therefore enrolling patients with longer disease of five years or more duration would potentially bias the results.

Additionally, MSD would like to make an amendment to Table 10 of Document B. Currently, it incorrectly states that disease duration is time since diagnosis, whereas it should be corrected to time since symptom onset.

A11. Document B, page 26, Table 10: Please supply rationale for the inclusion criteria of age ≤45 years and clarify if this is age at diagnosis or age at time of enrolment into the trial.

Response

The inclusion criterion of ≤45 years was selected as it is the ASAS criteria for axial spondyloarthritis. This maximum age was applied at the time of enrolment into the GO-AHEAD trial.

A12. Document B, page 29, Figure 2: Please state reasons for treatment discontinuation.

Response

The reasons for the seven discontinuations from the GO-AHEAD trial are summarised in Table 2.

Table 2: GO-AHEAD Discontinuations

Trial Arm	Reason for discontinuation	Number of patients
Placebo	Adverse event	1
	Withdrew consent	1
	Non-compliance	1
	Total	3 (3%)
Golimumab	Adverse event	1
	Protocol violation	1
	Withdrew consent	1
	Lost to follow-up	1
	Total	4 (4.1%)

A13. Document B: section B.3.3.1.3, Page 30: Please provide the number n/N (%) of patients who were from the UK by treatment group.

Response

The number of patients who were from the UK by treatment group is presented in Table 3 below.

Table 3 – UK patients in GO-AHEAD trial

	Golimumab 50mg	Placebo
UK patients	4/97 (4%)	5/100 (5%)

A14. Document B, Table 12, page 35: It is stated that a placebo response rate of 25% "based on estimates from pivotal anti-TNF trials in AS" was used to justify the sample size. Please comment on why this differed from the placebo response rate of 40% observed in the GO-AHEAD study (as reported on page 38 of Document B).

Response

As noted in Sieper et al. 2015, there was a relatively high ASAS20 placebo response rate (40% at 16 weeks), the potential reason for which is unclear. Variations in centres and the inclusion of patients with less advanced disease in comparison to AS studies with more advanced disease may play a role.

A similar placebo response was also seen in the trial of certolizumab pegol treatment for the patients with non-radiographic axial SpA, and those with radiographic axial SpA (AS) (Landewe et. al., 2014). This implies that the patient population in GO-AHEAD differs to the AS population in previous studies of TNF-alpha inhibitors. Despite the larger than expected placebo response, the golimumab efficacy effect was both statistically and clinically significant compared to placebo.

A15. Document B, section B.3.3.1.1, page 28: Patients were stratified based on whether they had evidence of sacroiliitis (active inflammation) on MRI of the sacroiliac joint (yes/no) and CRP level (≤ ULN/ > ULN [0.9mg/dL]). Please clarify whether the stratification factors used in the randomisation are considered to be prognostic variables or treatment effect modifiers.

Response

The stratification factors of sacroiliitis and CRP level were considered to be treatment effect modifiers. As noted in Document B, to ensure that the GO-AHEAD study assessed a substantial proportion of patients with active inflammation, the patient enrolment was based on the sacroiliitis and CRP level.

The study required that > 40% of the subjects enrolled had CRP > upper limit of normal; subjects without MRI evidence of sacroiliitis at baseline were limited to 50% of those enrolled.

As noted by Sieper et al. (2015), the large majority (80.2%) of subjects in the GO-AHEAD study were in the OSI population (showing evidence of sacroiliitis on MRI and/or screening CRP level > upper limit of normal). In this population, efficacy was clinically and statistically

significant. In contrast but consistent with expectations when the study was designed, subjects in the non-OSI population did not show significant efficacy, thus supporting that the presence of active inflammation (based on MRI and/or CRP testing) modified the treatment effect of golimumab.

A16. Analysis of covariance is generally preferred over change from baseline. Please provide results of analysis of covariance where change from baseline has been performed and assess whether there is evidence of a covariate by treatment interaction.

Response

Continuous secondary endpoints were analysed using the constrained longitudinal data analysis (cLDA) model proposed by Liang and Zeger (2000). The treatment difference in terms of mean change from baseline at Week 16 were estimated and tested from this model. In this model the baseline measurement is included in the response vector along with the post-baseline measurements and the model assumes a common ("constrained") mean across treatment groups at baseline as a result of randomization. In the event that there are no missing data, the estimated treatment difference from the cLDA model would be identical to that from a traditional longitudinal analysis of covariance (ANCOVA) model which uses the baseline value as a covariate.

However, the cLDA model is preferred over the ANCOVA model since unlike longitudinal ANCOVA, the cLDA model accounts for variability in the baseline values, thus providing more accurate standard errors and confidence intervals for individual treatment effects. Moreover, the cLDA model allows the inclusion of subjects who are missing either the baseline or post-baseline measurements, thereby increasing efficiency (Lu, 2010).

A17. Document B, Page 32, section 3.3.1.6: It is stated "All result at week 60 and 16 were compared. The results show no statistically difference between the outcomes at both time points" Please supply the results for the outcomes at week 60 that were compared with week 16, along with the methods for comparison.

Response

The statement in the Document B page 32 is unclear, and MSD would like to apologise for any confusion caused. The comparisons were conducted for all week 16 results run at the first and the final database lock and not between the 16 and 60 week results.

The primary and key secondary analyses at Week 16 were re-run on the final database lock (60 week). Table 4 below summarises the results for ASAS 20, ASAS 40, BASDAI 50, ASAS Partial Remission and SPARCC MRI SI joint score respectively. The results were identical to those reported in the 16 week CSR.

Table 4: Analysis of the proportion of patients achieving response at week 16 (FAS)

Response at Week 16	Treatment	Responder		Difference in % vs. placebo	
		n/N	%	Estimated (95% CI)*	P-value*
ASAS 20	Glm 50mg	69 /97	71.1	31.2 (17.5, 43.6)	<0.0001
	Placebo	40 /100	40.0		
ASAS 40	Glm 50mg	55 /97	56.7	33.8 (20.4, 46.1)	<0.0001
	Placebo	23 /100	23.0		
BASDAI 50	Glm 50mg	56 /97	57.7	28.0 (14.4, 40.6)	<0.0001
	Placebo	30 /100	30.0		
ASAS	Glm 50mg	32 /97	33.0	15.2 (3.2, 27.1)	0.0136

Partial Remission	Placebo	18 /100	18.0		

* Derived based on the stratified Miettinen and Nurminen method with baseline evidence of sacroiliitis on MRI (yes or no) and screening CRP level (≤ upper limit of normal or > upper limit of normal) as stratification factors.

In addition, tabulations and analyses were rerun using the final database lock (week 60) for other secondary endpoints; they are presented in the enclosed 60 week CSR as follows:

- Tables 14-27 to 14-91 for the FAS
- Tables 14-92 to 14-160 for the OSI population
- Tables 14-161 to 14-165 for the non-OSI population

There were no changes identified in the responses assessed at week 60 that would alter the conclusions of the 16 week CSR.

A18. Document B, Figure 13, please confirm is this any adverse event?

Response

Yes, the forest plot in Figure 13 in Document B presents any adverse event for the Haibel et. al. (2008) and ABILITY-1 (Sieper et. al., 2012) studies.

A19. Document B, Figure 15, please confirm is this a severe infection or any opportunistic infection?

Response

Sieper et al. (2015) in ABILITY-1, and Haibel et al. (2008) categorised the infection respectively as “infections AE” and “respiratory tract infections”. Sieper et al. (2015) noted that no opportunistic infections were reported.

A20. Document B, Page 67: Please clarify whether the data for other anti-TNFs included in sensitivity analysis 4 were restricted to patients with OSI and if not please explain why this was not done.

Response

Sensitivity analysis 4 investigated the OSI population of the intervention, but did not use the OSI population data for the comparators. This was due to a lack of available OSI population data for the comparators in the published studies.

A21. Document B, Appendix D (text above Table 11 of page 137), as well as the number of reviewers involved in study selection, please confirm how many reviewers were involved in data extraction and quality assessment.

Response

Data extraction was conducted by one reviewer with an independent quality check by a second reviewer. Any disagreement between the reviewers was resolved by a third, more senior investigator.

The quality assessment of each study included in the NMA was performed by one reviewer, which was then quality checked by a second reviewer. Any disagreements between the independent reviewers were resolved by a third investigator.

A22. Document B, Appendix C.2 EPAR report (page 102). It is stated that pre-specified subgroups were gender, age (>30 years and <=30 years), weight (<=median, 76 kg, >median, 76 kg), BASDAI score (<=median, 6.35 cm >median, 6.35 cm), HLA-B27 status, use of NSAIDS, region (Western Europe and US, Eastern Europe), MRI (positive, negative) and CRP status (≤ULN, >ULN [0.9 mg/dL]). Please provide the subgroup analysis for weight, BASDAI score, use of NSAIDS, and geographic region in a format similar to Table 14 of Document B. Please also comment on other potential reasons for heterogeneity in response between patients and describe any published meta-analyses which explore heterogeneity in treatment response for anti-TNFs in this disease area.

The requested subgroup analysis for weight, BASDAI score, use of NSAIDs and geographic region are presented below in Table 5:. With the exception of BASDAI scores less or equal to the median, which approached statistical significance, golimumab 50mg had statistically significantly more responders than placebo on the treatment effects of ASAS20 at week 16. Golimumab 50mg had consistent efficacy across subgroups.

Table 5: Primary outcomes assessment (ASAS20) by subgroups

		Golimumab		Placebo		Difference versus placebo, % (95% CI)	P-value*
		n/N	%	n/N	%		
Weight	>76Kg	38/52	73.1	22/44	50	23.9 (4.1, 41.9)	0.0181
	≤ 76Kg	31/45	68.9	18/56	32.1	36.4 (16.8, 53.1)	0.0003
BASDAI score	> Median	39/54	72.2	12/45	26.7	45.1 (25.9, 61.0)	<0.0001
	≤ Median	30/43	69.8	28/55	50.9	19.7 (-0.3, 37.5)	0.0537
NSAIDs	No	8/12	66.7	3/17	17.6	41.9 (2.9, 71.6)	0.0349
	Yes	61/85	71.8	37/83	44.6	27.3 (12.4, 40.9)	0.0004
Region	Eastern Europe	42/52	80.8	22/53	41.5	39.1 (20.9, 54.7)	<0.0001
	Western Europe and US	27 /45	60.0	18/47	38.3	20.8 (0.5, 39.7)	0.0450

*The statistical tests were conducted at the α= 0.05 (2-sided) level
No multiplicity control was applied to these statistical tests.
Abbreviations: CI, Confidential Interval; BASDAI, Bath ankylosing spondylitis disease activity index

TA383 notes the following as a potential reason for heterogeneity in outcomes; baseline characteristics in patients such as the variation seen in the levels of CRP, and the proportion of patients with MRI changes

There is only one published meta-analyses by Corbett et al. 2016, which explores heterogeneity in treatment response for anti-TNFs in non-radiographic axial spondyloarthritis.

As aforementioned, patients' characteristics may affect treatment response, but this is not supported by substantial evidence. However, Corbett et al. (2016) performed a meta-analysis to understand which factors are capable of modifying the anti-TNFs treatment effect in non-radiographic axial spondyloarthiritis.

Corbett et al. used a model that assumed the effect of anti-TNFs as a class, also including treatment effect interactions with baseline characteristics:

- BASDAI score
- BASFI score
- Age
- Sex
- Duration of symptoms (years)
- CRP level

Investigation of heterogeneity recognised sex as the only potential treatment effect modifier of anti-TNFs and this was particularly seen for change in BASDAI as outcome.
Despite this, when sex was applied in conjunction with other potential treatment effect modifiers, the impact on the effect response disappeared.

Section B: Clarification on cost-effectiveness data
NB: No questions for this section

Section C: Textual clarifications and additional points
C1. Please double check references against PDFs provided in Appendix N. We appear to be missing PDFs for following 7 references: 16, 24, 25 (the PDF provided is for the CSR and not for Landewé 2013) 30, 33, 35, 37.

Response

Please accept our apologies for the mistake with reference 25 and the missing references. The correct references are enclosed in zip file named 'Missing papers'.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Golimumab for treating non-radiographic axial spondyloarthritis [ID903]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted] **on behalf the BSR Spondyloarthritis Special Interest Group**
2. Name of organisation	**British Society for Rheumatology (BSR)**

3. Job title or position	**Consultant Rheumatologist and Associate Medical Director**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**British Society for Rheumatology which has membership of rheumatologists and allied health care professionals**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or	For the treatment of non-axial radiographic axial spondyloarthritis (nr-axSpA) by improving symptoms, preventing progression and reducing disability.

disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	% of patients achieving ASAS 20, ASAS 40, BASDAI 50, and ASAS PR compared to placebo. Other outcome measures including HAQ.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There remains a delay in the diagnosis of axial spondyloarthritis (axSpa). The ASAS criteria for non-radiographic axial spondyloarthritis (nr-axSpa) allows for earlier diagnosis using MRI instead of X-ray changes. Early diagnosis will lead to earlier treatment. There needs to be increased choice of treatments for nr-axSpa.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Patients who have active nr-axSpa despite the use of 2 different NSAIDs are treated with biologics anti-TNF agents.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE Guidance TA 383 NICE Guidance NG 65

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes, the use of anti-TNF agents are well defined. Patients with active disease, raised CRP and positive MRI are most likely to benefit from treatment with anti-TNF.
• What impact would the technology have on the current pathway of care?	This adds further choice to existing therapies in nr-axSpA
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Golimumab will be accessed using the same eligibility criteria as for other anti-TNF agents in nr-axSpA
• How does healthcare resource use differ between the technology and current care?	Golimumab allows for once every 4 week dosing, providing choice and more flexibility for patients. Golimumab is also indicated in ulcerative colitis (UC) which can be an extra-articular manifestation of axial spondyloarthritis. Patients with concomitant nr-axSpA and UC will have a therapy that potentially treat and improve both conditions
• In what clinical setting should the technology be used? (For example, primary or secondary	In secondary care with specialist input from Rheumatologists

care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Drug delivery, training and monitoring of treatment.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Data from the GO-AHEAD study at 16 weeks and 52 weeks showed that treatment with golimumab was effective and well tolerated in nr-axSpA.
• Do you expect the technology to increase length of life more than current care?	No
• Do you expect the technology to increase health-related quality of life more than current care?	No
12. Are there any groups of people for whom the technology would be more or	Golimumab has shown to be beneficial in patients with nr-axSpa compared to placebo.

less effective (or appropriate) than the general population?	
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Golimumab allows for a once in every 4 weeks dosing. This allows for choice and suitability for some patients with reduced injections in a year of treatment.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology?	This will be based on the current NICE guidance (TA 383 and NG 65)

Do these include any additional testing?	No
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	This is an effective and well tolerated treatment. It provides a once in 4 week dosing which is not available from the current subcutaneous anti-TNF therapies
• Is the technology a 'step-change' in the management of the	No

condition?	
• Does the use of the technology address any particular unmet need of the patient population?	No
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Golimumab is well tolerated and comparable to the existing anti-TNF agents.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they	% of patients achieving ASAS 20, ASAS 40, BASDAI 50, and ASAS PR compared to placebo. These were measured in the GO-AHEAD trial.

measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA383]?	No

21. How do data on real-world experience compare with the trial data?	This will need to be collected through registries eg. BSR Biologics Register
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	No
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your submission.

- Golimumab has been shown to be effective in the treatment of nr-axSpA
- Golimumab is well tolerated in patients receiving treatment for nr-axSpA
- The addition of Golimumab to the other existing anti-TNF treatments in nr-axSpA provides choice in treatment decisions
- Golimumab provides a once in 4 weeks treatment frequency
- Golimumab is indicated in other extra-articular manifestations of axial spondyloarthritis eg. ulcerative colitis

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Golimumab for treating non-radiographic axial spondyloarthritis [ID903]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	National Ankylosing Spondylitis Society (NASS)
3. Job title or position	Information & Communications Manager
4a. Brief description of the organisation (including who funds it). How many members does it have?	The National Ankylosing Spondylitis Society (NASS) was founded in 1976 by a group of patients, doctors and physiotherapists at the Royal National Hospital for Rheumatic Diseases in Bath. The 3 main aims of NASS are: • To seek a cure for ankylosing spondylitis (AS) and related conditions, and improve their treatment in the UK; • To promote awareness of these conditions in the UK; and • To provide guidance, advice and information for people affected by these conditions including their families, their carers and their employers. NASS is the only registered charity in the UK dedicated to the needs of people with ankylosing spondylitis (including axial spondyloarthritis) in the UK. NASS is a membership organisation, with around 4,000 members and receive no government or statutory funding. We are funded by membership subscriptions, donations and grants. The NASS head office is based in West London where we currently have 7 full time members of staff. However we have a network of 95 local branches spread throughout the UK, of which 80 are based in England. The branches provide regular physiotherapy, hydrotherapy and gym sessions that are supervised by physiotherapists with an interest in AS. Most branches meet weekly on weekday evenings. Although the main aim of meeting is for exercise, most branches also have an educational and social aspect.

4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	An important role of NASS is to give people living with AS a voice. We gather information by listening to patients informally via social media, the NASS Helpline and at NASS Members' Day. However, we also gather information more formally through surveys. We have used information from the NASS 'State of the Nation' survey which was carried out in March 2016 and included 2,000 people with AS living the the UK. We have also used information from the surveys we conducted of NASS Members in 2014 for the NICE MTA (TA383) TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Axial Spondyloarthritis (including the full spectrum of disease from non-radiographic axial spondyloarthritis to ankylosing spondylitis) (AS) is an inflammatory condition of the spine which often produces pain, stiffness, deformity and disability throughout adult life. It is a chronic progressive disease. It is characterised by periods of fluctuating intensity, leading to slowly increasing spinal and peripheral joint damage. The key symptom in early disease is inflammatory back pain (IBP). The onset of back pain and stiffness is usually gradual, being especially severe at night and following immobility. For many people sleep is disturbed, often causing them to get out of bed in the night to move around to improve their back pain and stiffness. Pain and stiffness in AS are commonly at their worst first thing in the morning and may improve with stretching and light exercise.

	Persistence of the disease leads to progressive spinal stiffness which may be accompanied by deformity. Up to 25% of people with AS eventually develop complete fusion of the spine which leads to substantial disability and restriction. 50% of people with AS also suffer from associated disorders at sites distant from the spine. In particular, 40% experience episodic eye inflammation (uveitis), 16% develop psoriasis and 10% inflammatory bowel disease. Symptoms of AS usually begin in adolescence or early adulthood, a critical period in terms of education, work and establishment of social frameworks and relationships. Symptoms are often present for a long time (7-10 years) before the diagnosis is made. The evidence suggests the delay to diagnosis is currently 8.5 years. Although most people with AS live a normal lifespan, there is an increased risk of premature death from cardiovascular disease in particular. Since many people with AS are neither deformed nor have peripheral joint abnormalities, much of the burden of living with AS is invisible. The spectrum of severity means that although many people with AS live active and rewarding lives, others experience progressive spinal pain, immobility and functional impairment. Work disability is a major problem with more than 50% of people who are affected suffering work instability. The average age of diagnosis is 24, a prime time for establishing a career. In addition, one-third of people with AS give up work before normal retirement age and another 15% reduce or change their work because of axial SpA. The work capacity of people with AS in the middle decades of life is similar to that of people with rheumatoid arthritis. Being unable to work has important consequences for the individual and his/her family through both loss of earnings and the loss of self-esteem that a career and income provide.

	People with AS are more likely to be divorced or never to have married and women with AS are less likely to have children. Many people with AS suffer with issues including depression, fatigue and poor sleep during their lives. All of these problems exert a profound influence on their quality of life.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	In February 2016, NICE published updated guidance for the use of anti TNF therapy (TA383). This updated guidance has meant: • All the licensed anti TNF therapies are recommended as options for treating ankylosing spondylitis • Adalimumab (Humira), certolizumab pegol (Cimzia) and etanercept (Enbrel) are recommended, as options for treating severe non-radiographic axial spondyloarthritis • Treatment with another anti TNF is recommended for people who cannot tolerate, or whose disease has not responded to, treatment with the first TNF-alpha inhibitor, or whose disease has stopped responding after an initial response Patients believe this has widened the options they have available and removed restrictions to early treatment for non-radiographic axial spondyloarthritis, as well as allowing for subsequent switches. In September 2016, NICE published TA407 which made secukinumab available for active ankylosing spondylitis after treatment with non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors. This further widened options for those with ankylosing spondylitis. This means that patients and carers are generally satisfied with the current treatments and care available on the NHS.
8. Is there an unmet need for patients with this condition?	There are fewer options available for people with non-radiographic axial spondyloarthritis and a further option would be welcomed.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Making golimumab available for non-radiographic axial spondyloarthritis would broaden the options available. Patients additionally perceive the once monthly dosing of golimumab as advantageous.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	None
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	None

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None
Other issues	
13. Are there any other issues that you would like the committee to consider?	No
Key messages	
14. In up to 5 bullet points, please summarise the key messages of your submission: • TA383 and TA407 have greatly widened the treatment options for people with axial spondyloarthritis. • Options for people with non-radiographic axial spondyloarthritis are more limited • Golimumab will be a good additional option for people with non radiographic axial spondyloarthritis • Golimumab will offer a once monthly option to people with non-radiographic axial spondyloarthritis	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Golimumab for treating non-radiographic axial spondyloarthritis [ID903]

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Information on completing this expert statement

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	[redacted]

3. Job title or position	**Consultant Rheumatologist & Hon Senior Lecturer.**
4. Are you (please tick all that apply):	☐ a specialist in the treatment of people with this condition?
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ Yes
The aim of treatment for this condition	

7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Spondyloarthroapthy is chronic inflammatory condition if untreated leads on poor mobility and restriction of spinal movement. The main stay of treatment includes Physiotherapy and NSAIDS . If not improved treatment includes Biological therapy. The main of the treatment is to reduce the inflammation and to stop progression and structural Changes in the spine. The therapeutic goal is to prevent progression and disability.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	To improve the BASDAI score To improve BASFI To Reduce structural changes
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes . Delay in diagnosis and treatment . Lesser therapeutic Options now and more option is benefit to this patient group.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Physio therapy NSAIDS Biological Therapies.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	BSR guidelines and ASAS Guidelines. NICE guidelines for Spondyloarthropathy
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes the pathway of care is well defined.
• What impact would the technology have on the current pathway of care?	To improve the patient care
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes as same way as current care.

• How does healthcare resource use differ between the technology and current care?	No difference
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care and specialist clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Circulation of Guidelines.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	In my opinion the drug will provide meaningful benefits to patient care.
• Do you expect the technology to increase length of life more than current care?	Yes.

• Do you expect the technology to increase health-related quality of life more than current care?	Yes
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	None
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	No practical difficulties in implementation is anticipated.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No additional testing needed other than standard screening and testing for any biological treatment.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	Non Radiographic Spondyloarthropathy is newer Emerging concept.

impact on health-related benefits and how might it improve the way that current need is met?	Currently only few therapeutic options are available for the Non Radiographic Spondyloarthropathy . Inclusion of another therapeutic agent will have a significant and substantial impact patient group with this condition.
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effects are monitored closely and safe to start
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	BASDAI, BASFI SCORE Improvement Radiological changes monitored .
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	None
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None

20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA383]?	No
22. How do data on real-world experience compare with the trial data?	It reflects on the real world data in my clinical experience .
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	None

23b. Consider whether these issues are different from issues with current care and why.	None
Key messages)	

24. In up to 5 bullet points, please summarise the key messages of your statement.

Non radiographic axial spondyloarthroapthy is emerging concept in the field of Spondyloarthropathy .

Golilumab is another therapeutic option for the management .

- reduces the signs and symptoms of Axial Inflammation significantly.
- Improves the health related quality of life and productivity

  slow down the radiological progression and structural damage of the Axial spine (MRI/CRP)
- shown greater tolerability and retention and sustained efficacy up-to 5years.
- once monthly dosage schedule is very convenient option to the patient group and preferred option by most patients .

References:

1.Two-year retention rate of golimumab in rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis: data from the LORHEN registry

Manara M[1], etal Clin Exp Rheumatol. 2017 Jul 27. [Epub ahead of print]

2. Report of real-life data on two-year survival on treatment with golimumab in RA, PsA and AS. Golimumabshowed a similar retention rate when given as first or second line of treatment.

Semin Arthritis Rheum. 2017 Aug;47(1):108-114. doi: 10.1016/j.semarthrit.2017.01.008. Epub 2017 Jan 18.

3.Golimumab in real-life settings: 2 Years drug survival and predictors of clinical outcomes in rheumatoid arthritis, spondyloarthritis, and psoriatic arthritis.

Iannone F[1] etal .

Semin Arthritis Rheum. 2017 Mar 21. pii: S0049-0172(16)30360-2. doi: 10.1016/j.semarthrit.2017.03.010. [Epub ahead of print]

4.Golimumab significantly reduced MRI-detected spinal inflammation of AS; improvements were sustained to week 104 and correlated with improvement in ASDAS and CRP. (GO-RAISE Study)

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology Appraisal (FTA)

Golimumab for treating non-radiographic axial spondyloarthritis [ID903]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the statement submitted by the National Ankylosing Spondylitis Society and consequently I will not be submitting a personal statement.

Name: [redacted]

Signed:

Date: 15 August 2017

Confidential until published

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

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Declared competing interests of the authors

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

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Rider on responsibility for report

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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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Golimumab for treating non-radiographic axial spondyloarthritis [ID903]: A Fast Track Appraisal

ERG response to issues raised by the company during the fact check on the ERG report.

Issue 1			
Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG response**
Page 4, paragraph 2 Incorrect reference to clarification question. 'the inclusion criteria of age ≤45 years at enrolment was selected because it is the ASAS criteria for axial spondyloarthritis (Company's clarification response, question A10)'	We propose the amendment: 'the inclusion criteria of age ≤45 years at enrolment was selected because it is the ASAS criteria for axial spondyloarthritis (Company's clarification response, question A11)	Reference to the clarification question is incorrect	The final reference should have been to clarification response A11. ERG report has been amended to correct this in the erratum.
Issue 2			
Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG response**
Page 6, paragraph 2 Incorrect reporting of nr-ax Spa population numbers for RAPID-axSpA study: 'The RAPID-axSpa study evaluated certolizumab pegol 200mg every other week or 400mg every four weeks versus placebo in 325 (107 placebo, 111 CZP 200mg and 107 CZP 400mg) adult patients with nr-axSpa'.	When looking at the nr-axial SpA population only, we suggest this amendment: "…evaluated certolizumab pegol 200mg every other week or 400mg every four weeks versus placebo in 147 (50 placebo, 46 CPZ 200mg and 51 CZP 400mg) adult patients with nr-axSpA."	Please see Landewe et al. 2014 supplementary Table 2. The total population of 325 (107 placebo, 111 CPZ 200mg and 107 CZP 400mg) refers to both AS and nr-axSpA patients	The ERG agrees that the text in the final ERG report is inaccurate for the reason described by the company. The text has been amended to provide accurate information on the numbers by trial arm for both the whole trial and the subgroup with nr-axSpA.

Issue 3			
Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG response**
Page 6, paragraph 3 We believe this is a misleading statement. '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.'	We propose this amendment: 'The GO-AHEAD[6] study was identified in the searches for TA383 but it was excluded due to the lack of marketing authorisation for this indication at the time.'	The revised statement provides clarity on why golimumab was omitted from TA383.	The text in the ERG report is not factually inaccurate so no amendment has been made.
Issue 4			
Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG response**
We believe page 7 incorrectly reports the percentages of HBA-L27 positive patients per study, with incorrect references: "the proportion of patients who were HBA-L27 positive was reasonably comparable across studies (78%[6] , 67%[8] , 71%[10], 75%[9])"	We suggest the amendment of '"The proportion of patients who were HBA-L27 positive was reasonably comparable across studies (82.7%[6] , 78%[7] , 67%[8] , 71%[10] , 75%[9])"	The proportion of patients who were HBA-L27 positive for GO-AHEAD, according to reference 6 (Sieper et al., 2015) was 82.7%. The proportion of patients who were HBA-L27 positive for ABILITY-1 (78%) is incorrectly referenced as the GO-AHEAD study in the ERG report. We believe the reference should be reference 7 (ABILITY-1) rather than 6 (GO-AHEAD).	The ERG agrees that the first figure given has been wrongly referenced as it relates to the ABILITY-1 study and not the GO-AHEAD study which wasn't actually discussed in the text and appeared only in the table. An erratum has been provided correcting the referencing error and adding the figure for GO-AHEAD to the text. (NB: the erratum page for this correction is page 8 not page 7)

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

ERRATUM

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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.

1.1 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 A11).

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).

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 certolizumab pegol 200mg and 107 certolizumab pegol 400mg) adult patients with AS (n=178) or nr-axSpA (n=147). The CS includes only the population with nr-axSpA, of which 50 were prescribed placebo, 46 certolizumab pegol 200mg and 51 certolizumab pegol 400mg. 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.

1.2 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

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 (82%,[6] 78%,[7] 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.