NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

TNF-alpha inhibitors for ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (including a review of TA143 and TA233)

This premeeting briefing is a summary of:

- the evidence and views submitted by the company(ies), the consultees and their nominated clinical experts and patient experts and
- the assessment report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document is a summary of the information available before comments on the assessment report have been received.

Key issues for consideration

Clinical effectiveness

- What is the Committee's view on the categorisation and reliability of the distinction between ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis? What is the likelihood of a differential response to TNF-inhibitors in the two patients groups, or is the response likely to be the same/similar?
- What does the Committee consider it can say about the sequential use of TNF-inhibitors?
- How generalisable are the trials to UK practice given the diagnostic difficulty (particularly for axial spondyloarthritis without radiographic evidence of ankylosing

spondylitis), and heterogeneity in the C-reactive protein values and MRI changes in patients recruited?

- The Assessment Group predominantly used the response at 12 weeks in their meta-analysis. Is this reasonable for all comparators? Should the trial of infliximab for axial spondyloarthritis without radiographic evidence of ankylosing spondylitis be removed as infliximab is not currently licensed for this indication?
- Is ASAS 20 or change in BASDAI a better reflection of the therapeutic effects of TNF-inhibitors?
- Does the Committee consider that the baseline BASDAI score is related to whether or not the patient responds to TNF-inhibitors?
- Does the Committee consider that there is a class effect of TNF-inhibitors (i.e. there is little, if any, difference in efficacy)?
- What is the Committee's view on the long-term effect of TNF-inhibitors on the disease, in terms of reducing disease activity and preserving function (through slowing or preventing irreversible bony changes)?
- Do non-skeletal manifestations of disease (such as uveitis) need to be taken into consideration?

Cost-effectiveness

- The Assessment Group noted that the ICER estimates in the companies' submissions were relatively similar to each other for ankylosing spondylitis, but differed more for axial spondyloarthritis without radiographic evidence of ankylosing spondylitis. The Assessment Group also noted differences in the company approaches to modelling and took a new approach to modelling, synthesising data on BASDAI 50, BASDAI score reductions and BASFI, and did not use ASAS 20 results. Does the Committee consider the Assessment Group's model robust enough to form a view on the cost-effectiveness of biological treatments?
  - The Assessment Group suggested that BASDAI and BASFI may not be the most appropriate conceptual basis for modelling progression of these diseases. But in the absence of data linking other disease measures to costs and QALYs,

they concluded that there were no other options. What is the Committee's view on this?

- The Assessment Group's model assumed that non-responders had higher baseline BASDAI and BASFI scores than responders (that is, response is unlikely to be independent of baseline patient characteristics). A commentator stated that this assumption is not supported by the Assessment of SpondyloArthritis international Society consensus statement (2006). Does the Committee consider this assumption appropriate?
  - ◊ Note that, in the sensitivity analyses, the ICERs for ankylosing spondylitis were sensitive to the source data used to inform the difference in baseline scores (using company clinical trial data made the ICERs more favourable towards TNF-inhibitors, compared with ICERs based on data from the Assessment Group's evidence synthesis). Which assumptions does the Committee find more plausible: the base case or Assessment Group's sensitivity analysis (scenario 2)?
- In the Assessment Group's base case model, a placebo effect was assumed in patients receiving conventional care. Does the Committee consider this assumption appropriate? Note that the ICERs for axial spondyloarthritis without radiographic evidence of ankylosing spondylitis were sensitive to the removal of the placebo effect.
- The Assessment Group model assumed that people whose disease responds to a TNF-inhibitor experienced a slower progression rate compared with the natural history of the disease. This was explored in sensitivity analysis (scenario 3: assumed TNF-inhibitors have no effect on BASFI progression). In response to consultation, a company presented published evidence that BASFI is stable during treatment with TNF-inhibitors (that is, TNF-inhibitors completely stop BASFI progression). Which assumption does the Committee find more plausible: the base case, the Assessment Group's sensitivity analysis (scenario 3) or the company's assumption?
- The effect of TNF-inhibitors on disease progression was delayed until year 4 of treatment in the Assessment Group's model. Does the Committee agree with

this delay or believe that reduced progression should be achieved immediately (scenario 4 of the Assessment Group's sensitivity analysis)?

  - The Assessment Group acknowledged that the QALY gains for TNF-inhibitors may be underestimated in their model, based on the algorithm for calculating EQ-5D. What is the Committee's view on this?

- Clinical trial data could not accurately characterise the extent of the rebound in BASFI/BASDAI scores after treatment withdrawal, so the Assessment Group presented 2 scenarios in their base case: 1 assuming rebound to baseline and 1 assuming rebound to natural history (representing the best-case and worst-case scenarios, respectively). Three consultees stated that the rebound to baseline scenario was more plausible, and may be conservative because there would be a delayed return to baseline and some people may get a sustained further benefit. Which scenario does the Committee consider to be the most plausible?
- The Assessment Group's model is based on an assumption that the 12-week continuation rules specified in the marketing authorisations for TNF-inhibitors are adhered to in clinical practice and does not consider evidence of further improvement after 12 weeks. Does the Committee consider these assumptions correct?
- For the economic analysis the Assessment Group have assumed a class effect of TNF-inhibitors (despite some evidence, identified by the Assessment Group in their meta-analysis, to suggest that infliximab has a greater effect than the other TNF-inhibitors), thereby assuming each produces the same number of QALYs and that any difference in ICERs is driven by difference in acquisition cost. What is the Committee's view on this?
- The Assessment Group's model does not account for improvements in non-skeletal manifestations (psoriasis, uveitis and inflammatory bowel disease), conferred by TNF-inhibitors, due to a lack of evidence. Given the comments received by a consultee and a commentator, does the Committee consider that data in people with psoriasis, uveitis and inflammatory bowel disease (but without axial spondyloarthritis) should be considered as part of this appraisal?

- Given the comments received by consultees for administration/acquisition costs of infliximab and administration costs of adalimumab, do the Committee consider that these should be revised in the Assessment Group's model?

1 Background: clinical need and practice

1.1 Ankylosing spondylitis is an inflammatory disease of unknown cause. It is one of a group of clinically heterogeneous inflammatory rheumatologic diseases known as spondyloarthritis. Spondyloarthritis can be categorised as having predominantly axial (sacroiliac joints or spine) or peripheral involvement. In people with axial spondyloarthritis, the predominant symptom is back pain, with inflammation of the sacroiliac joints (sacroiliitis), the spine or both. The onset of symptoms typically occurs in the third decade of life. Damage is progressive and irreversible and there is increased risk of spinal fracture later in life. There may also be peripheral joint involvement or extra-articular manifestations such as uveitis, inflammatory bowel disease and psoriasis.

1.2 If definite radiographic sacroiliitis (abnormalities seen in plain x-rays of the sacroiliac joints, such as erosions, sclerosis, and partial or total ankylosis) is present, the disease is classified as ankylosing spondylitis. The prevalence is thought to range from 0.05% to 0.23% and it is about 3 times more common in men than in women.

1.3 Not everyone with symptoms of axial spondyloarthritis will have x-ray evidence of the disease (although sacroiliitis or inflammation of the spine may be visible on MRI). This is referred to as axial spondyloarthritis without radiographic evidence of ankylosing spondylitis. Limited epidemiological data are available for axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, but it affects approximately equal numbers of men and women.

1.4 Conventional therapy for axial spondyloarthritis includes acute anti-inflammatory treatment with non-steroidal anti-inflammatory drugs

(NSAIDs) and physiotherapy. Tumour necrosis factor-alpha (TNF-alpha) inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab) are typically used when the disease has not responded adequately to conventional therapy. NICE technology appraisal 143 recommends adalimumab and etanercept as treatment options for adults with severe active ankylosing spondylitis only if certain criteria are fulfilled, but it does not recommend infliximab for ankylosing spondylitis. Golimumab is also recommended in NICE technology appraisal 233 as an option for the treatment of severe, active ankylosing spondylitis in adults only if it is used as described for adalimumab and etanercept in NICE technology appraisal 143.

1.5 Three key disease components are assessed in clinical trials of ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis: disease activity, physical function and structural damage. A number of assessment tools have been developed to measure these (presented in **Table** 22, Appendix A). For example, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is the most commonly used instrument to measure inflammatory activity. Physical function is widely assessed through the use of the Bath Ankylosing Spondylitis Functional Index (BASFI). Structural damage and disease progression are primarily evaluated using radiography, captured on the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS).

1.6 The Assessment of SpondyloArthritis international Society (ASAS) has developed a set of response criteria (presented in **Table** 23, Appendix A), which relate to improvement across a set of 4 domains. An ASAS 20 response (a common primary efficacy outcome in clinical trials) is defined as an improvement of greater than 20% and an absolute change of 1 or more points in at least 3 of the 4 domains. Other definitions of ASAS response (ASAS 40, 50 and 70, based on improvements of 40%, 50% and 70%, respectively) and an improvement of 50% or more in BASDAI score (BASDAI 50) are also used to measure outcomes in clinical studies.

2 The technologies

2.1 Adalimumab (Humira, AbbVie), certolizumab pegol (Cimzia, UCB Pharma), etanercept (Enbrel, Pfizer), golimumab (Simponi, Merck Sharp & Dohme), and infliximab (Remicade, Merck Sharp & Dohme; Inflectra, Hospira; Remsima, Celltrion) inhibit the pro-inflammatory cytokine, TNF-alpha. Agents that inhibit the action of TNF-alpha may modify the inflammatory process of the disease. Adalimumab, certolizumab pegol, golimumab and infliximab are monoclonal antibodies, and etanercept is a recombinant human TNF-receptor fusion protein.

2.2 Adalimumab, etanercept, golimumab and infliximab have marketing authorisations in the UK for the treatment of adults with severe active ankylosing spondylitis that has responded inadequately to conventional therapy. Certolizumab pegol has a marketing authorisation in the UK for the treatment of ‘adults with severe active ankylosing spondylitis who have had an inadequate response to, or are intolerant to, NSAIDs’.

2.3 Adalimumab, certolizumab pegol and etanercept are also licensed for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of ankylosing spondylitis but with objective signs of inflammation by elevated C-reactive protein and/or magnetic resonance imaging, whose disease has responded inadequately to, or who cannot tolerate, NSAIDs. Golimumab and infliximab do not currently have a market authorisation in the UK for axial spondyloarthritis without radiographic evidence of ankylosing spondylitis.

Adalimumab

2.4 Adalimumab is administered by subcutaneous injection. The recommended dose regimen for patients with ankylosing spondylitis, and for patients with axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, is 40 mg every other week. The summary of product characteristics recommends that continued adalimumab therapy

should be carefully reconsidered in patients whose disease does not respond within 12 weeks after starting treatment.

2.5 The summary of product characteristics lists the following adverse reactions for adalimumab: infections (such as nasopharyngitis, upper respiratory tract infection and sinusitis), injection site reactions (erythema, itching, haemorrhage, pain or swelling), headache, musculoskeletal pain, hepatitis B reactivation, various malignancies and serious haematological, neurological and autoimmune reactions. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.6 The price of adalimumab is £352.14 for a 40 mg pre-filled pen or pre-filled syringe, or a 40 mg/0.8-mL vial (excluding VAT; 'British National Formulary' [BNF] edition 68). The annual cost of treatment with adalimumab is estimated at £9156, assuming the patient receives 40 mg every other week (see section 2.4). Costs may vary in different settings because of negotiated procurement discounts.

Certolizumab pegol

2.7 Certolizumab pegol is administered by subcutaneous injection. The recommended induction dosage for patients with ankylosing spondylitis, and for patients with axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, is 400 mg (given as 2 injections of 200 mg each) at weeks 0, 2 and 4. The recommended maintenance dose regimen is 200 mg every other week or 400 mg every 4 weeks. The summary of product characteristics recommends that continued certolizumab pegol therapy should be carefully reconsidered if there is no evidence of therapeutic benefit within 12 weeks after starting treatment.

2.8 The summary of product characteristics lists the following adverse reactions for certolizumab pegol: infections (including sepsis, pneumonia, tuberculosis, invasive fungal and opportunistic infections), blood and lymphatic system malignancies (including lymphoma and leukaemia),

autoimmune conditions (including lupus-like syndrome), injection site reactions (erythema, itching, haematoma, pain or swelling), and hepatitis B reactivation. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.9 The price of certolizumab pegol is £357.50 for a 200 mg pre-filled syringe (excluding VAT; BNF edition 68). Assuming the recommended dosage is followed (see section 2.7), the annual cost for first year of treatment with certolizumab pegol is estimated at £10,368. Costs may vary in different settings because of negotiated procurement discounts.

Etanercept

2.10 Etanercept is administered by subcutaneous injection. The recommended dosage for patients with ankylosing spondylitis, and for patients with axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, is 25 mg administered twice weekly or 50 mg administered once weekly. The summary of product characteristics recommends that continued etanercept therapy should be carefully reconsidered in patients whose disease does not respond within 12 weeks after starting treatment.

2.11 The summary of product characteristics lists the following adverse reactions for etanercept: infections (including upper respiratory infections, bronchitis, bladder infections and skin infections, as well as serious infections such as sepsis), injection site reactions (such as pain, swelling, itching, reddening and bleeding at the puncture site), allergic reactions, development of auto-antibodies, itching, fever, various malignancies and serious haematological, neurological and autoimmune reactions. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.12 The price of etanercept is £89.38 for a 25 mg pre-filled syringe or a 25 mg vial containing powder for reconstitution (with solvent), and £178.75 for a 50 mg pre-filled pen or pre-filled syringe (excluding VAT; BNF edition 68). The annual cost of treatment with etanercept, using either twice weekly or

once weekly dosage frequency (see section 2.10), is estimated at £9295. Costs may vary in different settings because of negotiated procurement discounts.

Golimumab

2.13 Golimumab is administered by subcutaneous injection. The recommended dose regimen for patients with ankylosing spondylitis is 50 mg once a month, on the same date each month. The summary of product characteristics recommends that continued golimumab therapy should be carefully reconsidered if there is no evidence of therapeutic benefit within 12–14 weeks after starting treatment (that is, after 3–4 doses). For patients with a body weight greater than 100 kg whose disease does not respond adequately after 4 doses (50 mg each), the summary of product characteristics states that increasing the dosage of golimumab to 100 mg once a month may be considered. If there is still no evidence of therapeutic benefit after 3–4 additional doses of 100 mg, continued golimumab therapy should be carefully reconsidered.

2.14 The summary of product characteristics lists the following adverse reactions for golimumab: infections (including sepsis, pneumonia, tuberculosis, and invasive fungal and opportunistic infections), demyelinating disorders, lymphoma, hepatitis B reactivation, congestive heart failure, autoimmune processes (lupus-like syndrome) and haematologic reactions. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.15 The price of golimumab is £762.97 for a 50 mg pre-filled pen or pre-filled syringe and £1525.94 for a 100 mg pre-filled pen (excluding VAT; BNF edition 68). Merck Sharp & Dohme has agreed a patient access scheme with the Department of Health. This will make the 100 mg dose of golimumab available to the NHS at the same cost as the 50 mg dose. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS. Assuming

the patient receives 50 mg every month, the annual cost of treatment with golimumab is estimated at £9156. Because of the patient access scheme, this cost would remain the same for patients with a body weight greater than 100 kg whose disease does not respond adequately to the 50 mg per month dosage and who subsequently receive monthly doses of 100 mg (see section 2.13).

Infliximab

2.16 Infliximab is administered by intravenous infusion. The recommended dosage for patients with ankylosing spondylitis is a 5 mg/kg infusion at weeks 0, 2 and 6, then every 6–8 weeks. The summary of product characteristics states that if there is no response by 6 weeks (that is, after 2 doses), no additional treatment with infliximab should be given.

2.17 The summary of product characteristics lists the following adverse reactions for infliximab: infections (including upper respiratory tract infections, sepsis, opportunistic infections and tuberculosis), hepatitis B reactivation, congestive heart failure, serum sickness (delayed hypersensitivity reactions), haematologic reactions, systemic lupus erythematosus/lupus-like syndrome, demyelinating disorders, hepatobiliary events, lymphoma, hepatosplenic T-cell lymphoma, and serious infusion reactions. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.18 The price of infliximab is £419.62 for a 100 mg vial containing powder for reconstitution (excluding VAT; BNF edition 68). For a patient with a body weight of 73 kg, the annual cost for first year of treatment with infliximab therapy (including 3 induction doses) is estimated at between £16,785 and £13,428 (depending on whether the maintenance infusions are repeated every 6 or 8 weeks). Costs may vary in different settings because of negotiated procurement discounts.

2.19 Biosimilar versions of infliximab (Inflectra, Hospira; Remsima, Celltrion) have a marketing authorisation in the UK for the same indications. The

therapeutic indications, dosage and method of administration for Remisima and Inflectra are identical to those for Remicade. Adverse reactions are similar too. The price of Remsima is £377.66 for a 100 mg vial (price confirmed by Celltrion Healthcare and Napp Pharmaceuticals). For a patient with a body weight of 73 kg, the annual cost for first year of treatment with Remsima therapy is estimated at between £15,106 and £12,085 (depending on whether the maintenance infusions are repeated every 6 or 8 weeks). Inflectra did not have an approved list price in the UK at the time of the appraisal.

Table 1 Summary description of technologies

Non-proprietary name	Adalimumab	Certolizumab pegol	Etanercept	Golimumab	Infliximab (biosimilars)
Proprietary name	Humira	Cimzia	Enbrel	Simponi	Remicade (Inflectra and Remsima)
Company	AbbVie	UCB	Pfizer	Merck Sharp & Dohme	Merck Sharp & Dohme (Hospira and Celltrion Healthcare)
Dose	40 mg every other week	400 mg at weeks 0, 2 and 4 (induction) then 200 mg every 2 weeks or 400 mg every 4 weeks (maintenance)	25 mg twice weekly or 50 mg once weekly	50 mg once a month (may be increased to 100 mg once a month in patients with a body weight greater than 100 kg)	5 mg/kg infusion doses at weeks 0, 2 and 6 (induction), then every 6–8 weeks (maintenance)

Non-proprietary name	Adalimumab	Certolizumab pegol	Etanercept	Golimumab	Infliximab (biosimilars)
Acquisition cost (BNF edition 68)	£352.14 for a 40 mg pre-filled pen or pre-filled syringe, or a 40 mg/0.8-mL vial	£357.50 for a 200 mg pre-filled syringe	£89.38 for a 25 mg pre-filled syringe or a 25 mg vial; £178.75 for a 50 mg pre-filled pen or pre-filled syringe	£762.97 for a 50 mg pre-filled pen or pre-filled syringe; £1525.94 for a 100 mg pre-filled pen	Remicade: £419.62 for a 100 mg vial Remsima: £377.66 for a 100 mg vial Inflectra did not have an acquisition cost in the UK at the time of the appraisal

3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this appraisal was: To appraise the clinical and cost effectiveness of TNF-inhibitors within their licensed indications for treating ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis.

	Final scope issued by NICE	**Additional comments or specifications in the Assessment Group's protocol**
Population	• People with severe active ankylosing spondylitis whose disease has responded inadequately to, or who are intolerant to, NSAIDs. • People with severe axial spondyloarthritis without radiographic evidence of ankylosing spondylitis but with objective signs of inflammation, whose disease has responded inadequately to, or who are intolerant to, NSAIDs.	None

	Final scope issued by NICE	Additional comments or specifications in the Assessment Group's protocol
Intervention	• Adalimumab • Certolizumab pegol • Etanercept • Golimumab • Infliximab	Biosimilar versions of infliximab (Remsima, Celltrion Healthcare; Inflectra, Hospira) are licensed for the same indications and form part of the clinical evidence base for infliximab. Because biosimilars did not have a list price in the UK at the time of the appraisal, their cost effectiveness could not be established.
Comparators	• The interventions listed above compared with each other • Established clinical management without TNF-alpha inhibitors	The Assessment Group assessed the efficacy of sequential treatment with TNF-inhibitors in ankylosing spondylitis using results from 11 patient registry studies, but did not identify any efficacy data for people with axial spondyloarthritis without radiographic evidence of ankylosing spondylitis who had switched to a second or third TNF-inhibitor. The Assessment Group's model could not address the clinical questions concerning the issue of sequential use of TNF-inhibitors.
Outcomes	The outcome measures to be considered include: • 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.	All these outcomes were addressed by the included clinical trial evidence. However, little data were available on: • peripheral symptoms (except enthesitis) • symptoms of extra-articular manifestations.

	Final scope issued by NICE	Additional comments or specifications in the Assessment Group's protocol
Economic evaluation	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account.	Because the Assessment Group assumed a class effect of TNF-inhibitors (that is, the QALYs gained are the same for each), the difference in the ICERs between the individual TNF-inhibitors is driven entirely by the different acquisition and administration costs associated with each. Under this assumption, the TNF-inhibitor with the lowest cost would dominate the other treatments (that is, provide the same QALYs at a lower cost) in a fully incremental comparison of cost-effectiveness. Therefore, the Assessment Group presented pairwise ICERs comparing each TNF-inhibitor with conventional therapy.
NSAIDs, non-steroidal anti-inflammatory drugs.		

4 Clinical-effectiveness evidence

Systematic review

4.1 The Assessment Group conducted a systematic review and identified 24 relevant randomised controlled trials (RCTs): 19 recruited people with ankylosing spondylitis, 4 recruited people with axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, and 1 recruited both populations.

4.2 All, except 2, of the trials were placebo-controlled. One trial in ankylosing spondylitis (Giardina et al.) compared etanercept with infliximab and another trial (PLANETAS) compared infliximab with an infliximab

biosimilar. Of the 24 RCTs, 17 had open-label extension studies, with 11 studies having a total duration of at least a year.

4.3 Half of the trials included patients whose disease responded inadequately to, or who could not tolerate NSAIDs. However, in 7 of these 12 RCTs, between 80 and 100% of patients received NSAIDs during the trial. In the trials that did not require failure of NSAIDs as an inclusion criterion, a similar proportion of patients received NSAIDs during the trial. A BASDAI score of ≥4 was used as an inclusion criterion in most trials; however, the Assessment Group commented that the average baseline BASDAI scores were high, most were between 5.5 and 6.6 (on a scale from 0–10, 10 being most severe). BASFI scores and the concentration of C-reactive protein at baseline also varied across the RCTs, and so did the thresholds used to define elevated C-reactive protein in the trials in axial spondyloarthritis without radiographic evidence of ankylosing spondylitis. The Assessment Group noted that higher C-reactive protein levels are associated with an increased likelihood of BASDAI 50 response.

Ankylosing spondylitis

4.4 Of the 20 RCTs in ankylosing spondylitis, 4 were for adalimumab, 1 for certolizumab pegol, 7 for etanercept, 3 for golimumab and 5 for infliximab (Table 2). Most were conducted in Europe or North America; 4 were conducted in China (Hu et al., Huang et al., Bao et al. and Tam et al.). Among patients in the included RCTs, 65% to 97% were male, the average age ranged from 27 to 48, and the average duration of disease was 6.8 to 19 years. For further details of the trials see section 4.2.1 in assessment report.

Table 2 Overview of the clinical evidence for ankylosing spondylitis

Technology	Trial[1]	Treatment groups	Study duration, including open-label extension phase
Adalimumab	Hu 2012 (n=46)	• Adalimumab 40 mg every 2 weeks (n=26) • Placebo (n=20)	24 weeks
	Huang 2014 (n=344)	• Adalimumab 40 mg every 2 weeks (n=229) • Placebo (n=115)	24 weeks
	Lambert 2007 (n=82)	• Adalimumab 40 mg every 2 weeks (n=38) • Placebo (n=44)	1 year
	ATLAS 2006 (n=315) Included UK sites	• Adalimumab 40 mg every 2 weeks (n=208) • Placebo (n=107)	5 years
Certolizumab pegol	RAPID-axSpA 2014 (n=178)	• 200mg every 2 weeks (n=65) • 400mg every 4 weeks (n=56) • Placebo (n=57)	96 weeks
Etanercept	Barkham 2010 (n=40) UK only	• Etanercept 25 mg twice weekly (n=20) • Placebo (n=20)	12 weeks
	Davis 2003 (n=277)	• Etanercept 25 mg twice weekly (n=138) • Placebo (n=139)	168 weeks
	Dougados 2011 (n=82)	• Etanercept 50 mg weekly (n=39) • Placebo (n=43)	24 weeks
	Gorman 2002 (n=40)	• Etanercept 25 mg twice weekly (n=20) • Placebo (n=20)	40 weeks
	Calin 2004 (n=84) Included UK sites	• Etanercept 25 mg twice weekly (n=45) • Placebo (n=39)	5 years
	Van der Heijde 2006 (n=356) Included UK sites	• Etanercept 25 mg twice weekly (n=150) • Etanercept 50 mg weekly (n=155) • Placebo (n=51)	12 weeks
	Giardina 2010 (n=50)	• Etanercept 50 mg weekly (n=25) • Infliximab 5mg/kg (at week 0,2,6 and every 6 weeks) (n=25)	12 weeks

Technology	Trial[1]	Treatment groups	Study duration, including open-label extension phase
Golimumab	GO-RAISE 2008 (n=356)	• 50mg every 4 weeks (n=138) • 100mg every 4 weeks (n=140) • Placebo (n=78)	4 years
	Bao 2014 (n=213)	• 50mg every 4 weeks (n=108) • Placebo (n=105)	1 year
	Tam 2014 (n=41)	• 50mg every 4 weeks (n=20) • Placebo (n=21)	1 year
Infliximab	Braun 2002 (n=69)	• 5mg/kg (at weeks 0,2,6) (n=34) • Placebo (n=35)	8 years
	Marzo-Ortega 2005 (n=42) UK only	• 5mg/kg (at weeks 0,2,6,14,22) (n=28) • Placebo (n=14)	30 weeks
	Van den Bosch 2002 (n=21)	• 5mg/kg (at weeks 0,2,6) (n=9) • Placebo (n=12)	12 weeks
	ASSERT (n=279) Included UK sites	• Infliximab 5mg/kg (at weeks 0,2,6,12,18) (n=201) • Placebo (n=78)	2 years
	PLANETAS 2013 (n=250)	• Inflectra/Remsima (CT-P13) 5mg/kg (at weeks 0,2,6) (n=125) • Infliximab 5mg/kg (at weeks 0,2,6) (n=125)	2 years years (using randomised interventions up to 54 weeks)
[1] Unless stated otherwise, UK sites were not included in the trial			

Axial spondyloarthritis without radiographic evidence of ankylosing spondylitis

4.5 Of the 5 RCTs in axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, 2 were for adalimumab, 1 for certolizumab pegol and 1 for etanercept (Table 3). In addition, the Assessment Group included a trial for infliximab (Barkham et al.), although infliximab does not have a marketing authorisation in the UK for axial spondyloarthritis without radiographic evidence of ankylosing spondylitis. The Assessment Group stated that this was to inform the relative efficacy of TNF-inhibitors in this indication as the dose used in the identified trial was the same as that licensed for ankylosing spondylitis. Three RCTs were multicentre conducted worldwide, 1 was conducted in Germany and 1 was UK-based.

Among patients in the included RCTs, [redacted] to 75% were male, the average age ranged from 28.2 to [redacted], and the average duration of disease was 2.4 to 17.2 years. The Assessment Group noted substantial heterogeneity in the baseline characteristics across the trials, such as variation in C-reactive protein concentration and proportion of patients with MRI changes. For further details of the trials see section 4.2.1 in the assessment report.

Table 3 Overview of the clinical evidence for axial spondyloarthritis without radiographic evidence of ankylosing spondylitis

Technology	Trial[1]	Treatment groups	Study duration, including open-label extension phase
Adalimumab	Haibel 2008 (n=46)	Adalimumab 40 mg every 2 weeks (n=22) Placebo (n=24)	1 year
	ABILITY-1 2013 (n=142) Included UK sites	Adalimumab 40 mg every 2 weeks (n=[redacted]) Placebo (n=[redacted])	3 years
Certolizumab pegol	RAPID-axSpA 2014 (n=147) Included UK sites	200mg every 2 weeks (n=46) 400mg every 4 weeks (n=51) Placebo (n=50)	96 weeks
Etanercept	Dougados 2014 (n=215)	Etanercept 50 mg weekly (n=106) Placebo (n=109)	48 weeks
Infliximab	Barkham 2009 (n=40) UK only	5mg/kg (at weeks 0,2,6,12) (n=20) Placebo (n=20)	16 weeks

[1] Unless stated otherwise, UK sites were not included in the trial

Clinical efficacy

4.6 Individual results for all 24 trials are presented in Appendix 4 of the assessment report. The Assessment Group synthesised the data on clinical effectiveness using a Bayesian meta-analysis. For both indications, it included RCTs reporting results between 10 and 16 weeks

after starting treatment. Although Giardina et al. and PLANETAS 2013 provided this, the Assessment Group excluded them because they were either redundant in a class effect model (Giardina et al.; compared etanercept with infliximab) or did not include any of the relevant comparators needed for meta-analysis (PLANETAS 2013; compared infliximab with an infliximab biosimilar). In addition, the Assessment Group presented sensitivity analyses for ankylosing spondylitis in which it included studies reporting results between 24 and 30 weeks after excluding 5 eligible studies that it judged to be at risk of bias. No sensitivity analyses were presented for axial spondyloarthritis without radiographic evidence of ankylosing spondylitis. The Assessment Group presented results assuming that the treatment effects of the TNF-inhibitors differed and separately, assuming that TNF-inhibitors, as a class, had 1 treatment effect. Based on statistical tests, the Assessment Group chose to use a fixed-effect model for both analyses (this assumes that all the studies estimate exactly the same treatment effect and that the variability between individual study results occurs by chance).

4.7 The maximum number of studies included for any one endpoint was 13. Full details are presented in Tables 7–10 of the assessment report. Peripheral symptoms were not included as outcomes in the meta-analysis (with the exception of enthesitis) because very little data were available.

Ankylosing spondylitis

4.8 Meta-analysis results showed a consistent beneficial effect across all 5 TNF-inhibitors at 10–16 weeks, compared with placebo. The pooled relative risk of an ASAS 20 response ranged from 1.80 (certolizumab pegol) to 2.45 (infliximab); for ASAS 40 the relative risks ranged from 2.53 (certolizumab pegol) to 3.42 (adalimumab) and for BASDAI 50 the relative risks ranged from 3.16 (adalimumab) to 4.86 (infliximab) (Table 4). The additional reduction in BASDAI and BASFI scores achieved with adalimumab, certolizumab pegol, etanercept and infliximab compared with placebo were statistically significant and clinically important. Additional

reductions in BASDAI compared with placebo ranged from 1.46 units (certolizumab pegol) to 2.28 units (infliximab), and additional BASFI reductions ranged from 1.1 units (certolizumab pegol) to 2.16 units (infliximab) (Table 5). Results of the sensitivity analyses were very similar to the main analyses (refer to Table 7 and Table 9 of the assessment report).

Table 4 Individual TNF-inhibitors compared with placebo in ankylosing spondylitis: meta-analysis of binary outcomes at 10–16 weeks (main analysis)

	Relative risk (95% CI)		
	ASAS 20	**ASAS 40**	**BASDAI 50**
Adalimumab	2.28 (1.98 to 2.62)	3.42 (2.57 to 4.55)	3.16 (2.40 to 4.16)
Certolizumab pegol	1.80 (1.24 to 2.39)	2.53 (1.47 to 3.98)	3.60 (2.02 to 5.74)
Etanercept	2.23 (1.93 to 2.55)	2.75 (1.88 to 3.88)	3.17 (2.20 to 4.49)
Golimumab	2.14 (1.75 to 2.53)	3.11 (2.24 to 4.26)	3.57 (2.51 to 5.00)
Infliximab	2.45 (1.73 to 3.06)	-	4.86 (2.41 to 7.82)
ASAS, Assessment in SpondyloArthritis international Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CI, Confidence Interval			

Table 5 Individual TNF-inhibitors compared with placebo in ankylosing spondylitis: meta-analysis of continuous outcomes at 10–16 weeks (main analysis)

	Mean additional reduction from baseline (95% CI)		
	BASDAI	**BASFI**	**BASMI**
Adalimumab	−1.55 (−1.88 to −1.22)	−1.25 (−1.63 to −0.87)	−0.37 (−0.50 to −0.23)
Certolizumab pegol	−1.46 (−2.17 to −0.74)	−1.10 (−1.83 to −0.37)	−0.26 (−0.55 to 0.03)
Etanercept	−1.75 (−2.14 to −1.37)	−1.43 (−1.82 to −1.04)	−0.37 (−0.65 to −0.09)
Golimumab	−	−1.45 (−1.84 to −1.05)	−0.11 (−0.26 to 0.04)
Infliximab	−2.28 (−3.18 to −1.38)	−2.16 (−3.18 to −1.12)	−
BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CI, Confidence Interval			

4.9 When TNF-inhibitors were considered as a class, with 1 treatment effect, the meta-analysis showed statistically significant improvements compared

with placebo at 10–16 weeks for all outcomes (Table 6). ASAS 20 responses at 24–30 weeks were also reported by 4 trials; the relative risk for TNF-inhibitors as a class was 1.69 (a significant improvement compared with placebo). The Assessment Group reported little evidence of statistical heterogeneity for the key outcomes (ASAS outcomes, BASFI, BASDAI and BASDAI 50) but substantial heterogeneity for other outcomes. Results of the sensitivity analyses were very similar to the main analyses (refer to Table 7 and Table 9 of the assessment report).

Table 6 Estimated class effect of TNF-inhibitors compared with placebo in ankylosing spondylitis: meta-analysis of outcomes at 10–16 weeks (main analysis)

	Outcome	95% CI
ASAS 20 (relative risk)	2.21	2.01 to 2.43
ASAS 40 (relative risk)	3.06	2.52 to 3.76
BASDAI 50 (relative risk)	3.37	2.75 to 4.16
BASDAI (additional change from baseline)[1]	−1.66	−1.88 to −1.43
BASFI (additional change from baseline)[1]	−1.38	−1.59 to −1.18
BASMI (additional change from baseline)[1]	−0.27	−0.36 to −0.18
SF-36 PCS (additional change from baseline)[2]	4.40	3.60 to 5.21
SF-36 MCS (additional change from baseline)[2]	1.93	0.12 to 3.72
MASES	−0.54	−0.89 to −0.19

[1] Negative changes in BASDAI, BASFI and BASMI represent improvement (that is, a health benefit)
[2] Positive changes in SF-36 represent improvement (that is, a health benefit)

ASAS, Assessment in SpondyloArthritis international Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CI, confidence interval; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; SF-36 MCS, Short Form 36 mental component summary; SF-36 PCS Short Form 36 physical component summary

4.10 The Assessment Group did indirect comparisons of the TNF-inhibitors. There were no statistically significant differences between the 5 TNF-inhibitors for efficacy outcomes at 10–16 weeks (the results are presented in appendix 5 of the assessment report). The Assessment Group noted that the meta-analysis results for infliximab at 10–16 weeks appeared slightly better than results for the other TNF-inhibitors (although the credible intervals are wide). They suggested that this apparent

superiority could be due to infliximab producing a more rapid clinical improvement than the other treatments (but having equal effectiveness in the long-term). This conclusion was based on results from a trial comparing infliximab with etanercept (Giardina et al.; excluded from the meta-analysis). The BASDAI and BASFI outcomes at week 12 favoured treatment with infliximab, but by week 48 the results for infliximab and etanercept were similar (full details presented in section 4.2.2.3 of the assessment report).

4.11 Analysis of long-term efficacy results from open-label extension studies (based on non-responder imputation) showed that, after approximately 2 years of treatment, ankylosing spondylitis continues to respond well to TNF-inhibitors in around half of people with the disease (Table 7). Mean change from baseline for BASDAI, BASFI and BASMI (where reported) were generally maintained at clinically meaningful levels during long-term follow-up. However, the Assessment Group stated that open-label extension studies produced less reliable data than the RCTs. Results may not reflect clinical practice, as some people continued treatment after their disease did not respond to therapy (contrary to the stipulations in UK market authorisations), and people took the higher dose of golimumab (100 mg) without fulfilling the market authorisation requirements for this dose (body weight of more than 100 kg). In addition, the Assessment Group suggest that differences in outcomes may be due to differences in follow-up protocols rather than representing true treatment effects. The Assessment Group concluded that the long-term benefits of TNF-inhibitors appear similar across treatments.

Table 7 Long-term efficacy of TNF-inhibitors in ankylosing spondylitis (results calculated using non-responder imputation)

	Approx. 1 year	Approx. 2 years	Approx. 5 years
Adalimumab			
ASAS 20	62%	43%	36%
ASAS 40	44%	35%	28%
BASDAI 50	54%	39%	31%
Certolizumab pegol			
ASAS 20	74%	[redacted]	-
ASAS 40	58%	50%	-
Etanercept			
ASAS 20	-	64%	-
ASAS 40	-	54%	49%
BASDAI 50	-	52%	48%
Golimumab			
ASAS 20	-	66%	66%
ASAS 40	-	57%	57%
BASDAI 50	-	58%	58%
Infliximab			
ASAS 20	72%	73%	-
ASAS 40	53%	58%	-
BASDAI 50	48%	43%	-

ASAS, Assessment in SpondyloArthritis international Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index

4.12 The Assessment Group used results from 11 patient registry studies (identified in a separate screening of the systematic review results) to assess the efficacy of sequential treatment with TNF-inhibitors in ankylosing spondylitis. Full details are presented in section 4.2.4.2 of the assessment report. Most of the studies provided data on infliximab, etanercept and adalimumab; less evidence was available for certolizumab pegol and golimumab. The proportion of patients remaining on treatment with their first TNF-inhibitor was around 70–80% after 1 year, 65–75% after 2 years, 70% after 3 years and 55% after 5 years. Only 3 studies provided efficacy results for people who had switched to a second or third TNF-inhibitor; results generally showed a reduction in the number of people achieving a BASDAI 50 response with sequential TNF-inhibitors.

In addition, improvements in BASDAI and BASFI reported after a second and third TNF-inhibitor were not as good the improvements achieved with the first TNF-inhibitor, as observed in the largest registry (DANBIO) (Table 8). Despite a reduction in efficacy with sequential treatment, the Assessment Group highlighted that, on average, people receiving a third TNF-inhibitor continued treatment for as long as people receiving their second.

Table 8 Efficacy of sequential TNF-inhibitors in ankylosing spondylitis, based on results from the DANBIO registry

	1st TNF-inhibitor (n=1436)	**2nd TNF-inhibitor (n=432)**	**3rd TNF-inhibitor (n=137)**
BASDAI 50 at 3 months	54%	37%	30%
BASDAI: median change from baseline at 3 months	−3.1	−2.0	−1.3
BASFI: median change from baseline at 3 months	−2.2	−1.6	−1.3
Median time to drug discontinuation (95% CI)	3.1 years (2.6 to 3.7)	1.6 years (1.0 to 2.2)	1.8 years (0.9 to 2.7)
BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CI, Confidence Interval			

4.13 The Assessment Group concluded that, despite a decrease in response rates, sequential treatment with TNF-inhibitors can be beneficial for people with ankylosing spondylitis.

Axial spondyloarthritis without radiographic evidence of ankylosing spondylitis

4.14 Outcomes for 3 of the 4 treatments in the meta-analysis (certolizumab pegol, etanercept and infliximab) were based on results from single trials. The relative risks, compared with placebo, of an ASAS 20 response were similar for adalimumab, certolizumab pegol and etanercept (ASAS 20 was not reported in the trial of infliximab), ranging from 1.46 to 1.92 (Table 9). A greater variation in results was observed in the ASAS 40 response and

reductions in BASDAI and BASFI (Table 10). Infliximab appeared to be the most effective, but this trial was judged to have a high risk of bias.

Table 9 Individual TNF-inhibitors compared with placebo in axial spondyloarthritis without radiographic evidence of ankylosing spondylitis: meta-analysis of binary outcomes at 10–16 weeks

	Relative risk (95% CI)		
	ASAS 20	**ASAS 40**	**BASDAI 50**
Adalimumab	1.92 (1.47 to 2.56)	3.14 (1.99 to 4.68)	2.52 (1.65 to 3.83)
Certolizumab pegol	1.59 (1.10 to 2.21)	3.04 (1.74 to 4.81)	2.80 (1.71 to 4.47)
Etanercept	1.46 (1.08 to 1.94)	2.07 (1.26 to 3.20)	1.92 (1.27 to 2.82)
Infliximab	-	3.63 (1.41 to 6.44)	-
ASAS, Assessment in SpondyloArthritis international Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CI, Confidence Interval			

Table 10 Individual TNF-inhibitors compared with placebo in axial spondyloarthritis without radiographic evidence of ankylosing spondylitis: meta-analysis of continuous outcomes at 10–16 weeks

	Mean additional reduction from baseline (95% CI)		
	BASDAI	**BASFI**	**BASMI**
Adalimumab	−1.23 (−1.83 to −0.62)	−0.90 (−1.44 to −0.36)	−0.02 (−0.24 to 0.20)
Certolizumab pegol	−1.85 (−2.83 to −0.88)	−1.90 (−2.87 to −0.94)	−0.55 (−0.89 to −0.20)
Etanercept	−0.70 (−1.54 to 0.12)	−0.60 (−1.16 to −0.06)	-
Infliximab	−2.67 (−4.21 to −1.13)	−2.24 (−3.67 to −0.80)	0.00 (−0.44 to 0.44)
BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CI, Confidence Interval			

4.15 When TNF-inhibitors were considered as a class, with 1 treatment effect, the meta-analysis showed statistically significant improvements compared with placebo at 10–16 weeks for all outcomes (Table 11). The Assessment Group reported that statistical heterogeneity was apparent in the analyses, and therefore the reliability of the pooled estimates, and their true relevance to people seen in clinical practice, is questionable. Estimates of the class effect of TNF-inhibitors were consistently smaller in axial spondyloarthritis without radiographic evidence of ankylosing

spondylitis, compared with those observed in ankylosing spondylitis (most noticeably for BASFI and BASDAI 50).

Table 11 Estimated class effect of TNF-inhibitors compared with placebo in axial spondyloarthritis without radiographic evidence of ankylosing spondylitis: meta-analysis of outcomes at 10–16 weeks (main analysis)

	Outcome	95% CI
ASAS 20 (relative risk)	1.65	1.37 to 2.04
ASAS 40 (relative risk)	2.74	2.08 to 3.62
BASDAI 50 (relative risk)	2.31	1.76 to 3.10
BASDAI (additional reduction from baseline)[1]	−1.32	−1.74 to −0.90
BASFI (additional reduction from baseline)[1]	−0.99	−1.34 to −0.64
BASMI (additional reduction from baseline)[1]	−0.15	−0.32 to 0.02
SF-36 PCS (additional reduction from baseline)[2]	4.41	3.04 to 5.81
SF-36 MCS (additional reduction from baseline)[2]	2.33	0.07 to 4.62
[1] Negative changes in BASDAI, BASFI and BASMI represent improvement (that is, a health benefit) [2] Positive changes in SF-36 represent improvement (that is, a health benefit)		
ASAS, Assessment in SpondyloArthritis international Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CI, Confidence Interval; SF-36 MCS, Short Form 36 mental component summary; SF-36 PCS Short Form 36 physical component summary		

4.16 The Assessment Group did indirect comparisons of the TNF-inhibitors. There were no statistically significant differences between the 5 TNF-inhibitors for efficacy outcomes at 10–16 weeks (the results are presented in appendix 5 of the assessment report).

4.17 Analysis of long-term efficacy results from open-label extension studies (based on non-responder imputation) showed that, after 1 year of treatment, axial spondyloarthritis without radiographic evidence of ankylosing spondylitis continues to respond well to TNF-inhibitors in around half of people with the disease (Table 12). This level of response is maintained with certolizumab pegol at 2 years and up to 3 years with adalimumab. Mean change from baseline for BASDAI, BASFI and BASMI (where reported) were generally maintained at clinically meaningful levels during long-term follow-up (data available up to 1 year). However, the

open-label extension studies produced less reliable data than the RCTs. Results may not reflect clinical practice, as some people continued treatment after their disease did not respond to therapy (contrary to the stipulations in UK market authorisations). The Assessment Group concluded that the long-term benefits of TNF-inhibitors appear similar across treatments.

Table 12 Long-term efficacy of TNF-inhibitors in axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (results calculated using non-responder imputation)

	Approx. 1 year	Approx. 2 years	Approx. 3 years
Adalimumab			
ASAS 20	-	-	58%
ASAS 40	50–54%	-	47%
BASDAI 50	52%	-	49%
Certolizumab pegol			
ASAS 20	70%	61%	-
ASAS 40	58%	51%	-
Etanercept			
ASAS 20	[redacted]	-	-
ASAS 40	53%	-	-
BASDAI 50	[redacted]	-	-
ASAS, Assessment in SpondyloArthritis international Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index			

4.18 The Assessment Group reported issues with 2 of the trials in axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (ABILITY-1 for adalimumab and Rapid axSpA for certolizumab pegol), which were highlighted by the FDA. These 2 trials included sizable proportions of ankylosing spondylitis patients (for full details, refer to section 4.2.2.7 of the assessment report). This led to an overestimation of the treatment benefit observed with TNF-inhibitors in 1 of the trials (ABILITY 1) but not the other (Rapid axSpA). This difference further emphasised the heterogeneity across the trials in axial spondyloarthritis without radiographic evidence of ankylosing spondylitis.

4.19 The Assessment Group did not identify any efficacy data for people with axial spondyloarthritis without radiographic evidence of ankylosing spondylitis who had switched to a second or third TNF-inhibitor.

Clinical safety

4.20 The RCTs identified did not allow for a meaningful analysis of adverse events (due to limitations in the number and size of RCTs, and the short duration of the placebo-controlled periods). As a result, the Assessment Group evaluated adverse event rates derived from a Cochrane review and network meta-analysis of nine biologic interventions (abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituzimab and tocilizumab) in adults with any disease, except HIV/AIDS. The Cochrane review included 160 RCTs (n=48,676), 115 (72%) of which included the TNF-inhibitors under consideration in this appraisal. Results are presented Table 23 and Table 24 of the assessment report.

4.21 Analysis of the Cochrane Review showed that TNF-inhibitors as a group are associated with significantly higher rates of serious infections, tuberculosis reactivation, non-melanoma skin cancer, total adverse events, and withdrawals due to adverse events, when compared with control treatments in the short-term (median treatment duration of the RCTs was 6 months).

4.22 When individual TNF-inhibitors were analysed separately, only infliximab and certolizumab pegol were associated with statistically significant increases in adverse events compared with control treatments:

- infliximab was associated with higher rates of total adverse events (number needed to harm [NNH] 13, 95% credible interval [CrI] 8 to 505) and withdrawals due to adverse events (NNH 10, 95% CrI 5 to 30)
- certolizumab pegol was associated with higher rates of serious infections (NNH 12, 95% CrI 4 to 79) and serious adverse events (NNH 18, 95% CrI 9 to 162).

4.23 Cancer risk was not analysed as part of the Cochrane review. As TNF-inhibitors are known to have a possible association with cancer, the Assessment Group identified an individual patient data meta-analysis (including 22,904 patients from 74 RCTs) which assessed the cancer risk associated with 3 of the TNF-inhibitors under consideration in this appraisal (adalimumab, etanercept and infliximab). When considering the class effect of the 3 TNF-inhibitors, there was no increase in risk of cancers excluding non-melanoma skin cancer (RR 0.99, 95% CI 0.61 to 1.68). However TNF-inhibitors were associated with a doubling in the risk of non-melanoma skin cancer (RR 2.02, 95% CI 1.11 to 3.95).

Additional evidence

Natural history of disease

4.24 The Assessment Group conducted a review of the natural history of ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis. The studies identified explored the associations between key disease components including disease activity, structural damage, physical function and spinal mobility. Analysis of baseline data from the ASSERT trial revealed that:

- health-related quality of life is determined by
  - disease activity (assessed by BASDAI) **and**
  - physical function (assessed by BASFI)
- BASFI is determined by
  - BASDAI **and**
  - spinal damage (assessed by the modified Stoke Ankylosing Spondylitis Spinal Score [mSASSS]) **and**
  - spinal mobility (assessed by BASMI)
- BASMI is independently determined by
  - reversible spinal damage in early stage disease (assessed by MRI) **and**

- irreversible spinal damage in late stage disease (assessed by mSASSS).

4.25 The studies reviewed by the Assessment Group showed that disease activity (BASDAI) is fairly stable over time and does not change. Physical function (assessed by BASFI) does deteriorate ('progress') over time, but the rate of progression is not constant or predictable. Since BASFI is determined by both disease activity and bone formation, progression of BASFI over time is driven by progression of spinal damage as assessed by mSASSS (see above, section 4.24).

4.26 Evidence suggested that disease progression (BASFI) is faster in ankylosing spondylitis.

Impact of TNF-inhibitors on spinal damage

4.27 The impact of TNF-inhibitors on spinal damage (that is, radiographic progression; assessed by mSASSS) is unclear. There are some data that suggest a benefit of TNF-inhibitors after approximately four years. The Assessment Group suggested that the uncertainty may be due to lack of long-term follow-up data and the insensitivity of x-rays as a tool for evaluating disease progression in ankylosing spondylitis.

5 Comments from other consultees

5.1 Patient experts discussed the 2 indications together, referring to them collectively as 'axial spondyloarthritis'. They indicated that the key symptom in the early stages of the disease is inflammatory back pain, which becomes increasingly severe over time. Up to 25% of people with axial spondyloarthritis eventually develop complete fusion of the spine, which leads to substantial disability and restriction. Patient experts noted that, since axial spondyloarthritis presents at an early age when people are beginning their career (average age of onset is 24), the progression of axial spondyloarthritis leads to substantial losses in work productivity. One third of people will give up work before normal retirement age and another

15% reduce or change their work because of axial spondyloarthritis. Being unable to work has important consequences both for the individual and for their family; people with axial spondyloarthritis are more likely to be divorced or never to have married and women with axial spondyloarthritis are less likely to have children. Many people with axial spondyloarthritis report depression and fatigue. Patient experts reported that, in addition to local spinal symptoms, 50% of people suffer from associated disorders elsewhere. For example, 40% experience eye inflammation, 16% develop psoriasis and 10% have inflammatory bowel disease. Patient experts also highlighted the issue of underdiagnoses – symptoms are often present for 7–10 years before a diagnosis is made.

5.2 Comments from patient experts indicated the outcome most important to people with axial spondyloarthritis was the prevention of further damage to their spine and joints. A reduction in pain and fatigue was also important. The experts stated that patients receiving TNF-inhibitors have reported substantial improvements in pain and stiffness, leading to improvements in mobility and an improved quality of life. People reported that they were able to independently manage activities of daily living that were previously problematic. However, patient experts estimated that 2 in 10 cases of axial spondyloarthritis do not respond to treatment with a TNF-inhibitor. Based on current NICE guidance, these people would not be offered an alternative TNF-inhibitor. This knowledge leads to high levels of anxiety in people axial spondyloarthritis. The option to switch to a second TNF-inhibitor would reduce fears and anxiety. There is also anecdotal evidence suggesting that a second or third TNF-inhibitor can be clinically effective after the first has failed.

5.3 When experts asked people with axial spondyloarthritis about the potential benefits of being prescribed new treatments (infliximab and certolizumab pegol), there was consensus that these treatments would be beneficial. When asked about infliximab specifically, people preferred its mode of administration (an infusion administered by a healthcare professional) to

the method of self-injection. Infliximab's mode of administration might benefit people with: a fear of needles, memory problems, learning difficulties, or dexterity problems. However some people were worried about the potential for postponed appointments (leading to a return of symptoms) and the requirement to take time off work and travel for treatment with infliximab.

5.4 Patient experts highlighted that people with axial spondyloarthritis without radiographic evidence of ankylosing spondylitis lack effective treatment options, and are keen to have the option of treatment with TNF-inhibitors.

6 Cost-effectiveness evidence

Published evidence

6.1 The Assessment Group's systematic review of cost-effectiveness evidence identified 5 published economic evaluations of TNF-inhibitors in patients with ankylosing spondylitis (**Table 13**). All 5 studies used a UK perspective; 3 were based on the economic analyses submitted by the manufacturers to NICE as part of the previous multiple technology appraisal for infliximab, etanercept and adalimumab in ankylosing spondylitis (TA143). The remaining 2 were publications of the assessments by the independent Assessment Group/Evidence Review Group for the previous multiple technology appraisal (TA143) and the single technology appraisal of golimumab (TA233) in ankylosing spondylitis.

6.2 No published economic evaluations were identified for patients with axial spondyloarthritis without radiographic evidence of ankylosing spondylitis.

Table 13 Summary of published economic evaluations in people with ankylosing spondylitis (UK-based)

Study	Intervention	Comparator	ICER (intervention versus comparator)	Most sensitive parameters
Kobelt et al. 2007 Lifetime horizon	Infliximab	Standard care	Assuming no BASFI progression on treatment: £28,332 and £26,751 per QALY gained Same as natural history (no effect of treatment on progression): £49,417 and £46,167 per QALY gained	Impact of treatment on disease progression; time horizon; withdrawal rate
Ara et al. 2007 25 year time horizon	Etanercept	Conventional care	£22,704 per QALY gained	Withdrawal rate
Botteman et al. 2007 30 year time horizon	Adalimumab	Conventional care	£23,097 per QALY gained	Time horizon
McLeod et al. 2007 1 year time horizon	Adalimumab, etanercept and infliximab	Conventional care	For adalimumab and etanercept: £57,000 per QALY gained (£30,100 per QALY gained after additional NICE Decision Support Unit analyses)[1] For infliximab: >£120,000 per QALY gained	Time horizon (ICERs increased with increasing time horizon)
Armstrong et al. 2013 Base case: 20 year time horizon Sensitivity analysis: Lifetime	Golimumab	Conventional care, adalimumab and etanercept	Manufacturer base case (20 year time horizon): £26,597 per QALY gained compared with conventional care. Adalimumab and etanercept extendedly dominated by golimumab. ERG exploratory re-analyses (lifetime horizon): golimumab extendedly dominated by adalimumab and etanercept	Impact of treatment on disease progression; time horizon

Study	Intervention	Comparator	ICER (intervention versus comparator)	Most sensitive parameters
[1] Due to discrepancies between the results reported by McLeod et al. 2007 and the other publications in 2007 (which informed the manufacturer submissions for TA143) NICE's Decision Support Unit tried to reconcile the different models BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year				

6.3 All published economic evaluations used a 2 part structure to compare treatment strategies: a short-term model to determine initial response rate, and a long-term model for the post-response period (to characterise the natural history of disease [without TNF-inhibitors] and the impact of TNF-inhibitors, both during treatment and when treatment has stopped). However, the Assessment Group noted substantial differences between published models in relation to the data sources, methods and assumptions used for long-term modelling, which may explain the differences in cost-effectiveness results (see section 5.1.4 of the assessment report). In particular, long-term projections of BASDAI and BASFI scores were speculative. Assumptions about the magnitude and duration of the differences between responders and non-responders (related to BASDAI and BASFI measurements) during treatment varied between models. There were also differences in assumptions about BASFI progression after withdrawal from treatment in patients whose disease initially responded to therapy (referred to as 'rebound'). The models assumed 1 of 2 scenarios. An optimistic scenario assumes an ongoing benefit of TNF-inhibitors after withdrawal (known as 'rebound equal to gain' or 'rebound to baseline'). In this scenario, the BASFI score deteriorates ('rebounds') to the patient's baseline score. The alternative scenario assumes a greater deterioration in BASFI after treatment withdrawal, to the level that it would have been if the disease had not initially responded to therapy (known as 'rebound to natural history' or 'rebound to conventional care'); this is a pessimistic outlook. In both scenarios, the subsequent trajectory of BASFI progression (after rebound) mirrors the natural history of the disease. The Assessment Group also

highlighted issues with the use of open-label study data to inform long-term response rate estimates. The treatment benefits observed in these studies may not represent true treatment effects, but could instead be a result of selection bias in the trials. Finally, the Assessment Group noted that assumptions about the impact of treatment on disease progression (measured by BASFI) were not appropriately justified. As noted in Table 13, the ICERs in several economic evaluations were sensitive to these assumptions. There were 3 possible scenarios:

- no change in BASFI while receiving TNF-inhibitors (this assumes implicitly that further deterioration in functional progression is completely prevented during treatment)
- lower BASFI changes while receiving TNF-inhibitors (this assumes that TNF-inhibitors do not completely halt further deterioration in functional progression, but that the rate of progression is reduced relative to the natural history of the disease)
- while receiving TNF-inhibitors, changes in BASFI reflect the natural history of the disease (this assumes that TNF-inhibitors do not affect the functional progression of the disease).

6.4 The Assessment Group considered that the published models lacked evidence-based justifications for parameter estimates and structural assumptions.

Company submissions

6.5 The companies' submissions to NICE for adalimumab, certolizumab pegol, etanercept, golimumab and infliximab included economic models which the Assessment Group critiqued (the models for golimumab and infliximab were critiqued together because they were submitted by the same company and the Assessment Group indicated that they were identical). The 2 populations were modelled separately. For ankylosing spondylitis, all of the companies compared the 5 TNF-inhibitors with a marketing authorisation for this indication (adalimumab, certolizumab

pegol, etanercept, golimumab and infliximab) with each other, and with conventional care. For axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, the companies compared the 3 TNF-inhibitors with a marketing authorisation in this indication (adalimumab, certolizumab pegol and etanercept) with each other and with conventional therapy (with the exception of Abbvie, who did not include etanercept in their model). Based on recommendations in NICE technology appraisal guidance 143, all models included a response criteria at week 12 (with the exception of UCB who used response criteria at week 24) to decide whether TNF-inhibitors were continued or withdrawn.

6.6 All evaluations adopted an NHS perspective. Costs and benefits in all cases were discounted at 3.5%. In common with previously published models, the models were based on the estimation of BASDAI and BASFI scores over time. An overview of model structure and key structural assumptions (including those relating to BASDAI and BASFI progression) is provided in Table 14 and Table 15.

Table 14 Model structure and key assumptions: ankylosing spondylitis

Parameter	Infliximab, Golimumab (MSD model)	Adalimumab (Abbvie model)	Certolizumab pegol (UCB model)	Etanercept (Pfizer model)
Model type	Decision tree followed by Markov model	Markov model	Decision tree followed by Markov model	Patient-level simulation model
Time horizon	Lifetime	40 years	Lifetime	Lifetime
Response criteria	BASDAI 50 response, week 12	ASAS 20 response, week 12	ASAS 20 response, week 24	BASDAI 50 response, week 12
Response criteria justification	Outcome in GO-RAISE study; recommended by ASAS Working Group	Primary endpoint of ATLAS study	Primary endpoint of RAPID-axSpA study	Current NICE definition of treatment response (TA143)
Mortality (SMR)	Male: 1.63 Female: 1.38	1.5	1.5	1.5

Parameter	Infliximab, Golimumab (MSD model)	Adalimumab (Abbvie model)	Certolizumab pegol (UCB model)	Etanercept (Pfizer model)
Annual rate of withdrawal (long-term)	6.1% (GO-RAISE)	<15% projected to stay on treatment at year 40 (ATLAS)	7% (NICE TA143)	11% for etanercept (HR applied for other TNF-inhibitors, Glintborg 2010)
Progression assumptions: BASDAI score projections				
TNF-inhibitor responders	Constant after week 108	Constant after week 260	Constant after week 24	Constant after week 48
TNF-inhibitor non-responders	Constant	Constant	Constant	Constant
Conventional care	Constant after week 24	Constant	Constant	Constant after week 12
Progression assumptions: BASFI score projections				
TNF-inhibitor responders	Constant after week 108; 0.035 after week 256	Constant after week 260	Constant after week 24	Constant after week 48
TNF-inhibitor non-responders	0.07 (Kobelt 2007)	0.056 (ATLAS study)	0.07 (Kobelt 2007)	0.07 (Kobelt 2007)
Conventional care	0.07 after week 24	0.056	0.07	0.07 after week 12
Rebound assumption	Rebound to baseline	Rebound to baseline	Rebound to conventional therapy	Rebound to baseline
Rebound assumption duration	Over a 6 month period	Immediately	Over a 6 month period	Over a 6 month period
Placebo response	14.5% at week 12	BASDAI and BASFI return to baseline at week 12	No placebo response	BASDAI and BASFI return to baseline at 12 weeks
ASAS, Assessment in SpondyloArthritis international Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; HR, Hazard Ratio; SMR, Standardised Mortality Ratio				

Table 15 Model structure and key assumptions: axial spondyloarthritis without radiographic evidence of ankylosing spondylitis

Parameter	Adalimumab (Abbvie model)	Certolizumab pegol (UCB model)	Etanercept (Pfzier model)
Model type	Markov model	Markov model	Patient-level simulation model

Parameter	Adalimumab (Abbvie model)	Certolizumab pegol (UCB model)	Etanercept (Pfzier model)
Time horizon	40 years	Lifetime	Lifetime
Response criteria	ASAS 40 response, week 12	ASAS 20 response, week 12	BASDAI 50 response, week 12
Response criteria justification	Primary endpoint of ABILITY-1 study	Primary endpoint of RAPID-axSpA study	Current NICE definition of treatment response (TA143)
Mortality (SMR)	1.0	1.5	1.0
Annual rate of withdrawal (long-term)	<10% projected to stay on treatment at year 40 (ATLAS)	7% (NICE TA143)	5% for etanercept (HR applied for other TNF-inhibitors, Glintborg 2010)
Progression assumptions: BASDAI score projections			
TNF-inhibitor responders	Constant after week 140	Constant after week 12	Constant after week 48
TNF-inhibitor non-responders	Constant	Constant	Constant
Conventional care	Constant	Constant	Constant after week 12
Progression assumptions: BASFI score projections			
TNF-inhibitor responders	Constant after week 140	Constant after week 12	Constant after week 48
TNF-inhibitor non-responders	0.084 (ABILITY-1 study)	0.07 (Kobelt 2007)	Constant/0.07 (Kobelt 2007)
Conventional care	0.084	0.07	0.07 after week 12
Rebound assumption	Rebound to baseline	Rebound to conventional therapy	Rebound to baseline
Rebound assumption duration	Immediately	Over a 6 month period	Over a 6 month period
Placebo response	BASDAI and BASFI return to baseline at week 12	No placebo response	BASDAI and BASFI return to baseline at 12 weeks
ASAS, Assessment in SpondyloArthritis international Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; SMR, Standardised Mortality Ratio			

Company's model: adalimumab

6.7 The company developed 2 separate state-transition models (Markov models) for the 2 populations, using a 40-year time horizon. It was assumed that all patients receiving a TNF-inhibitor were also receiving

conventional therapy (NSAIDs). For a diagram of the model, see section 3.1.1 of the company submission (page 167–169).

6.8 The model consisted of a short-term component (first 12 weeks, with an assessment of ASAS 20 response) and a long-term component (40 years). The company used data from long-term open-label extension studies of adalimumab (up to 260 weeks in the ATLAS trial for ankylosing spondylitis, and 156 weeks in the ABILITY-1 trial for axial spondyloarthritis without radiographic evidence of ankylosing spondylitis). The assumptions regarding disease progression (as measured by BASDAI and BASFI) beyond these study durations are summarised in Table 14 and Table 15 (above).

6.9 Disease-specific costs in ankylosing spondylitis were derived from the OASIS ('Outcome in ankylosing spondylitis international study')[1] observational database, using BASDAI data as a measure of disease severity. In addition to drugs costs, costs associated with drug administration, initiation, monitoring, and adverse events were included in the model. Ankylosing spondylitis data were also used to inform the relationship between costs and disease severity in axial spondyloarthritis without radiographic evidence of ankylosing spondylitis; the company was not aware of any disease-specific information in the literature. The company justified this approach as utilities and disease severity were very similar between the two populations (according to data from the ABILITY-1 and ATLAS studies).

6.10 Health-related quality of life was estimated using BASDAI and BASFI data. For the ankylosing spondylitis model, health utility index (HUI) scores collected in the ATLAS trial were mapped to BASDAI and BASFI scores (EQ-5D was not collected in the ATLAS study). In the model for

[1] Data from patients of three European countries (Netherlands, Belgium and France). See: Boonen A, van der Heijde D, Landewé R et al. (2003) Direct costs of ankylosing spondylitis and its determinants: an analysis among three European countries. *Annals of the Rheumatic Diseases* 62: 732–-40. Also available at: http://ard.bmjjournals.com/cgi/content/full/62/8/732

axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, observed EQ-5D scores from the ABILITY-1 trial were used.

6.11 In the ankylosing spondylitis model: the base case ICERs ranged from £16,391 per QALY gained for adalimumab to £44,448 per QALY gained for infliximab, compared with conventional care (Table 16). In the Assessment Group's fully incremental analysis (using the company's base case) certolizumab pegol, etanercept and golimumab were ruled out by extended dominance (that is, a QALY was attained at a higher cost with these 3 treatments than with adalimumab and infliximab because the ICERs for certolizumab pegol, etanercept and golimumab compared with conventional therapy were higher than the ICERs for adalimumab and infliximab compared with conventional therapy). The ICER of the next more costly and effective TNF-inhibitor (after adalimumab) was £238,500 per QALY gained for the comparison between infliximab and adalimumab.

6.12 In the model for axial spondyloarthritis without radiographic evidence of ankylosing spondylitis: the base case ICERs ranged from £12,866 per QALY gained for certolizumab pegol to £13,288 per QALY gained for adalimumab, compared with conventional care (Table 17). In the Assessment Group's fully incremental analysis, adalimumab was extendedly dominated by certolizumab pegol and conventional care (that is, a QALY was attained at a higher cost with adalimumab than with certolizumab pegol because the ICER for adalimumab compared with conventional therapy was higher than that for certolizumab pegol compared with conventional therapy).

6.13 The company reported that the ICERs for adalimumab were robust to a range of deterministic and probabilistic sensitivity analyses.

Company's model: certolizumab pegol

6.14 The company's model was based on a short-term decision tree (based on an assessment of ASAS 20 response at either 12 or 24 weeks) and a long-term Markov model, using a lifetime horizon. For illustrations of the

model, see figures 8-3 and 8-4 on page 76 of the company submission. Separate analyses were performed for the 2 populations, but it was assumed that patients could progress from a diagnosis of axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, to a diagnosis of ankylosing spondylitis, during their course of treatment. An estimate was included for the rate of movement from one disease state to the other (presented in page 72 of the company submission). Assumptions relating to long-term disease progression specific to each population are summarised in Table 14 and Table 15 (above).

6.15 The company used data from the RAPID-axSpa trial for both populations. The primary endpoint of the trial was ASAS 20 response at week 12, but the model for ankylosing spondylitis uses ASAS 20 response at week 24. The company argued that a week 24 response is aligned with clinical practice (as indicated key British opinion leaders). But the Assessment Group noted that results at week 24 are no longer based on the original randomised trial population, because patients were allowed an 'early escape' from placebo at week 16.

6.16 Disease-specific costs were derived from the OASIS database, using BASFI data as a measure of disease severity. Costs of drugs, administration, initiation, and monitoring were included in the models (but not the costs of adverse events). The costs of certolizumab pegol were based on patient access scheme which has been proposed but is not yet formally agreed with the Department of Health and NICE (in which the first 12 weeks of certolizumab pegol will be provided free of charge to the NHS). BASDAI and BASFI scores were used jointly to estimate health related quality of life in both populations, using EQ-5D data collected in the RAPID-axSpa study.

6.17 In the ankylosing spondylitis model: the base case ICERs ranged from £16,647 per QALY gained for certolizumab pegol to £42,671 per QALY gained for infliximab, compared with conventional care (Table 16). In the

Assessment Group's fully incremental analysis (using the company's base case), certolizumab pegol provided more QALYs at a lower cost than all TNF-inhibitors (that is, they were dominated by certolizumab pegol) apart from infliximab. Results without the patient access scheme for certolizumab pegol will be higher than the estimates reported here (but these were not provided by the company).

6.18 In the model for axial spondyloarthritis without radiographic evidence of ankylosing spondylitis: the base case ICERs ranged from £15,615 per QALY gained for certolizumab pegol to £50,692 per QALY gained for etanercept, compared with conventional care (Table 17). In the Assessment Group's fully incremental analysis, certolizumab pegol dominated (was less costly and more effective) adalimumab and etanercept.

6.19 The company reported that the results of one-way and probabilistic sensitivity analyses, as well as scenario analyses, indicated that certolizumab pegol remains cost-effective (full results are presented in Appendix 11.5.2.1.2 of the company submission).

Company's model: etanercept

6.20 The company submitted a patient-level simulation model based on a discrete event simulation (for an illustration, see figure 10 on page 234 of the company submission), using a lifetime horizon. The economic model used analysis of patient-level data from 4 studies in ankylosing spondylitis (314-EU, 311-EU, 312-EU, 907-EU) and 1 study in axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (study 1031). An initial 12-week response (BASDAI 50) was predicted using trial data; assumptions about ongoing disease progression (as measured by BASDAI and BASFI) are summarised in Table 14 and Table 15 (above).

6.21 It was the only company submission which attempted to adjust for differences in baseline characteristics between trials of certolizumab pegol and adalimumab (for example the issues raised by the FDA, as discussed

in section 4.18), and the only model to explore the cost-effectiveness of switching treatments. The company justified its choice of model structure by explaining the advantages in relation to modelling heterogeneous populations and sequential therapy.

6.22 Costs in the model included: drug costs, administration costs of intravenous TNF-inhibitors, cost of adverse events (serious infections only), pre-treatment monitoring costs, and general medical resource use (assumed to be a function of BASDAI and BASFI). Monitoring costs were not explicitly included in order to avoid counting such costs twice. Unlike other company submissions, which derived disease-specific costs from the OASIS database, Pfizer used data from Rafia et al. 2012[2] (based on BASDAI scores only). The company justified the use of this source as it provided the most recent UK-specific data and permitted separation of particular cost items. The patient access scheme for certolizumab pegol was used (although not yet confirmed for this indication by the Department of Health).

6.23 Similar to the approach used in other company submissions, RCT data were used to estimate the relationship between BASDAI/BASFI and EQ-5D utility scores (using study 314-EU for ankylosing spondylitis, and study 1031 for axial spondyloarthritis without radiographic evidence of ankylosing spondylitis).

6.24 In the ankylosing spondylitis model: the base case ICERs ranged from £19,586 per QALY gained for certolizumab pegol to £37,741 per QALY gained for infliximab, compared with conventional care (Table 16). In the Assessment Group's fully incremental analysis, adalimumab was extendedly dominated. Of the remaining non-dominated treatments, the ICER of the next most costly intervention compared with the previous non-dominated alternative was: £19,586 (certolizumab pegol compared with conventional therapy), £28,834 (etanercept compared with certolizumab

[2] Rafia R, Ara R, Packham J, Haywood K, Healey E. Healthcare costs and productivity losses directly attributable to ankylosing spondylitis. Clin Exp Rheumatol 2012;30:246-53

pegol), £30,376 (golimumab compared with etanercept) and £1,131,181 (infliximab compared with golimumab).

6.25 In the model for axial spondyloarthritis without radiographic evidence of ankylosing spondylitis: the base case ICERs ranged from £23,195 per QALY gained for etanercept to £23,575 per QALY gained for certolizumab pegol, compared with conventional care (Table 17). After adjusting for differences in study baseline characteristics across the different trials in this population, the ICER for etanercept compared with adalimumab was £26,176 per QALY gained. In the Assessment Group's fully incremental analysis, none of the TNF-inhibitors were excluded through dominance or extended dominance, and the ICER of each comparison remained below £30,000 per QALY gained for each successively more expensive and effective treatment.

6.26 The Assessment Group considered that the company's exploration of the cost-effectiveness of sequential treatment was not sufficiently robust. In their base case analysis, the use of a second TNF-inhibitor was restricted to patients who withdrew due to adverse events. It was also assumed that the second TNF-inhibitor showed equal efficacy to the first treatment. The company's assumptions were based on observational data which are subject to potential confounding, due to the lack of robust clinical data.

Company's model: golimumab and infliximab

6.27 The company made separate submissions for golimumab and infliximab (for ankylosing spondylitis population only), which the Assessment Group critiqued together as the model structures and data sources were identical across the submissions. The economic evaluation was based on the same model structure submitted as part of the previous NICE technology appraisal (TA 233; Armstrong et al. 2013).

6.28 The company's model was hybrid in that it used a decision tree to model the short-term probabilities of a response (BASDAI 50 at 12 weeks), then a Markov model to estimate the long-term outcomes. The company used

data from the GO-RAISE trial in ankylosing spondylitis, including the open-label extension period (up to 108 weeks). The assumptions regarding disease progression (as measured by BASDAI and BASFI) beyond this are summarised in Table 14 and Table 15 (above).

6.29 Utility values were derived from the previous NICE technology appraisal (TA 143) and incorporated age, sex, and BASFI and BASDAI scores. Costs included in the model comprised drug acquisition, short-term (12 week) costs, longer-term disease costs and adverse events. Longer-term disease costs were based on BASFI scores from the GO-RAISE trial using the same regression equation used by the Assessment Group for NICE technology appraisal guidance 143. The costs of certolizumab pegol were based on patient access scheme which has not been confirmed for this indication by the Department of Health.

6.30 The base case ICERs compared with conventional care ranged from £19,070 (golimumab) to £42,532 (infliximab). In the Assessment Group's fully incremental analysis, adalimumab, etanercept and infliximab were dominated (was more expensive and less effective). The ICER for golimumab compared with conventional therapy was £19,070 and for certolizumab pegol compared with golimumab was £21,441 per QALY gained.

Comparison of company models

6.31 A comparison of the ICER estimates compared with conventional therapy submitted by each company is provided in Table 16 (ankylosing spondylitis) and Table 17 (axial spondyloarthritis without radiographic evidence of ankylosing spondylitis).

Table 16 Ankylosing spondylitis: comparisons of company ICER estimates (per QALY gained) compared with conventional therapy

	Abbvie submission (adalimumab)	UCB submission (certolizumab pegol)	Pfizer submission (etanercept)	MSD submission (golimumab, infliximab)
Conventional care	-	-	-	-
Adalimumab	**16,391**	19,932	20,909	19,275
Certolizumab pegol	17,067[1]	**16,647[2]**	**19,586[2]**	19,401[2]
Etanercept	16,897	19,272	20,938	21,972
Golimumab	16,535	19,049	21,288	**19,070**
Infliximab	44,448	42,671	37,741	42,532
[1] Based on list price for certolizumab pegol [2] Based on patient access scheme for certolizumab pegol				
ICERs in bold text show the lowest estimate submitted by each company				

Table 17 Axial spondyloarthritis without radiographic evidence of ankylosing spondylitis: comparisons of company ICER estimates (per QALY gained) compared with conventional therapy

	Abbvie submission (adalimumab)	UCB submission (certolizumab pegol)	Pfizer submission (etanercept)
Conventional care	-	-	-
Adalimumab	13,228	30,370	23,242
Certolizumab pegol	**12,866[1]**	**15,615[2]**	23,575[2]
Etanercept	Not Assessed	50,692	**23,195**
[1] Based on list price for certolizumab pegol [2] Based on patient access scheme for certolizumab pegol			
ICERs in bold text show the lowest estimate submitted by each company			

6.32 The Assessment Group commented that, in general, the companies submitted good quality models. Despite the different model structures and assumptions used across the company submissions, similar ICERs were reported for each of the TNF-inhibitors compared with conventional care in ankylosing spondylitis. There were greater differences between company submissions in the ICERs reported for axial spondyloarthritis

without radiographic evidence of ankylosing spondylitis. The Assessment Group suggested that the variation in ICER estimates reported across the submissions (both within and between populations) might be explained by differences in the following parameters and underlying assumptions (see Table 14 and Table 15):

- the response criteria and timing applied
- the magnitude of improvement in outcomes and the time at which these were assumed to 'level off' (that is, plateau)
- the underlying rate of progression (change in BASFI scores) without treatment ('natural history' of disease), and the impact of TNF-inhibitors on this rate
- progression after withdrawal from treatment (the 'rebound' assumption) and timing of this.

6.33 Although there was consistency across the companies' ICER estimates for the ankylosing spondylitis population, the Assessment Group considered them (and the ICERS reported in axial spondyloarthritis without radiographic evidence of ankylosing spondylitis) to be both speculative and highly uncertain. The uncertainty is due to unresolved issues with parameter estimates and structural assumptions used in published cost-effectiveness evaluations (highlighted in the Assessment Group's review). For example, several company models used data from open-label extension studies without any formal consideration of the selection bias inherent in these studies. The Assessment Group were also concerned about the appropriateness of the sources of natural history data, and subsequent assumptions made about the trajectories of BASDAI and BASFI progression. Related to this are the assumptions about the effect of TNF-inhibitors on disease progression, and a lack of consensus on whether TNF-inhibitors are primarily symptom control treatments or whether they are also disease modifiers. The Assessment Group noted that identical assumptions with respect to the impact of treatment on progression were applied across both populations, without

consideration of how generalisable these assumptions were. Finally, the Assessment Group suggested that BASDAI and BASFI may not be the most appropriate conceptual basis for modelling progression of these diseases. But in the absence of data linking other disease measures to costs and utilities, they concluded that there were no other options.

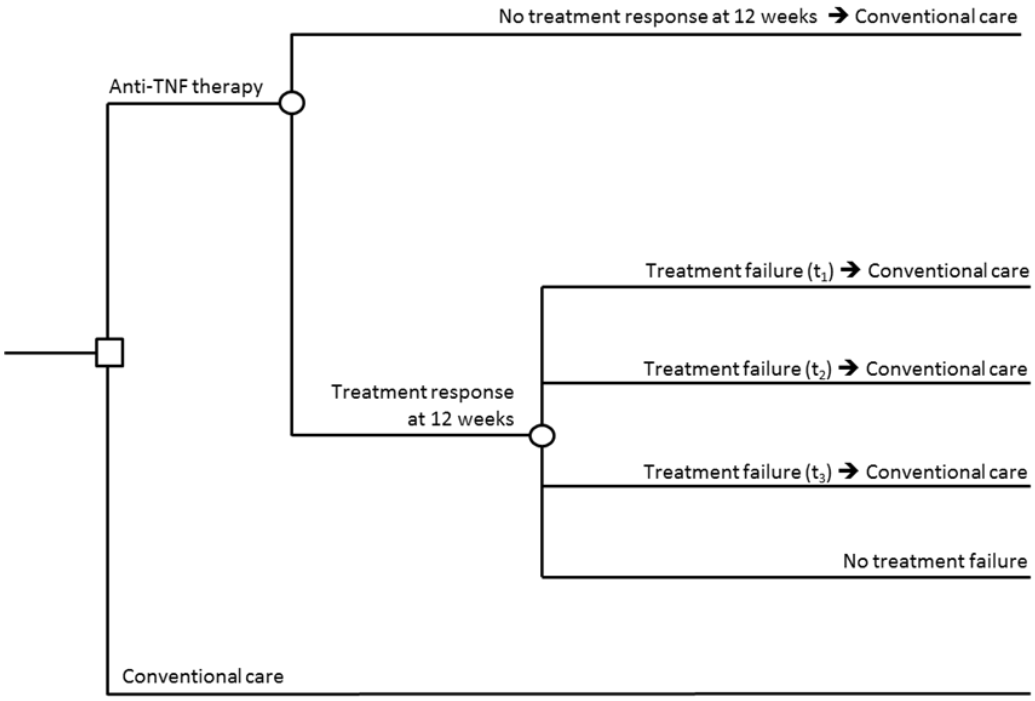
6.34 The company submissions did not provide a robust basis for informing cost-effectiveness of intermittent and sequential use of TNF-inhibitors.

Assessment Group's model

6.35 The Assessment Group developed a de novo economic model to assess the cost-effectiveness of all 5 TNF-inhibitors for ankylosing spondylitis and 3 for axial spondyloarthritis without radiographic evidence of ankylosing spondylitis.

6.36 The Assessment Group developed a cohort model in the form of a modified decision tree (see Figure 1). The model used a lifetime horizon, assuming that patients enter the model at the age of 40 years and have an average body weight of 73 kg. BASDAI 50 response at 12 weeks determines whether patients continue receiving a TNF-inhibitor or withdraw from treatment. For those who respond, there is an ongoing risk of withdrawal of treatment at any time point. Patients who withdraw from treatment (at either 12 weeks, or later) are assumed to move on to conventional care. The perspective of the analysis was that of the NHS and personal social services, and costs and health effects were discounted at an annual rate of 3.5%. The mean costs and QALYs reported are derived from probabilistic sensitivity analysis (that is, produced by varying the input parameters simultaneously with values from a probability distribution).

Figure 1 A simplified diagram of the Assessment Group model structure



Source: Figure 15 in section 7.4 of the assessment report

6.37 To address some of the uncertainties identified in published economic evaluations and company submissions, and generate more appropriate parameter estimates (and associated uncertainties) for their de novo model, the Assessment Group performed an extended evidence synthesis of the available clinical data (presented in chapter 6 and appendices 9–11 of the assessment report). The evidence synthesis was used to estimate baseline BASDAI/BASFI scores, the effect of treatment on these scores, and the probability of a response (BASDAI 50) at 12 weeks. The Assessment Group also used an alternative conceptual approach to model long-term disease progression and the impact of treatment on the natural history of disease, by relating the assumptions more explicitly to the existing clinical data for TNF-inhibitors. Specifically, the Assessment Group accounted for the independent effects of symptomatic improvements (that is, reduction in disease activity according to BASDAI) on BASFI scores. They also considered the separate independent effect of changes in radiographic progression (measured by the Modified Stoke

Ankylosing Spondylitis Spinal Score [mSASSS]) on BASFI. The Assessment Group considered that this approach captured the potential impact of TNF-inhibitors on different clinical/biological processes (in addition to disease activity according to BASDAI) which independently affect BASFI. The Assessment Group considered that the effect of symptomatic improvements (that is, changes in BASDAI scores) on BASFI was captured in the scores applied to responders (see below). Since long-term BASDAI was assumed to be constant after the response period, long-term changes in BASFI (for conventional care and TNF-inhibitor responders) were modelled as a function of mSASSS scores using a series of epidemiological studies and assumptions (described in Section 7.5.3 on pages 190–193 of the assessment report). As a result of these analyses, the model assumed that patients who continued to receive and respond to a TNF-inhibitor after week 12 experienced a slower progression rate (according to BASFI scores) compared with the natural history of the disease (this effect was delayed until year 4). For responders who subsequently withdraw from TNF-inhibitor treatment, there is some form of rebound in BASFI and BASDAI scores (this is also relevant for patients who withdraw earlier, at 12 weeks). As trial data could not accurately characterise the extent of this rebound, the Assessment Group presented 2 scenarios in their base case: 1 assuming rebound to baseline and 1 assuming rebound to natural history (representing the best-case and worst-case scenarios, respectively). The Assessment Group's model used different baseline BASDAI/BASFI scores for responders and non-responders. Therefore, in the rebound to baseline scenario responders and non-responders revert to different baseline scores after treatment discontinuation. This assumption is based on results from the extended synthesis which estimated that non-responders had higher baseline BASDAI and BASFI scores than responders (that is, response is unlikely to be independent of baseline patient characteristics). A full list of parameter estimates used in the

model is presented in Table 82 and Table 83 (section 7.5) of the assessment report.

6.38 Health-related quality of life was estimated using BASDAI and BASFI data, using the approach submitted by Pfizer. Separate algorithms were used for each population, using data from the 1031 study and the 314-EU study (both mapped to EQ-5D).

6.39 A breakdown of costs included in the model (drug acquisition, administration, and monitoring; resource use; and adverse events) are presented in Table 88–Table 94 of the assessment report. Only serious infections and tuberculosis reactivation were included in the modelling of adverse event costs. All other costs were assumed to vary according to BASFI score (data were derived from the OASIS database). The Assessment Group's model used the list price for certolizumab and the patient access scheme. As the patient access scheme has not been agreed by the Department of Health, only the results using the list price are presented here.

6.40 The Assessment Group did 6 sensitivity analyses:

- **Scenario 1:** assumed no 'placebo effect'. That is, no patients receiving conventional care achieve a BASDAI 50 response at week 12. By contract, the base case model incorporated a probability of response to conventional care at 12 weeks.
- **Scenario 2:** varied the difference between responders' and non-responders' baseline BASDAI/BASFI scores. As in the base case, a difference still exists (conditional on response). But whereas the base case used estimates from the Assessment Group's extended synthesis, the sensitivity analysis was informed by data from company submissions. This scenario also used data pooled from the company submissions (instead of the extended synthesis) to estimate the change in BASDAI and BASFI scores for responders and non-responders.

- **Scenario 3:** assumed TNF-inhibitors have no effect on BASFI progression (in the base case, BASFI progression is slowed in responders).
- **Scenario 4:** treatment effect of TNF-inhibitors (on BASFI progression) was achieved immediately. By contrast, in the base case model, disease modification was delayed until year 4.
- **Scenario 5:** mapped utilities using a linear model (consistent with previous NICE appraisals TA143 and TA233). The base case used a non linear mapping algorithm.
- **Scenario 6** (relevant only to axial spondyloarthritis without radiographic evidence of ankylosing spondylitis): the base case for this population is based only on trials reporting in this population. In the sensitivity analysis, results from ankylosing spondylitis trials were also used.

Results for patients with ankylosing spondylitis

6.41 In the rebound to baseline scenario (Table 18), pair-wise comparison of the TNF-inhibitors with conventional care showed that infliximab had the highest ICER (£40,576 per QALY) and the lowest probability of being cost-effective at a £20,000 and £30,000 per QALY threshold (0% and 9%, respectively). Excluding infliximab, the ICERs of the other TNF-inhibitors were similar, ranging from £21,079 (golimumab) to £23,133 (certolizumab pegol). At a maximum acceptable ICER of £20,000 per QALY gained, golimumab had a 43% probability of being cost-effective compared with conventional therapy. Its probability of being cost-effective compared with conventional therapy at a maximum acceptable ICER of £30,000 per QALY gained was approximately 84%.

6.42 As previously highlighted, the difference in the ICERs between the individual TNF-inhibitors is driven entirely by the different acquisition and administration costs associated with each, because the QALYs gained are the same (that is, a class effect is assumed).

Table 18 Base case results for ankylosing spondylitis: rebound to baseline

	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Conventional therapy	110,821	7.245	-	-	-
Golimumab	130,173	8.163	19,352	0.918	21,079
Adalimumab	130,257	8.163	19,436	0.918	21,170
Etanercept	130,630	8.163	19,810	0.918	21,577
Certolizumab	132,059	8.163	21,238	0.918	23,133
Infliximab	148,073	8.163	37,252	0.918	40,576
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year					

Adapted from table 95 in section 7.7 of the assessment report

6.43 In the rebound to natural history scenario (Table 19), the ICERs of the alternative anti-TNFs varied between £36,554 (golimumab) to £66,529 (infliximab) per additional QALY gained compared with conventional care. At a maximum acceptable ICER of £20,000 per QALY gained, golimumab had only a 2% probability of being cost-effective compared with conventional therapy. This probability rose to 30% at a maximum acceptable ICER of £30,000 per QALY gained. As before, infliximab had the lowest probability of being cost-effective (0% likelihood, at both thresholds).

Table 19 Base case results for ankylosing spondylitis: rebound to natural history

	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Conventional therapy	109,933	7.265	-	-	-
Golimumab	131,960	7.867	22,027	0.603	36,554
Adalimumab	132,045	7.867	22,111	0.603	36,695
Etanercept	132,423	7.867	22,489	0.603	37,322
Certolizumab	133,851	7.867	23,918	0.603	39,693
Infliximab	150,022	7.867	40,088	0.603	66,529
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year					

Adapted from table 96 in section 7.7 of the assessment report

6.44 The ICER estimates appeared to remain relatively stable (compared to the base case results) across most of the 6 sensitivity analyses. The exception to this was 'Scenario 2', where company data were used to inform the difference in BASDAI/BASFI scores, conditional on response. When the company data were used, the ICER estimates became more favourable towards the TNF-inhibitors, driven by smaller differences between responders and non-responders. Results of the sensitivity analyses are presented in Table 100 and Table 101 of the Assessment Report.

6.45 For the probabilities of each TNF-inhibitor being cost-effective at maximum acceptable ICERs of £20,000 or £30,000 per QALY gained, see table 95 and table 96 of the assessment report.

Results for patients with axial spondyloarthritis without radiographic evidence of ankylosing spondylitis

6.46 In the rebound to baseline scenario (Table 20), the ICERs of the alternative TNF-inhibitors ranged from £29,253 (adalimumab) to £30,807 (certolizumab) per QALY, compared with conventional care. At a maximum acceptable ICER of £20,000 per QALY gained, adalimumab had a 11% probability of being cost-effective compared with conventional therapy, which rose to 55% at a maximum acceptable ICER of £30,000 per QALY gained.

Table 20 Base case results for axial spondyloarthritis without radiographic evidence of ankylosing spondylitis: rebound to baseline

	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Conventional therapy	89,493	9.956	-	-	-
Adalimumab	130,316	11.351	40,823	1.395	29,253
Etanercept	131,057	11.351	41,563	1.395	29,784
Certolizumab	132,484	11.351	42,991	1.395	30,807
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year					

Adapted from table 97 in section 7.7 of the assessment report

6.47 In the rebound to natural history scenario (Table 21), the ICER of the alternative anti-TNFs varied between £33,639 (adalimumab) to £35,365 per additional QALY (certolizumab). At a maximum acceptable ICER of £20,000 per QALY gained, adalimumab had a 5% probability of being cost-effective compared with conventional therapy. Its probability of being cost-effective compared with conventional therapy at a maximum acceptable ICER of £30,000 per QALY gained was approximately 39%.

Table 21 Base case results for axial spondyloarthritis without radiographic evidence of ankylosing spondylitis: rebound to natural history

	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Conventional therapy	89,395	9.880	-	-	-
Adalimumab	131,740	11.139	42,346	1.259	33,639
Etanercept	132,486	11.139	43,091	1.259	34,232
Certolizumab	133,913	11.139	44,518	1.259	35,365
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year					

Adapted from table 98 in section 7.7 of the assessment report

6.48 The ICER estimates appeared to remain relatively stable (compared to the base case results) across most of the 6 sensitivity analyses. The scenario which showed the largest variation compared to the base case analysis was ‘Scenario 1’, which excluded any placebo effect where company data were used to inform the difference in BASDAI/BASFI scores, conditional on response. ICER estimates became more favourable towards the TNF-inhibitors (full results present in Table 103 and Table 104 of the assessment report).

6.49 For the probabilities of each TNF-inhibitor being cost-effective at maximum acceptable ICERs of £20,000 or £30,000 per QALY gained, see table 97 and table 98 of the assessment report.

Discussion of Assessment Group's model and comparison with company submissions

6.50 The ICERs produced by the Assessment Group's model appeared to be consistent with the results of the company models, despite methodological differences, in both populations.

6.51 Based on the rebound equal to gain scenario in the Assessment Group's model, the ICER estimates for TNF-inhibitors appeared more favourable for ankylosing spondylitis, relative to those estimated for axial spondyloarthritis without radiographic evidence of ankylosing spondylitis. This finding was reversed in the rebound to conventional care scenario.

6.52 Based on an underlying assumption of similarity in the clinical effectiveness of each of the TNF-inhibitors, the Assessment Group's model demonstrated that the cost-effectiveness results are dependent on several factors (although the importance of specific factors varied across the 2 indications), including:

- the different acquisition and administration costs of each intervention
- the rebound assumption applied after treatment withdrawal
- the magnitude of the change in BASDAI/BASFI scores assumed for responders compared with non-responders
- the different baseline BASDAI/BASFI scores assumed for responders compared with non-responders
- the impact of TNF-inhibitors on the rate of long-term BASFI progression.

6.53 The Assessment Group listed the following as the main limitations in its model:

- in common with all existing models, BASDAI and BASFI may not be the most appropriate tools for modelling disease progression (used due to a lack of data linking costs and QALYs to other disease measures)
- uncertainty remains in long-term projections of BASDAI and BASFI

- there are potential benefits which have not been formally captured and quantified, such as potential impact on productivity costs and benefits that TNF-inhibitors may confer for extra-articular manifestations
- the model could not address important clinical questions concerning the issue of sequential use of TNF-inhibitors
- the model is based on an assumption that 12-week continuation rules are adhered to in clinical practice (it does not necessarily reflect the cost-effectiveness of how TNF-inhibitors are currently used within the NHS)
- it was not possible to include the generic version of infliximab within the analysis because a formal list price was not available at the time of the assessment.

6.54 The Assessment Group acknowledged that BASDAI and BASFI may not be the most appropriate modelling tools. However, they considered that their approach captured the potential impact of TNF-inhibitors on long-term BASFI changes more explicitly than existing models. The de novo model included changes in different clinical/biological processes (in addition to disease activity according to BASDAI) which independently affect BASFI. The Assessment Group considered that the effect of symptomatic improvements (that is, changes in BASDAI scores) on BASFI was captured in the conditional scores applied to responders. In addition, since long-term BASDAI was assumed to be constant after the short-term response period (see section 4.25), long-term changes in BASFI were modelled as a function of mSASSS scores. Assumptions were based on the Assessment Group's extensive evidence review and epidemiological studies (described in section 7.5.3 of the assessment report).

7 Comments received during consultation of the Assessment Report

Clinical effectiveness and relevance to clinical practice

7.1 A consultee noted some issues with the trials included in the Assessment Group's meta-analysis which may impact the estimates of efficacy for TNF-inhibitors:

- 2 studies of adalimumab in ankylosing spondylitis (Hu 2012 and Huang 2014) may not be generalisable to the UK because they included an entirely Chinese population
- 1 study (Haibel 2008) may underestimate the benefit of adalimumab in axial spondyloarthritis without radiographic evidence of ankylosing spondylitis because it covers a much broader patient population than the marketing authorisation for adalimumab
- 2 studies (Haibel 2008 and Barkham 2009) may not be representative of clinical practice, because their eligibility criteria pre-date the classification system used in current practice (developed by the Assessment of SpondyloArthritis international Society).

7.2 A consultee suggested that the results of the Assessment Group's meta-analysis for golimumab may overestimate its effectiveness compared with clinical practice. The consultee suggested that the benefit in patients receiving the higher dose of golimumab (100 mg) without fulfilling the market authorisation requirements for this dose (body weight of more than 100 kg) would be counteracted by a lower response in patients with a greater body weight who received the lower dose (50 mg). This is based on data in the golimumab EPAR (presented on page 6 of the response from MSD).

7.3 A commentator disagreed with the Assessment Group's conclusion that the meta-analysis of axial spondyloarthritis without radiographic evidence

of ankylosing spondylitis might not be relevant to clinical practice, due to statistical heterogeneity. The commentator suggested that clinical practice is usually more heterogeneous than study populations.

7.4 A consultee disagreed with the FDA's conclusion (reported by the Assessment Group) that the ABILITY-1 trial overestimated the treatment benefit of adalimumab due to including ankylosing spondylitis patients. The FDA based this conclusion on a post hoc analysis of the x-ray results used to determine patient eligibility for the ABILITY-1 trial. During the post hoc analysis, X-ray readers diagnosed many patients differently. The consultee stated that x-ray readers in the post hoc analysis did not have access to the complete set of clinical information on the patients and therefore could not make a fully informed diagnosis. They also noted that the FDA assessment was restricted by the limitations associated with post hoc analyses. For full details, see page 4–6 of the Abbvie response to consultation on the Assessment Report.

Assumptions in the Assessment Group's model

Rebound effect after treatment withdrawal

7.5 Three consultees suggested that the rebound to baseline scenario was more plausible than the rebound to natural history scenario. Two of them based this assumption on clinical opinion, and the other submitted a rationale supported by published clinical trial data (presented on pages 2–3 of the response from MSD).

7.6 One consultee suggested that the rebound to baseline scenario underestimates the benefits of TNF-inhibitors and that the Assessment Group should conduct sensitivity analysis either side of this scenario. The consultee also submitted evidence showing that the rebound effect can take 3–6 months (the most recent technology appraisal in ankylosing spondylitis, TA233, used this assumption). The consultee suggested that the Assessment Group's assumption that the rebound effect is immediate further underestimates the benefit of TNF-inhibitors.

Disease progression

7.7 The Assessment Group modelled long-term changes in BASFI as a function of Modified Stoke Ankylosing Spondylitis Spinal (mSASSS) scores. A consultee suggested that this was not appropriate for axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, as these patients do not have structural damage that would be detected using this assessment tool.

7.8 A consultee suggested that scenario 4 of the sensitivity analysis (in which the effect of TNF-inhibitors on progression was achieved immediately) is more appropriate than the base case (in which disease modification was delayed until year 4). The company suggest that published evidence (Haroon et al. 2010) showing that TNF-inhibitors do not reduce disease progression until year 4 may be incorrect. They suggest that is more plausible to assume that disease progression is reduced immediately (in people whose disease responds to treatment), but that the cumulative difference compared with conventional care is only statistically significant after 3.9 years.

7.9 A consultee presented published evidence to suggest that people whose disease responds to TNF-inhibitor treatment do not experience any BASFI progression. This opinion contradicts assumptions in the Assessment Group's base case model (in which long-term disease progression is slowed) and the sensitivity analyses (in which TNF-inhibitors have no impact on progression; scenario 3).

Baseline BASDAI/BASFI scores

7.10 The Assessment Group's base case model used estimates of baseline BASDAI/BASFI scores from their extended synthesis, and data from company submissions were used to inform a sensitivity analysis. Two consultees suggested that the sensitivity analysis (scenario 2) is more appropriate than the base case. The consultees noted that the base case model might underestimate the improvement in BASDAI for responders

and overestimate the improvement for non-responders, therefore producing higher ICERs than those produced with observed data. The consultee suggested additional limitations of the synthesis model data (presented on pages 4–6 of the response from Pfizer).

7.11 Both the base case and sensitivity analysis assumed higher baseline BASDAI and BASFI scores for non-responders compared with responders. A commentator noted that this assumption is not supported by the Assessment of SpondyloArthritis international Society consensus statement (2006).

Extra-articular manifestations

7.12 One consultee and a commentator, highlighted that the Assessment Group's model did not account for improvements in extra-articular manifestations associated with axial spondyloarthritis (a limitation already acknowledged by the Assessment Group). Improvements in these symptoms may improve health related quality of life and reduce overall treatment costs. The consultee submitted published evidence to show the differences in the effect of alternative TNF-inhibitors on extra-articular manifestations. Adalimumab conferred a greater benefit than the other TNF-inhibitors. The consultee also noted that guidelines from the Assessment of SpondyloArthritis international Society and the European League Against Rheumatism (2010) state that "the treatment of patients with ankylosing spondylitis should be tailored according to: the current manifestation of the disease (axial, peripheral, entheseal, extra-articular symptoms and signs)." The commentator suggested that, in the absence of evidence for the effect of TNF-inhibitors on extra-articular manifestations in the axial spondyloarthritis population, data in people with psoriasis, uveitis and inflammatory bowel disease (but without axial spondyloarthritis) should be considered as part of this appraisal.

Class effect

7.13 A commentator questioned the assumption of a class effect. They noted that adalimumab and certolizumab pegol result in better BASDAI and BASFI improvements compared with other TNF-inhibitors (in ankylosing spondylitis).

7.14 A consultee suggested that the high ICER for infliximab may result from the underestimation of the treatment effect for infliximab, through assuming a single class effect across all TNF-inhibitors. The consultee noted evidence to suggest that infliximab has a greater effect than the other TNF-inhibitors in Table 11 of the assessment report.

Other

7.15 A consultee suggested that the Assessment Group's model underestimates the efficacy and cost-effectiveness of TNF-inhibitors by not including a benefit in people who continue treatment beyond 10–16 weeks (observed in open label extension studies).

7.16 The Assessment Group used a fixed cost for infliximab based on a mean weight of 73 kg. A consultee considered that this underestimated the ICER for infliximab. They suggested that the model should account for the distribution of patient weight in the UK, and not solely on an average value. In addition, the consultee highlighted that the Assessment Group's model assumes a less frequent dosing schedule for infliximab (50% of patients every 6 weeks and 50% of patients every 8 weeks) than the clinical trials (all patients every 6 weeks).

7.17 The Assessment Group's model assumes that all patients receiving a subcutaneously injected TNF-inhibitor incur a cost of £49 in their first cycle. Abbvie commented that they provide injection training free of charge and therefore suggest that the £49 cost is an overestimate for people receiving adalimumab.

ICER calculations

7.18 A commentator queried the difference between QALYs gained with conventional therapy across the 2 populations in the Assessment Group's ICER calculations (QALYs for people receiving conventional care were lower in ankylosing spondylitis compared with axial spondyloarthritis without radiographic evidence of ankylosing spondylitis), given that the Assessment Group acknowledge that the impact of disease is the same across both populations.

7.19 A company noted that the Assessment Group's algorithm for calculating EQ-5D results in less favourable ICERs for TNF-inhibitors, due to underestimation of the comparative QALY gain. The Assessment Group has acknowledged this limitation.

Potential economic benefits of TNF-inhibitors not captured by the reference case

7.20 Two consultees and a commentator suggested that considering the impact of treatment on the indirect costs of ankylosing spondylitis (that is, costs of unemployment, absenteeism from work and reduced productivity at work) would improve the cost-effectiveness of TNF-inhibitors compared with conventional care. It was suggested that indirect costs account for 85% of the total costs of ankylosing spondylitis.

7.21 A consultee highlighted that treatment options are limited for people with axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, although they experience similar levels of pain and stiffness to people ankylosing spondylitis and that patients with non-radiographic disease have reportedly stopped exercising, in an attempt to reduce their mobility and allow their disease to progress to fulfil the requirements to qualify for TNF-inhibitor treatment.

8 Equality issues

8.1 During the scoping process it was noted that, although the prevalence of axial spondyloarthritis without radiographic evidence of ankylosing spondylitis affects equal numbers of men and women, women are less likely than men to develop radiographic changes (leading to a diagnosis of ankylosing spondylitis. Therefore, based on current NICE guidance (technology appraisal TA143 and TA233), women are less likely to meet the criteria for treatment with TNF-inhibitors. Consultees suggested that if TNF-inhibitor therapy could be prescribed for axial spondyloarthritis without radiographic evidence of ankylosing spondylitis then women would have more equal access to TNF-inhibitors than at present. NICE noted that this appraisal will consider the use of TNF-inhibitors for both ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, within the marketing authorisation for the technologies under consideration. The Committee will not discriminate between male and female patients and will ensure that any recommendations do not discriminate against any groups protected under the Equality Act. No additional equality issues were identified in the evidence submitted.

9 Innovation

9.1 A company noted that the use of TNF-inhibitors in axial spondyloarthritis without radiographic evidence of ankylosing spondylitis represents a step change in the management of the condition, as no other drug or class of drugs has a marketing authorisation in the UK for this indication.

9.2 A company suggested that the QALY calculation may not account for the benefits that treatment with TNF-inhibitors provide relating to a reduction in the incidence and/or symptoms associated with extra-articular manifestations often associated with axial spondyloarthritis (such as enthesitis, uveitis, inflammatory bowel disease and psoriasis). The company cited publications to support this. Other benefits not captured in

the QALY, noted during the scoping process, are improvements in work productivity and a reduced burden on caregivers.

9.3 A company noted that, unlike monoclonal antibodies (adalimumab, infliximab, golimumab and certolizumab), the recombinant human TNF-receptor fusion protein etanercept is not associated with neutralising antibodies and a consequent reduction in efficacy.

10 Authors

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Appendix A: Supporting evidence

Outcome measures

Table 22. Disease assessment tools for ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis

Disease component	Tool	Description
Physical function	BASFI	Patient assesses difficulty on a 10 point scale (1 is easy and 10 is impossible) for each of 10 items: • putting on socks or tights without help or aids • bending from the waist to pick up a pen from the floor without aid • reaching up to a high shelf without help or aids • getting up from an armless chair without hands or any other help • getting up off the floor without help from lying on back • standing unsupported for 10 minutes without discomfort • climbing 12–15 steps without using a handrail or walking aid • looking over shoulder without turning body • doing physically demanding activities • doing a full day's activities (at home or at work)
Disease activity	BASDAI	Patient describes the severity of 5 symptoms on a 10 point scale (1 is no problem and 10 is very severe): • fatigue • spinal pain • joint pain / swelling • areas of localised tenderness (also called enthesitis) • morning stiffness severity Duration of morning stiffness is also provided.
Disease activity	ASDAS	Calculated from BASDAI questions on spinal pain, peripheral arthritis, and duration of morning stiffness, patients global assessment of disease activity, and C-reactive protein (or erythrocyte sedimentation rate if C-reactive protein not available)
Disease activity Spinal mobility	BASMI	Clinician assessment of: lateral spine flexion, tragus to wall distance, lumbar side flexion (modified Schober), intermalleolar distance and cervical rotation

Disease component	Tool	Description
Structural damage	mSASSS	Clinician assessment of 24 sites on the lateral cervical and lumbar spine. Sites are scored on a 4 point scale (0 is normal; 1 is sclerosis, squaring or erosion; 2 is syndesmophyte; 3 is bony bridge). The total score ranges from 0 to 72.
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; mSASSS, modified Stoke Ankylosing Spondylitis Spinal Score		

Table 23 Response criteria to evaluate treatments for ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis

Response outcome	Response criteria
BASDAI 50	≥50% improvement in BASDAI score
ASAS 20	Improvement of ≥20% and ≥1 unit in at least 3 of the following 4 domains (each with a 10 point scale): • patient global disease assessment • spinal pain • function (BASFI score) • inflammation (using mean score from 2 questions of the BASDAI). No worsening of ≥20% and ≥1 unit in the 4th domain.
ASAS 40	Improvement of ≥40% and ≥2 units in at least 3 of the following 4 domains (each with a 10 point scale): • patient global disease assessment • spinal pain • function (BASFI score) • inflammation (using mean score from 2 questions of the BASDAI). No worsening at all in the 4th domain.
ASAS, Assessment in SpondyloArthritis international Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index	

Related NICE guidance

Published

- Golimumab for the treatment of ankylosing spondylitis. NICE technology appraisal guidance 233 (2011).

"Golimumab is recommended as an option for the treatment of severe, active ankylosing spondylitis in adults only if:

- it is used as described for adalimumab and etanercept in 'Adalimumab, etanercept and infliximab for ankylosing spondylitis' (NICE technology appraisal guidance 143) and
- the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose in accordance with the patient access scheme.

People currently receiving golimumab for the treatment of severe, active Aankylosing spondylitis who do not fulfil the criteria for treatment with adalimumab and etanercept described in NICE technology appraisal guidance 143 should have the option to continue golimumab until they and their clinician consider it appropriate to stop."

- Adalimumab, etanercept and infliximab for ankylosing spondylitis. NICE technology appraisal guidance 143 (2008).

"Adalimumab or etanercept are recommended as treatment options for adults with severe active ankylosing spondylitis only if all of the following criteria are fulfilled.

- The patient's disease satisfies the modified New York criteria for diagnosis of ankylosing spondylitis.
- There is confirmation of sustained active spinal disease, demonstrated by:
  - a score of at least 4 units on the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) **and**

  - at least 4 cm on the 0 to 10 cm spinal pain visual analogue scale (VAS).

    These should both be demonstrated on two occasions at least 12 weeks apart without any change of treatment.
- Conventional treatment with two or more non-steroidal anti-inflammatory drugs taken sequentially at maximum tolerated or recommended dosage for 4 weeks has failed to control symptoms.

When using BASDAI and spinal pain VAS scores to inform conclusions about whether or not sustained active spinal disease is present, healthcare professionals should be mindful of the need to secure equality of access to treatment for patients with disabilities and patients from different ethnic groups. There are circumstances in which it may not be appropriate for healthcare professionals to use a patient's BASDAI and spinal pain VAS scores to inform their conclusion about the presence of sustained active spinal disease. These are:

- where the BASDAI or spinal pain VAS score is not a clinically appropriate tool to inform a clinician's conclusion on the presence of sustained active spinal disease because of a patient's learning or other disabilities (for example, sensory impairments) or linguistic or other communication difficulties

or

- where it is not possible to administer the BASDAI or spinal pain VAS questionnaire in a language in which the patient is sufficiently fluent for it to be an appropriate tool to inform a conclusion on the presence of sustained active spinal disease, or there are similarly exceptional reasons why use of a patient's BASDAI or spinal pain VAS score would be an inappropriate tool to inform a conclusion on the presence of sustained active spinal disease in that individual patient's case.

In such cases, healthcare professionals should make use of another appropriate method of assessment, which may include adapting the use of the questionnaire to suit the patient's circumstances.

The same approach should apply in the context of a decision about whether to continue the use of the drug in accordance with sections 1.3 and 1.4.

1.3 It is recommended that the response to adalimumab or etanercept treatment should be assessed 12 weeks after treatment is initiated, and that treatment should be only continued in the presence of an adequate response as defined in section 1.4.

1.4 For the purposes of this guidance, an adequate response to treatment is defined as a:

- reduction of the BASDAI score to 50% of the pre-treatment value or by 2 or more units and
- reduction of the spinal pain VAS by 2 cm or more.

Patients who have experienced an adequate response to adalimumab or etanercept treatment, as defined in section 1.4, should have their condition monitored at 12-week intervals. If the response to treatment, as defined in section 1.4, is not maintained, a repeat assessment should be made after a further 6 weeks. If at this 6-week assessment the response defined in section 1.4 has not been maintained, treatment should be discontinued.

For patients who have been shown to be intolerant of adalimumab or etanercept before the end of the 12-week initial assessment period, as in section 1.3, the other one of this pair of TNF-alpha inhibitor treatments is recommended as an alternative treatment.

Prescription of an alternative TNF-alpha inhibitor is not recommended in patients who have either not achieved an adequate initial response to treatment with

adalimumab or etanercept, as defined in section 1.4, or who experience loss of the initially adequate response during treatment.

It is recommended that the use of adalimumab or etanercept for severe active ankylosing spondylitis should be initiated and supervised only by specialist physicians experienced in the diagnosis and treatment of this condition.

Infliximab is not recommended for the treatment of ankylosing spondylitis.

Patients currently receiving infliximab for the treatment of ankylosing spondylitis should have the option to continue therapy until they and their clinicians consider it appropriate to stop."

Under development

Spondyloarthiritis: diagnosis and management of spondyloarthritis. NICE clinical guideline. Publication date to be confirmed.

NICE pathways

There is a NICE pathway on ankylosing spondylitis, which is available from http://pathways.nice.org.uk/pathways/musculoskeletal-conditions/arthritis#content=view-node%3Anodes-ankylosing-spondylitis

Appendix B: Clinical efficacy section of the draft European public assessment report

Links to European public assessment reports:

- Adalimumab
- Certolizumab pegol
- Etanercept
- Golimumab
- Infliximab
  - Inflectra (biosimilar)
  - Remsima (biosimilar)