.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis (including review of TA35)

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

- The marketing authorisations for abatacept, adalimumab, etanercept and tocilizumab cover a population whose condition has not responded to a disease modifying anti-rheumatic drug (DMARD) such as methotrexate. However, whereas adalimumab, etanercept and tocilizumab can be taken as the first biological treatment after methotrexate, abatacept must be taken after an anti-TNF inhibitor. What are the comparators at these positions in the treatment pathway?
- The marketing authorisations for abatacept, adalimumab, etanercept and tocilizumab stipulate the minimum, but not the maximum, age of the population for which they are indicated. However, the marketing authorisation for abatacept

refers to a 'paediatric' population and the one for etanercept refers to 'children and young people'. To what extent would people with JIA take the biological treatments into adulthood? Are there any potential equalities issues relating to age?

- Would people with JIA stop treatment with biologics if in remission? What are the reasons for stopping treatment in clinical practice? What are the relapse rates for people who stop treatment with a biologic because of being in remission?
- The 4 RCTs (1 each) of abatacept, adalimumab, etanercept and tocilizumab compared with placebo in people with polyarticular course JIA differed in terms of the:
  - proportion of people with different subtypes of JIA
  - Duration that the trial populations had JIA before entering trial
  - Previous treatments
  - proportion of people taking methotrexate in both study arms
  - age of the trial population
  - length of open label lead in phase and follow-up

  Can a robust comparison of the clinical effectiveness be made for the 4 technologies?
- Is disease flare the most important clinical outcome for patients and carers? Is definition of a flare in the pivotal trials the same as how a flare would be defined in clinical practice? Are any of the other trial outcomes relevant to capture the benefits (and costs) of the 4 technologies?
- The marketing authorisations for etanercept and adalimumab cover paediatric enthesitis-related arthritis; etanercept is also licensed for use by children and adolescents with psoriatic arthritis. Is the clinical effectiveness of etanercept and adalimumab in these JIA subtypes similar to the population with polyarticular course JIA that were included in the 4 RCTs?
- What is the proportion of people with polyarthritis, extended oligoarthritis enthesitis-related arthritis and psoriatic arthritis subtypes of JIA who have uveitis?
- Would etanercept be the first line of biologic treatment for the majority of people except people with uveitis who would have adalimumab?

- To what extent do methotrexate, abatacept, adalimumab, etanercept and tocilizumab affect long term outcomes such as progressive joint damage associated with JIA, joint function, growth and osteoporosis in people who have had an inadequate response with or are intolerant to methotrexate?
- Is the use of corticosteroids in JIA associated with any adverse effects? Would abatacept, adalimumab, etanercept and tocilizumab be expected to reduce the need for long term treatment with corticosteroids?

Cost effectiveness

- Do the 1st and 2nd line biologic models reflect the sequence of treatments used in clinical practice?
- The Assessment Group presented scenarios comparing treatment sequences of 3 biologics. Is it appropriate to compare different treatment sequences of biologics in the economic modelling?
- Is disease flare the most appropriate clinical outcome to capture the costs and benefits of the 4 technologies? Are any of the other trial outcomes relevant?
- No data were identified for the utility values of people with JIA having disease flare and carers of people with JIA. Are the Assessment group's estimates of a disutility of 0.03 (over the course of a year) for disease flare and caregiver disutility of between 0.01 and 0.035 for people with JIA taking biologics and between 0.02 and 0.07 for people not taking biologics reasonable assumptions?
- The Assessment Group model is based on a population with predominately polyarticular course JIA . Would the cost-effectiveness of adalimumab and etanercept for enthesitis-related JIA, and the cost effectiveness of etanercept for psoriatic arthritis be expected to be similar to that for polyarticular course JIA?
- The costs and benefits associated with biological treatments on uveitis, long term outcomes (such as progressive joint disease) and corticosteroid use were not included in the economic modelling. What effect would incorporating these costs and benefits have on the ICERs for abatacept, adalimumab, etanercept and tocilizumab compared with methotrexate? Would the ICERs for the 4 technologies compared with methotrexate be likely to fall below £30,000 per QALY gained if these factors were included in the modelling?

- Are the Assessment Group base case and scenarios plausible?
- The Assessment Group presented results from pairwise comparisons of abatacept, adalimumab, etanercept and tocilizumab with methotrexate rather than a fully incremental analysis because it stated that the indirect comparison of clinical effectiveness the technologies was not robust. Are the pairwise comparisons with methotrexate the most appropriate for the Committee to base its decisions?
- In technology appraisal 35 in 2002 etanercept was found to be cost effective compared with 'placebo' with a most plausible ICER of between £15,000 to £30,000 per QALY gained in people with polyarticular course JIA (n.b. the NICE reference case in 2002 included a different discounting rate to the current 3.5% for costs and QALYs). Is there any new evidence to support changing that recommendation?

1 Background: clinical need and practice

1.1 Juvenile idiopathic arthritis (JIA) describes all forms of arthritis of unknown cause with an onset under 16 years of age and in which the joint inflammation lasts more than 6 weeks. JIA is classified by the number of joints affected. **Oligoarthritis** is diagnosed when 4 or fewer joints are affected and **polyarthritis** is diagnosed when 5 or more joints are affected in the first 6 months. Polyarthritis is further characterised depending on whether people have rheumatoid factor or not (this is, an antibody directed against the person's own tissues). People who had 4 joints affected in the first 6 months but then who go on to have more joints affected have **extended oligoarthritis**. Some subtypes (**systemic, enthesitis-related** and **psoriatic**) of JIA have additional symptoms including:

- **Systemic**: fever, tiredness, rash, loss of appetite and weight loss.
- **Enthesitis-related**: arthritis which affects entheses (where tendons attach to the bones).

- **Psoriatic arthritis**: psoriasis

People who go on to have 5 or more joints affected after the first 6 months are said to have **polyarticular course** JIA. This includes people with enthesitis-related and psoriatic arthritis and can include people with systemic JIA providing there have been no active systemic symptoms during the previous 6 months.

1.2 JIA has an annual incidence of 0.1 per 1000 children in the UK (1000 children diagnosed per year). The prevalence of JIA is approximately 1 per 1,000. (~10,000 children affected in the UK), however the condition may continue into adulthood, so adults have JIA. It is estimated that a third or more of children with JIA will still require treatment in adult life. JIA which persists into adulthood is distinct from adulthood rheumatoid arthritis.

Table 1: Proportions of different sub-types of JIA, estimates from 3 cohort studies (table 3, assessment report page 25).

JIA classification	Newly diagnosed children (n=1014)	From 17 centres within the UK (n=521)	[redacted]
Oligoarthritis:			
Persistent oligoarthritis	48.2% (502/1041)	30.1% (157/521)	[redacted]
Extended oligoarthritis	5.5% (57/1041)	15.2% (79/521)	[redacted]
Polyarthritis - RF+ve	3.6% (37/1041)	7.1% (37/521)	[redacted]
Polyarthritis - RF-ve	20.6% (214/1041)	19.6% (102/521)	
Enthesitis-related arthritis	5.6% (58/1041)	6.5% (34/521)	[redacted]

Psoriatic arthritis	7.0% (73/1041)	7.1% (37/521)	[redacted]
Systemic arthritis	6.0% (62/1041)	14.4% (75/521)	[redacted]
Undifferentiated arthritis	3.7% (38/1041)	not reported	[redacted]
Not recorded	N/A	N/A	[redacted]

1.3 At the onset of JIA, swollen and painful joints can limit movement while later, progressive joint damage can permanently disable patients who may need joint replacements (AbbVie, manufacturer of adalimumab, estimated between 7 and 28%). About 10-20% of patients with JIA (mainly those with systemic or polyarticular JIA who require high doses of corticosteroids) have impaired growth. JIA can decrease bone mass and increase the risk of osteoporosis. JIA is associated with a range of extra-articular manifestations, notably, uveitis (inflammation of the middle layer of the eye). It is estimated that 30 to 50% of children with JIA have uveitis at diagnosis. Untreated uveitis can be associated with cataracts, glaucoma, and macular oedema, and can lead to sight impairment and blindness. It is estimated that 50 to 70% of people with severe uveitis develop visual impairment. Children with JIA are screened for uveitis in England.

1.4 Physicians measure disease activity in JIA takes into account a ‘global assessment’, wellbeing and function, number of joints affected and biochemical markers of inflammation. Clinicians use the American College of Rheumatology Pediatric (ACR Pedi) system, a scoring system that has been used widely in clinical trials . ACR Pedi 30, 50,70,90 and 100 reflect increasing response. An ACR Pedi 30 corresponds to 3 of the 6 core variables improving by at least 30% and no more than 1 of the remaining variables worsening by more than 30%; An ACR Pedi 50 corresponds to 3 of the 6 core variables improving by at least 50% and, like ACR Pedi 30, no more than 1 of the remaining variables worsening by at least 30%.

Regulators consider response levels of ACR Pedi 50 or 70 as clinically relevant in drugs trials.

Table 2 definition of the ACR Pedi scoring system core variables

Physicians Global Assessment: Visual analogue scale (VAS); 0 best score 10 worst score.
Patient or parent assessment of wellbeing: VAS; 0 best score, 10 worst score.
Functional ability: Childhood Health Assessment Questionnaire (CHAQ, range 0-3, 0 best score)
Number of joints with active arthritis
Number of joints with limited range of motion
Laboratory marker of inflammation: Erthrocyte Sedimentation Rate (ESR) or c Reactive Protein level (CRP)

1.5 The NHS England interim policy on Biologic Therapies for the Treatment of JIA includes the following definitions in table 3 of response and remission to be used in clinical practice.

Table 3 definitions of response and remission in NHS England interim commissioning policy on biologic therapies for treating JIA

Response to therapy	Should be assessed after 3 months of therapy and every 3 months while treatment continues. For every synovial joint the status should be recorded: Active synovitis No active synovitis but decreased range of movement No synovitis and full range of movement In addition the presence or absence of extra-articular complications should be noted. (e.g. psoriasis, inflammatory bowel disease, uveitis, fever, rash, serositic, splenomegaly,or generalised lymphadenopathy attributed to JIA)
Clinical inactive disease	All must be met: • No joints with active disease • No fever, rash, serositis, splenomegaly or generalised lymphadenopathy attributed to JIA • No active uveitis • Erthrocyte Sedimentation Rate or c Reactive Protein level (both if tested) within normal limits for the laboratory where tested or, if elevated, not attributable to JIA • Physician's global assessment of disease activity score as lowest possible on whichever scale is used • Duration of morning stiffness ≤15 min
Clinical remission on medication	Satisfaction of the definition of clinical inactive disease for at least 6 continuous months while on therapy for JIA

Clinical remission off medication	Satisfaction of the definition of clinical inactive disease for at least 12 continuous months while off all therapy for JIA
Treatment failure	• Persistent synovitis in 2 or more joints • Within 12 months; 2 or more separate episodes of corticosteroid use to control flares of disease • Development/worsening of erosive disease due to ongoing synovitis • Intolerance of therapy- including inability to tolerate the injections • Ongoing evidence of active uveitis, even in the presence of quiescent joint disease

1.6 NICE issued guidance on the use of etanercept for the treatment of juvenile idiopathic arthritis in 2002 (technology appraisal guidance, TA35). The recommendation is 'etanercept is recommended for children aged 4 to 17 years who have active JIA in at least 5 joints and whose condition has not responded adequately to methotrexate or who have been unable to tolerate treatment with methotrexate'. This guidance is being reviewed in the current appraisal because the marketing authorisation for etanercept has been extended to include people from the age of 2 years with polyarthritis and children and young people with extended oligoarthritis, enthesitis related arthritis and psoriatic arthritis. NICE technology appraisal guidance 238 (2011) recommends tocilizumab 'as a possible treatment for some children and young people with systemic juvenile idiopathic arthritis'. NICE does not recommend tocilizumab for children and young people whose disease is improving with methotrexate treatment, or who have not yet been treated with methotrexate. Children and young people should be able to have tocilizumab if they all of the following drugs have not worked: NSAIDs (non-steroidal anti-inflammatory drugs), systemic corticosteroids and methotrexate.

1.7 There is no NICE clinical guideline for the treatment of JIA. The treatment pathway outlined in 'Biologic Therapies for the treatment of Juvenile Idiopathic Arthritis' published (January 2015) by NHS England Clinical Reference Group for Paediatric Medicine is presented in Figure 1. The

Assessment Group stated that its clinical advisers advised that the statement largely reflects clinical practice, but there may be variability across England because of clinicians interpret it differently and have limited access and prescribing. There is also an interim policy for severe refractory uveitis in paediatric patients. The policy states that etanercept is not suitable for use in patients with JIA and uveitis or uveitis not associated with JIA. Adalimumab is recommended where methotrexate does not control symptoms of uveitis. Infliximab may be used in patients in whom adalimumab is not tolerated, or not effective.

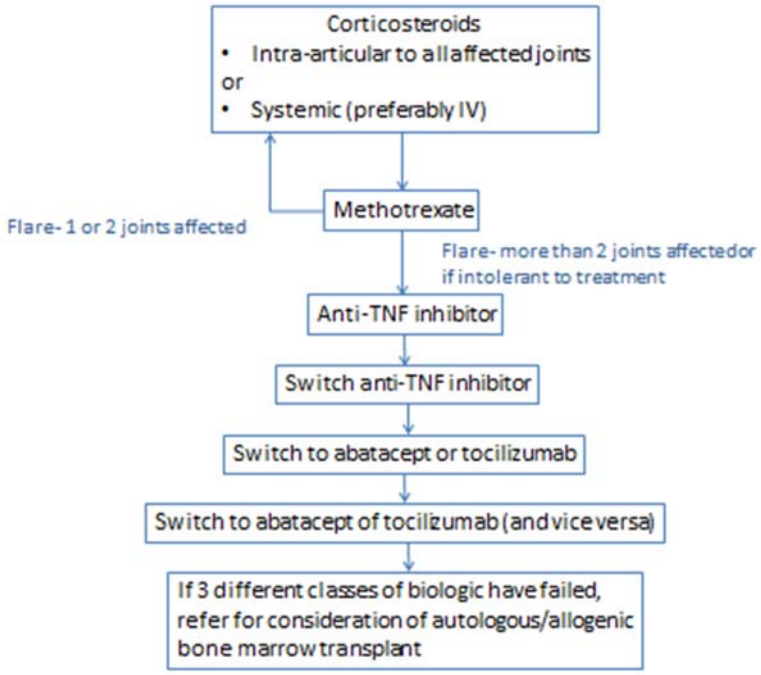


Figure 1. Treatment pathway, simplified representation to that presented in the NHS England interim commissioning policy

1.8 The scope does not include people with systemic onset JIA because tocilizumab is the only intervention licensed to treat this type of JIA and is already recommended for people whose disease has failed to respond to methotrexate in NICE technology appraisal guidance 238). Of note, people with systemic onset JIA may develop a polyarticular course JIA (see section 1.1).

2 The technologies

Abatacept

2.1 Abatacept (Orencia, Bristol-Myers Squibb) is a fusion protein that inhibits the activation of T-Cells. It is administered by intravenous infusion. Abatacept in combination with methotrexate is indicated for the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis in paediatric patients 6 years of age and older who have had an insufficient response to other DMARDs including at least one TNF inhibitor.

2.2 The summary of product characteristics lists the following adverse reactions for abatacept as the most common (affecting more than 1 in 10 people): upper-respiratory-tract infection. For full details of adverse reactions and contraindications, see the summary of product characteristics.

Adalimumab

2.3 Adalimumab (Humira, AbbVie), is an antibody that inhibits Tumour Necrosis Factor (TNF). It is administered by subcutaneous injection. Adalimumab in combination with methotrexate (or as monotherapy if methotrexate is not tolerated or is inappropriate) is indicated for

- treating active polyarticular juvenile idiopathic arthritis, in patients from the age of 2 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs).
- treating severe chronic active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy.

2.4 The summary of product characteristics lists the following adverse reactions for adalimumab (seen in more than 1 patient in 10): respiratory tract infections, leukopenia (low white blood cell count), anaemia (low red blood cell counts), increased blood levels of lipids, headache, abdominal pain. Nausea and vomiting, rash, musculoskeletal pain, injection site

reactions and increased levels of liver enzymes. For full details of adverse reactions and contraindications, see the summary of product characteristics.

Etanercept

2.5 Etanercept (Enbrel, Pfizer) is an antibody that inhibits the activity of TNF. It is administered by subcutaneous injection. It is indicated for:

- treating polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.
- Treating psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, methotrexate.
- Treating enthesitis-related arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy.

2.6 The summary of product characteristics lists the following adverse reactions for etanercept (seen in more than 1 patient in 10): injection site reactions and infections (including colds, and lung, bladder and skin infections. For full details of adverse reactions and contraindications, see the summary of product characteristics.

Tocilizumab

2.7 Tocilizumab (RoActemra, Roche) is an antibody which inhibits the action of interleukin-6 (IL-6). It is administered by intravenous infusion. It is indicated in combination with methotrexate(or as monotherapy if methotrexate is not tolerated or is inappropriate) for:

- Treating juvenile idiopathic polyarthritis (pJIA; rheumatoid factor positive or negative and extended oligoarthritis) in patients 2 years and

older, who have responded inadequately to previous therapy with methotrexate.

- Treating active systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age or older, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids.

2.8 The summary of product characteristics lists the following adverse reactions for tocilizumab (seen in more than 5 patients in 100): upper respiratory tract infections, nasopharyngitis, headache, hypertension, abnormal liver function tests.

2.9 Table 4 shows a summary of the indications for abatacept, adalimumab, etanercept and tocilizumab. All 4 technologies are indicated for polyarthritis, but differ in the marketing authorisations with respect to: other subtypes of JIA covered by the licence; whether the technology is taken with methotrexate; and which treatments patients must have previously taken.

Table 4 summary of indications covered by 4 technologies, assessment report table 5 page 31

	abatacept	adalimumab	etanercept	tocilizumab
Polyarthritis (including RF+/- polyarticular and extended oligoarthritis)	With MTX. Patients ≥ 6yrs. with insufficient response to DMARDs including at least 1 TNF inhibitor	With MTX unless not tolerated/not appropriate. Patients ≥2 yrs. With inadequate response to 1 or more DMARDs	Patients ≥ 2yrs, whose arthritis has responded inadequately to previous treatment with MTX	With MTX unless not appropriate. Patients ≥2 years, have responded inadequately to previous treatment with MTX
Enthesitis-related arthritis	-	Patients ≥ 6 yrs. with inadequate response to or intolerant of conventional therapy	Patients ≥ 12 years with inadequate response or intolerant of MTX	-
Psoriatic arthritis	-	-	Patients ≥ 12 years with inadequate response or intolerant to MTX	-
Systemic onset*		-	-	With MTX unless not appropriately.

*not in the decision problem				Patients ≥2 yrs. with inadequate response to NSAIDs and systemic corticosteroids

Table 1 Summary description of technologies

	Abatacept	Adalimumab	Etanercept	Tocilizumab
Proprietary name	Orencia	Humira	Enbrel	RoActemra
Company	Bristol Myers Squibb	AbbVie	Pfizer	Roche
Target	T-cell (activation of)	TNF	TNF	IL-6
administration	IV over 30 mins, 2 weeks and 4 weeks after initial infusion then every 4 weeks	SC every other week	SC twice weekly with an interval of 3-4 days between doses (0.4 mg/kg dose) or once weekly (0.8 mg/kg dose). Twice weekly dosing regimen used in modelling	IV over 1 hour every 4 weeks
Dose	*Body-weight* <75kg: 10mg/kg 75-100kg: 750 mg >100 kg: 1g Review treatment if no response within 6 months	**Polyarticular JIA** *Age* 2 to < 4yrs: 24 mg/m^2 body surface area up to a maximum single dose of 20 mg 4 to 12 years: 24 mg/m^2 body surface area up to a maximum single dose of 40 mg adalimumab 13 years and older: 40 mg regardless of body surface area. A clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period **Enthesitis-related JIA**: 24 mg/m^2 up to a maximum single dose of 40 mg	0.4mg/kg (up to maximum of 25 mg per dose) or 0.8 mg/kg (up to a maximum of 50 mg/dose) Consider discontinuation in patients who show no response after 4 months	*Body weight* <30 kg: 10 mg/kg ≥30 kg: 8 mg/kg
Acquisition	Powder for	40-mg prefilled syringe pen or prefilled syringe = £352.14;	Net price 10-mg vial	Net price 4mL

cost (BNF edition xx)	reconstitution, net price 250-mg vial	40 mg/0.8-mL vial = £352.14	(with solvent) = £33.75; 25-mg vial (with solvent) = £89.38; 25-mg prefilled syringe =£89.38; 50-mg prefilled pen or prefilled syringe = £178.75	(80-mg vial) = £102.40, 10 mL (200-mg vial)= £256.00, 20 mL (400-mg vial) =£512.00
Administration cost	£154	£0	£0	£154
Patient Access Scheme	[redacted]	None	none	[redacted]

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 etanercept, adalimumab, tocilizumab and abatacept within their licensed indications for treating juvenile idiopathic arthritis.

	Final scope issued by NICE
Population	People with the following forms of juvenile idiopathic arthritis: • Polyarthritis (rheumatoid factor positive, rheumatoid factor negative and extended oligoarthritis, both onset and course) • Enthesitis related arthritis, and • Psoriatic arthritis
Intervention	Etanercept, abatacept, adalimumab and tocilizumab within their licensed indications
Comparators	• Disease modifying anti-rheumatic drugs (DMARDs) (such as methotrexate), if DMARDs can be tolerated • Best supportive care, if DMARDs are not tolerated • Etanercept, abatacept, adalimumab and tocilizumab should be compared with each other within their licensed indications where appropriate. Biosimilars are not expected to be in established NHS practice at the time of appraisal and are not included as comparators.
Outcomes	The outcome measures to be considered include: • Disease activity • Disease flares • Physical function • Joint damage • Pain • Corticosteroid reducing regimens • Extra-articular manifestations (such as uveitis) • Body weight and height • Mortality • Adverse effects of treatment • Health-related quality of life

3.2 The Assessment Group only made comments on the population. It stated it is also relevant to consider children/young people with uveitis. It noted

the age of children/young people varies by intervention because of differing licenced indications. The Assessment Group presents estimates of cost effectiveness separately for people taking their first biological treatment and for people taking their second biological treatment.

Comments on decision problem from consultees

3.3 With respect to appropriate comparators to the biologics, The British Society for Paediatric and Adolescent Rheumatology (BSPAR) stated that 'best supportive care, if DMARDs are not tolerated' is not a valid comparator, because the efficacy of methotrexate over placebo is well established and no child who cannot tolerate methotrexate should be denied access to biologics. It also stated that a significant proportion of children with systemic-onset JIA follow a polyarticular course and these people would receive tocilizumab as a first line biologic to treat systemic onset JIA. BSPAR consider that the review should include systemic onset JIA. It also considered that the appraisal should include children with less than 5 joints affected but with bilateral sacroilitis because a high proportion will proceed to develop ankylosing spondylitis as adults,.

3.4 With respect to appropriate comparators, the manufacturer of abatacept considered that the most appropriate comparators for abatacept would be other biological treatments (rather than methotrexate) because people take abatacept after an anti-TNF inhibitor in the treatment pathway.

3.5 Also with respect to appropriate comparators, the manufacturer of etanercept stated that because the marketing authorisations substantially differ, this could lead to inappropriate comparisons outside of the license, and thought it was inappropriate to compare abatacept, adalimumab, etanercept and tocilizumab with each other. Several of the consultee companies did not think it appropriate to meta-analyse or indirectly compare abatacept, adalimumab, etanercept and tocilizumab because of differences in the populations and study designs for the main trials

providing evidence for the European Medicines Agency's regulatory decision.

4 Clinical-effectiveness evidence

4.1 The evidence presented in this section includes:

- Randomised Controlled Trial (RCT) data for abatacept, adalimumab, etanercept, tocilizumab in which the populations include people with polyarthritis which may include people with psoriatic arthritis, enthesitis-related JIA and systemic arthritis.
- Open label extensions of the RCTs (for adverse events)
- Single arm studies for people with enthesitis-related JIA and psoriatic arthritis which in these populations informed the regulatory decisions for adalimumab and etanercept.
- The data from the above studies were extracted from published studies identified by the Assessment Group in its systematic review and was supplemented by data reported in the company submissions. Additional information and comments provided by the companies on the strengths and limitations of the data are summarised at the end of this section.

4.2 The Assessment Group identified 1 randomised placebo controlled trial each for
abatacept (AWAKEN),
adalimumab (Lovell et al 2008),
etanercept (Lovell et al 2000) and
tocilizumab (CHERISH).
All 4 trials were multicentre and international, but only the tocilizumab CHERISH trial included people from the UK. All 4 trials had an open-label lead in phase, a randomised double blind withdrawal phase and an open-label extension phase. In the open label lead in phase all patients received the biological treatment, but only people who had an ACR pedi 30 response by the end of this phase entered the double blind withdrawal

phase of the trial and were randomised to either the biological drug or placebo. The length of the open label lead in phase and double blind phase differed between the trials:

- Abatacept, lead in phase 16 weeks, double blind phase 24 weeks
- Adalimumab, lead in phase 16 weeks, double blind phase 32 weeks
- Etanercept, lead in phase 12 weeks, double blind phase 16 weeks
- Tocilizumab, lead in phase 16 weeks, double blind phase 24 weeks (table 5).

4.3 The dosages of the study drugs in the 4 RCTs are summarised in table 5. The trials differed in the background medication people could take in either the placebo or intervention arms. The majority of people in the trials were treated with methotrexate in addition to the study drug, with the exception of the etanercept trial which did not permit concomitant methotrexate.

4.4 The eligibility criteria for the trials are summarised in table 5; these differed in terms of

- **Age** which ranged from a starting age of 2 years with toclizumab to 6 years with abatacept to a maximum age of 17 years,
- **Definition of polyarthritis symptoms** The adalimumab, etanercept and tocilizumab trials defined eligible people as needing to have at least 5 swollen joints and at least 3 joints with limited motion. By comparison, the abatacept trial defined people as needing at least 5 active joints with swelling or limited motion accompanied by pain or tenderness and active disease (at least 2 active joints and 2 joints with limitation of motion).
- **Previous treatments**
  - Abatacept: inadequate response to 1 or more DMARD including a biological agent;
  - Adalimumab: inadequate response to prior treatment with NSAIDs;
  - Etanercept: inadequate response to NSAIDs and methotrexate

  - Tocilizumab: inadequate response to or be intolerant of methotrexate and either never been treated with biologics or had discontinued for a specified minimum period.
- The abatacept trial excluded people with active uveitis

4.5 The baseline characteristics of the participants in the trials are summarised in table 6. The trials' populations differed in how long patients had JIA before entering the trial, and the relative proportions of people with different subtypes of JIA. The Assessment Group noted that the publications from the trials did not explicitly report the proportions of people who had polyarthritis JIA with systemic onset or enthesitis-related or psoriatic athritis.

Table 5: summary of included studies, table 10 page 43 assessment report

	Abatacept	Adalimumab	Etanercept	Tocilizumab
Study details	AWAKEN, Ruperto et al.[57-60] Multi-centre withdrawal RCT at 45 centres in Europe (not UK), Latin America & USA	Lovell et al. 2008[61-64] Multi-centre withdrawal RCT at 31 centres in Europe (not UK) & USA	Lovell et al. 2000[42;65-67] Multi-centre withdrawal RCT at 9 centres in Canada & the USA	CHERISH, Brunner et al.[68-76] Multi-centre withdrawal RCT at 58 centres in Australia, Europe (inc. UK), Latin America, Russia & USA
Study phases[1]	16-week open-label lead-in 24-week randomised double-blind withdrawal Open-label extension	16-week randomised open-label 32-week randomised double-blind withdrawal Open-label extension	12-week open-label 16-week randomised double-blind withdrawal Open-label extension	16-week open-label lead-in 24-week randomised double-blind withdrawal Open-label extension
Intervention[2]	Abatacept: n=60 Abatacept 10 mg/kg at about 28-day intervals for 24 weeks or until disease flare	Adalimumab /Methotrexate: n=38 Adalimumab 24 mg/m^2 BSA (to max. 40 mg) every other week for 32 weeks + MTX ≥10 mg/m^2 BSA/week	Etanercept: n=25 Etanercept 0.4 mg/kg twice weekly until disease flare or for 16 weeks	Tocilizumab: n=82 10 mg/kg <30kg BW, n= 16; 8 mg/kg <30 kg BW n=11; 8 mg/kg ≥30kg BW n=55
Comparator[2]	Placebo n = 62	Placebo/Methotrexate: n= 37 Placebo + Methotrexate ≥10 mg/m^2 body surface area/week	Placebo: n = 26	Placebo: n=84 10 mg/kg <30kg BW, n=15; 8 mg/kg <30kg BW n=13; 8 mg/kg ≥30kg BW n=56
Key inclusion criteria	Age 6-17 years Active[3] JIA (extended oligoarticular, polyarticular, RF+ve or RF-ve, systemic without systemic manifestations) Inadequate response or intolerance to ≥1 DMARD including biological agents ACR Pedi 30 for entry to randomised double-blind phase	Age 4-17 years Active[3] polyarticular-course JIA (any onset type) Inadequate response to NSAIDs ACR Pedi30 at week 16 for entry to double-blind withdrawal phase	Age 4-17 years Active[3] JIA Inadequate response to NSAIDs and methotrexate at doses of ≤10 mg/m^2 body surface area/week	Age 2-17 years Active[3] polyarticular course or extended oligoarticular JIA (RF+ve or RF-ve) for ≥6months. Inadequate responses to or intolerant of methotrexate. Either never treated with biologics or had discontinued for a specified minimum period

Table 6 Selected baseline characteristics of trial participants, table 12 page 49 of the assessment report

Baseline characteristics	Abatacept[57]		Adalimumab[61]		Etanercept[42]		Tocilizumab[68]		
	Abatacept (n=60)	Placebo (n=62)	Adalimumab (n=38)	Placebo (n=37)	Etanercept (n=25)	Placebo (n=26)	*TCZ 8 mg/kg <30kg (n=34)*[1]	*TCZ 10 mg/kg <30kg (n=35)*[1]	*TCZ 10 mg/kg ≥30kg (n=119)*[1]
Age, years; mean (SD)	12.6 (3)	12.0 (3)	11.7 (3.3)	10.8 (3.4)	8.9	12.2	*7.6 (2.71)*	*6.9 (3.02)*	*13.1 (2.78)*
Sex female, n (%)	43 (72)	45 (73)	30 (79)	30 (81)	19 (76)	15 (58)	*24 (71)*	*30 (86)*	*90 (76)*
Ethnicity white, n (%)	46 (77)	49 (79)	36 (95)	36 (97)	14 (56)	23 (88)	NR		
Black n (%)	5 (8)	4 (7)	0	0	3 (12)	1 (4)			
Hispanic n (%)	NR	NR	NR	NR	6 (24)	2 (8)			
Other	9 (15)	9 (15)	2 (5)	1 (3)	2 (8)	0			
Type of JIA									
Pauciarticular[2]					2 (8)	1 (4)	Eligible patients had RF +ve or RF -ve polyarticular-course JIA or extended oligoarticular JIA but provided no further detail.		
Persistent oligoarthritis n (%)	0	2 (3)	Described as 'polyarticular course' no further detail (This older nomenclature could have included patients who would now be defined as having ERA or PA)						
Extended oligoarthritis n (%)	9 (15)	7 (11)							
Polyarthritis (RF +ve) n (%)	14 (23)	12 (19)			14 (56)	17 (65)			
Polyarthritis (RF -ve) n (%)	26 (43)	28 (45)							
Systemic n (%)	11 (18)[3]	12 (19)[3]			9 (36)	8 (31)			
RF +ve, n (%)	19 (32)	12 (19)	10/37 (27)[4]	6/36 (17)[4]	4 (16)	8 (31)	*2 (6)*	*4 (11)*	*48 (40)*
Duration of JIA, years; mean (SD)	3.8 (3.7)	3.9 (3.5)	4.3 (4.1)	4.0 (3.5)	5.3	6.4	*3.5 (2.57)*	*3.4 (2.39)*	*4.7 (4.16)*

4.6 The primary outcome for all 4 trials was 'disease flare'. The definitions of disease flare were broadly consistent between the studies: a worsening of at least 30% or more in at least 3 of the six core (ACR Pedi) criteria for JIA, and an improvement of 30% or more in no more than 1 of the criteria, with some studies also defining flares based on global assessments and number of active joints. The outcome for analysis was time to flare, or proportion of people having a disease flare over the course of the double-blind phase of the trials. In all 4 trials the proportion of people experiencing flare was lower with the biological treatment than with placebo.

Table 7 disease flare during the randomised withdrawal phase, table 14 page 51 Assessment Report

Study (Length: Open label (OL), RCT1), Outcome	Intervention	Comparator	
Abatacept (4mo OL, 6mo RCT)	ABA (n=60)	PBO (n=62)	p value
Time to flare, median months	Not reached	6	0.0002
Disease flares, n (%)	12 (20)	33 (53)	0.0003
Disease flares, hazard ratio	0.31 (95% CI 0.16 to 0.59)		NR
Adalimumab (4mo OL, 8mo RCT)	ADA (n=38)	PBO (n=37)	p value
Disease flares, n/N (%)	14/ 38 (37)	24/37 (65)	0.02
Etanercept (3mo OL, 8mo RCT)	ETA (n=25)	PBO (n=26)	p value
Disease flare, n (%) Corticosteroid use at baseline3 Yes No	7 (28) 3/6 (50) 4/19 (21)	21 (81) 12/13 (92) 9/13 (69)	0.00312 0.05
Time to flare, median days	>116	28	p<0.001
Tocilizumab (4mo OL, 6mo RCTs)	TCZ (n=82)	PBO (n=81)4	Difference5 TCZ vs PBO (95% CI); p value
Proportion with JIA flare, n (%)	21 (25.6)	39 (48.1)	–0.21 (–0.35, -0.08); 0.0024

ABA, abatacept. ADA, adalimumab. ETA, etanercept. mo, months. NR, not reported. OL, open-label. PBO, placebo. TCZ, tocilizumab.

4.7 All 4 studies reported ACR Pedi 30, 50 and 70 responses , with all but the etanercept study also reporting ACR Pedi 90 responses. The abatacept and tocilizumab studies additionally reported the proportion of people with inactive disease over the course of the double blind withdrawal phase of the trial. Inactive disease was defined as: no joints with active arthritis, normal erythrocyte sedimentation rate (ESR) of 20 mm per hour or less, a

physician's global assessment (PGA) <10 on a 100 mm visual analogue scale. The tocilizumab study added the criterion for inactive disease of an absence of uveitis. The results are shown in table 8. People randomised to the technologies responded better than patients randomised to placebo and in most cut-offs, this difference was statistically significant.

Table 8, ACR paediatric responses relative to baseline, table 15 page 53 Assessment report

Study, Study (Length: OL, RCT), Outcome	Intervention	Comparator	
Abatacept[57] (4mo OL, 6mo RCT)			
ACR Pedi, n (%)[1]	ABA (n=60)	PBO (n=62)	p value
30	49 (82)	43 (69)	0.1712
50	46 (77)	32 (52)	0.0071
70	32 (53)	19 (31)	0.0185
90	24 (40)	10 (16)	0.0062
Inactive disease[2]	18 (30)	7 (11)	0.0195
Adalimumab[61] (4mo OL, 8mo RCT)			
ACR Pedi, %	ADA (n=38)	PBO (n=37)	p value
30	63	38	0.03
50	63	38	0.03
70	63	27	0.002
90	42	27	0.17
Etanercept[42] (3mo OL, 4mo RCT)			
ACR Pedi, n (%)[3]	ETA (n=25)	PBO (n=26)	p value
30	20 (80)	9 (35)	p<0.01
50	18 (72)	6 (23)	NR
70	11 (44)	5 (19)	NR
Tocilizumab[68] (4mo OL, 6mo RCT)			
ACR Pedi, n (%)	TCZ (n=82)	PBO (n=81)	Difference[4] TCZ vs PBO (95% CI); p value
30	61 (74.4)	44 (54.3)	0.09 (0.05, 0.33); 0.0084
50	60 (73.2)	42 (51.9)	0.20 (0.06, 0.34) ; 0.0050
70	53 (64.6)	34 (42.0)	0.22 (0.07, 0.37); 0.0032
90	37 (45.1)	19 (23.5)	0.21 (0.07, 0.35); NR
Inactive disease	30 (36.6)	14 (17.3)	0.18 (0.05, 0.32); NR

ABA, abatacept. ADA, adalimumab. D-B, double-blind. ETA, etanercept. mo, months. NR, not reported. OL, open-label. PBO, placebo. TCZ, tocilizumab.

4.8 With respect to health-related quality of life, only the abatacept trial reported quality of life data. There were no statistically significant differences in the physical or psychosocial summary scores from the

Childhood Health Assessment Questionnaire (CHAQ) between the abatacept and placebo arms of the trial (p=0.666 for physical summary score and p=0.056 for the psychosocial summary score).

4.9 With respect to pain, the abatacept, etanercept and tocilizumab trials reported change from pain at baseline to follow-up assessed using a visual analogue scale. In all 3 of these studies, pain improved more with biological treatment than with placebo, but the difference was statistically significant only in the tocilizumab study (table 18 page 56 assessment report).

4.10 With regard to the additional outcomes listed in the final scope issued by NICE, none of the studies reported on whether the biological treatments reduced the use of corticosteroid use, the incidence of uveitis or affected height and body weight.

4.11 The trials results included adverse event rates which occurred during the placebo controlled period and the open label extension period. During the placebo controlled period, people in the biologic and placebo arms experienced similar rates of adverse events.

- In the abatacept trial the most common class of adverse events in both treatment groups were ‘infections and infestations’ (44-45%).
- In the adalimumab trial, the only serious adverse event possibly related to the study drug was gastroduodenitis, occurring in 1 patient in the placebo group. The most common adverse events were related to injection site reactions (adalimumab 57 events in 3.8 patient-years; placebo 73 events in 4.0 patient years).
- In the etanercept trial, 2 patients who received etanercept needed hospitalisation for serious adverse events (1 for ‘depression and personality disorder’, and the other for gastroenteritis-flu syndrome). One patient withdrew after the first dose of etanercept because of urticaria (hives). 1 person in each study arm had injection-site reactions.

- In the tocilizumab trial the frequently reported adverse event in the tocilizumab trial was nasopharyngitis (17% people in the tocilizumab arm and 11% people in the placebo arm).

Serious adverse event rates in the extension phases of the trials were 5.6 per 100 patient years for abatacept; 7 (time period of extension unclear) for adalimumab; 39 per 318 patient years for etanercept and 11.1 per 100 patient years for tocilizumab.

Table 9, adverse events during double blind phase of trial, table 20 Assessment Report page 59

Study, Outcome	Intervention	Comparator	
Abatacept[57] (during 6-month DB period)	ABA (n=60)	PBO (n=62)	p value
Total serious AEs, n (%)	0	2 (3)	0.50
Total AEs,[1] n (%)	37 (62)	34 (55)	0.47
Adalimumab[61] (during 8-month DB period)	ADA (+MTX) (n=37; 15 Pt-yrs)	PBO (+MTX) (n=38; 18.3 Pt-yrs)	
Any AE, n of events (n of events per patient-year)	234 (12.8)	155 (10.3)	
Serious AEs, possibly related to study drug,[2] n of events (n of events per patient-year)	0	1 (0.1)	
AEs leading to the discontinuation of the drug, n	0	0	
Etanercept[42] (time period unclear unless stated below)	ETA (n=25)	PBO (n=26)	
Hospitalisation for serious AEs, n	2	0	
Injection-site reactions during the 4-month double-blind period, n	1	1	
Most common AEs - injection-site reaction, no. of events (no. of events per patient-year)	57 (3.8)	73 (4.0)	
Tocilizumab[68] (during 6-month DB period)	TCZ[4] (n=82)	PBO[4] (n=81)	
Serious AEs and AEs occurring ≥5% of patients, n (%)			
Duration in study (years)	32.33	27.41	
Patients with ≥1 AE	58 (70.7)	60 (74.1)	
Total no. of AEs[5]	147	141	
Rate of AEs per 100 patient-years	454.7	514.4	
Serious AEs			
Patients with ≥1 serious AE	3 (3.7)	3 (3.7)	
Rate of serious AEs per 100 patient-years	9.3	10.9	
Patients with ≥1 infectious serious	1 (1.2)	0	

AE			
Rates of infectious serious AEs per 100 pt-years	3.1	0	
AEs leading to study drug discontinuation	1 (1.2)[6]	1 (1.2)[7]	

ABA, abatacept. ADA, adalimumab. AE, adverse event. DB, double-blind. ETA, etanercept. MTX, methotrexate. no, number. PBO, placebo. Pt-yrs, patient years. NR, not reported. TCZ, tocilizumab.

Assessment Group's indirect comparison of trials of abatacept, adalimumab, etanercept and tocilizumab for polyarticular JIA

4.12 The Assessment Group indirect compared abatacept, adalimumab, etanercept and tocilizumab using placebo as a common comparator for people with JIA with a **polyarticular** course. The Assessment Group noted that its methodology was similar to that reported in Otten et al (2012) which had compared abatacept, adalimumab and etanercept but excluding tocilizumab . The Assessment Group identified limitations with the evidence base which included:

- **Size of network**. Data from only 1 trial available for each drug; small numbers of studies and small numbers of participants weaken evidence networks
- **Variation in proportion of sub-types of JIA in the included trials**. A third of the people in the etanercept trial had systemic JIA (outside the scope of this appraisal). The Assessment Group noted insufficient evidence from RCTs to estimate the effectiveness of biologics in psoriatic arthritis or enthesitis related arthritis because the trials did not report outcome data for these types of JIA even in trials which included people with these subtypes.
- **The duration of JIA** ranged from ~4 years to 6 years across the trials, and disease duration may be associated with response to treatment **Concomitant methotrexate**. In the abatacept, adalimumab and tocilizumab trials people could take methotrexate in addition to the

biologic DMARD (in proportions of patients varying from 74% to 100%). The etanercept trial did not allow the concomitant use of methotrexate.

- **Previous treatments**. A third of people in the abatacept and tocilizumab trials had received a biological treatment before the start of the lead-in phase of the trial. Nobody in the adalimumab trial had done so and the numbers of people who had received a prior biological treatment in the etanercept trial are unknown. The Assessment Group stated that it is unclear whether prior biologic treatment influences the effectiveness of subsequent biologic treatment.
- **Age of trial populations**. The mean age of the trials varied from around 7.5 years to 13 years. Age could modify the effect of treatment given the progressive nature of JIA.
- **Duration of double-blind randomised treatment phase** varied, from 4 months to 8 months. The Assessment Group stated that treatment duration may affect outcomes which are time dependent such as disease flare.

4.13 The results showed that there were no statistically significant differences between the 4 treatments (flare, ACR pedi response) (exception etanercept vs. tocilizumab for ACR Pedi 50). The wide confidence intervals reflected the heterogeneity of the trials. The Assessment Group noted that the results in the placebo groups may have differed from each other. For example, in the etanercept trial (where participants could not receive methotrexate and had had JIA for a longer time than other trials), the rate of flares in the placebo arm was 81% compared with 48% to 65% in the other trials. The Assessment Group concluded that the results showed that the 4 technologies had similar short term effectiveness and reported that its clinical advisors stated that ‘the data generally reflect clinical practice in that when used for the same indication in the same population effectiveness was likely to be similar’. The clinical advisers also said that for individual patents and for sub-groups any differences in

effects of each technology, if they exist, have not yet been captured by current trial data.

Table 10 indirect comparisons, Assessment report tables 26, 27 and 28 pages 69 and 70.

Disease flare	
Comparison	**Relative risk**
Etanercept vs adalimumab	0.61 (95% CI 0.27 to 1.38)
Etanercept vs abatacept	0.92 (95% CI 0.39 to 2.18)
Etanercept vs tocilizumab	0.65 (95% CI 0.30 to 1.43)
Adalimumab vs abatacept	1.51 (95% CI 0.72 to 3.15)
Adalimumab vs tocilizumab	1.07 (95% CI 0.56 to 2.04)
Abatacept vs tocilizumab	0.71 (95% CI 0.35 to 1.43)
ACR Pedi 50	
Comparison	Relative Risk
Etanercept vs adalimumab	1.87 (95% CI 0.77 to 4.53)
Etanercept vs abatacept	2.10 (95% CI 0.95 to 4.64)
Etanercept vs tocilizumab	2.21 (95% CI 1.01 to 4.84)
Adalimumab vs abatacept	1.12 (95% CI 0.65 to 1.96)
Adalimumab vs tocilizumab	1.18 (95% CI 0.69 to 2.02)
Abatacept vs tocilizumab	1.05 (95% CI 0.72 to 1.53)
ACR Pedi 70	
Comparison	Relative Risk
Etanercept vs adalimumab	0.98 (95% CI 0.33 to 2.87)
Etanercept vs abatacept	1.31 (95% CI 0.48 to 3.60)
Etanercept vs tocilizumab	1.49 (95% CI 0.57 to 3.85)
Adalimumab vs abatacept	1.34 (95% CI 0.65 to 2.79)
Adalimumab vs tocilizumab	1.52 (95% CI 0.79 to 2.92)
Abatacept vs tocilizumab	1.13 (95% CI 0.66 to 1.93)

Clinical evidence for etanercept for enthesitis-related JIA and psoriatic arthritis

4.14 Etanercept is licensed for treating enthesitis-related JIA and psoriatic arthritis. The CLIPPER trial was a **single arm** open-label multi-centre trial including children and adolescents with

- extended oligoarticular JIA (n = 60 age 12-17 years),
- enthesitis related arthritis (n= 38, age 12-17 years) and
- psoriatic arthritis (n = 29 age 12-17 years . The study had 2 parts, 1) a

12 week phase, and 2) a 96 week extension phase. The trial included people with: ≥ 2 active joints (swollen or limitation of motion with pain or tenderness); history of intolerance or unsatisfactory response to at least a 3-month course of ≥ 1 DMARD or, only for enthesitis related arthritis, unsatisfactory response to at least a 1 month course of ≥ 1 NSAID (i.e people with enthesitis-related arthritis did not need to have prior methotrexate). People with uveitis, other rheumatic diseases, or who had received a previous biological treatment were excluded. People in the trial could have 1 DMARD, 1 oral corticosteroids and 1 NSAID at the same time as etanercept. Etanercept was given 0.8 mg/kg once weekly (maximum dose 50 mg/kg). The baseline characteristics of this trial are reported in table 34 page 87 of the assessment report.

4.15 The primary outcome at week 12 was ACR Pedi 30 which 83% of patients with enthesitis-related JIA, 93% in people with psoriatic arthritis and 90% people with extended oligoarthritis achieved. The proportion of people with inactive disease at week 12 was 17% in the enteritis related arthritis group, 7% in the psoriatic arthritis group and 12% in the extended oligoarthritis group. The proportion of people having inactive disease was greater at week 96, 29% of people in both the enthesitis-related arthritis group and the psoriatic arthritis group had inactive disease and 37% of people in the extended oligoarthritis at this point. The Assessment Group commented that patients in the enthesitis related group appeared to have the greatest benefit from etanercept therapy at 12 weeks but at 96 weeks the subgroups had a similar response. All subtypes improved from baseline the Child Health Assessment Questionnaire (a measure of quality of life), pain and number of active joints. People with psoriatic arthritis had an improvement in the body surface area covered by psoriasis (48.2% improvement) and in the physician's global assessment (39.6% improvement). See tables 35 and 36 on pages 88 and 89 of the assessment report for these results in full.

Clinical evidence for adalimumab for enthesitis-related arthritis

4.16 The Assessment Group noted an ongoing trial of adalimumab in people with enthesitis-related arthritis has to date published only abstracts. Data from this trial was used by the European Medicines Agency to extend the MA for adalimumab to cover enthesitis related arthritis. The summary of product characteristics for adalimumab states: The safety and efficacy of adalimumab were assessed in a multicentre, randomised double-blind study in 46 people (aged 6-17 years old) with moderate enthesitis-related arthritis. Patients were randomised to receive either 24 mg/m2 body surface area (BSA) of adalimumab up to a maximum of 40 mg, or placebo every other week for 12 weeks. The double-blind period was followed by an open-label (OL) period during which patients received 24 mg/m2 BSA of adalimumab up to a maximum of 40 mg every other week subcutaneously for up to an additional 192 weeks. The 12 week results are reported in table 13.

Table 11, 12 week results (assessment report table 30 page 81)

Primary outcome[1]	ADA (n=31)	PBO (n=15)	p value
Active Joint Count, % change from baseline at week 12	-62.6 (59.5) (median percent change -88.9%)	-11.6 (100.5) (median percent change -50.0%)	p=0.039
Secondary outcomes, change from baseline,[2] mean (SD)			
Number of enthesitis sites (0-35)	-4.4 (6.2)	-2.7 (5.0)	NS
Tender joint count (0-72)	-7.9 (8.3)	-4.5 (9.0)	NS
Swollen joint count (0-8)	-3.5 (5.6)	-2.4 (4.7)	NS
ACR Pedi Response,[3] (n, %)			
ACR Pedi 30 responder	21 (67.7)	10 (66.7)	NS
ACR Pedi 50 responder	20 (64.5)	7 (46.7)	NS
ACR Pedi 70 responder	16 (51.6)	4 (26.7)	NS

ADA, adalimumab. PBO, placebo. SD, standard deviation.
[1] Presumed mean and SD, but not specifically stated.
[2] Last observation carried forward.
[3] Analysed with non-responder imputation.

Clinical evidence for anti-TNF inhibitors for treating uveitis

4.17 The Assessment Group discussed the evidence for the effect of biological treatments on uveitis. It noted 2 systematic reviews by Simonini et al 2014 and Cordero-Coma et al. 2013 and commented that these reviews included predominantly observational studies relating to using adalimumab, etanercept and infliximab. The Assessment Group reported the authors' concluded that adalimumab was associated with better outcomes than etanercept, but considered these conclusions to be highly uncertain. This discussion is reported in section 4.4.2 on pages 91-92 of the assessment report. The Assessment Group noted that the NHS interim commissioning policy states that etanercept should not be used in people with JIA and uveitis. The Assessment Group also noted that there are 2 ongoing trials (SYCAMORE, ISRCTN10065623; ADJUVITE, NCT01385826) assessing adalimumab in patients with JIA and uveitis..

Company submission comments on clinical effectiveness data

4.18 Pfizer, the manufacturer of etanercept, stated that the substantial differences in the marketing authorisations of the biologics may lead to inappropriate comparisons outside of their licenses. It considered that any

sort of meta-analysis or indirect comparison is inappropriate because of differences between the 4 RCTs in their populations (e.g. age, disease, subtype of arthritis, and treatment history), trial design, evolution of licenses. In addition to presenting data from the CLIPPER trial (sections 4.14-4.15 of this document), it also reported outcomes from registry and observational studies which showed over the long term around 50% of people taking etanercept have inactive disease. An Italian registry study showed that during the first year of treatment with etanercept, patients with JIA showed a reduction in radiographic disease progression. Pfizer further stated that results from the British Society of Paediatric and adolescent Rheumatology etanercept cohort study has shown that etanercept was associated with improved growth over the first 2 years.

4.19 BMS, the manufacturer of abatacept, discussed the results of the AWAKEN trial in its submission (sections 4.2-4.11). The company stated that 2 small single arm studies (n=10 and 21 respectively) had assessed whether abatacept improved uveitis in people who had not responded to an anti-TNF inhibitor, had conflicting conclusions.

4.20 Roche, the manufacturer of tocilizumab presented results from the CHERISH trial (sections 4.2-4.11). It also presented results from a single arm study of tocilizumab in a Japanese population.

4.21 AbbVie, the manufacturer of adalimumab presented results from the DE038 trial (sections 4.2-4.11) and the M11-328 trial in paediatric patients with enthesitis related arthritis (section 4.16). It also presented results from study M10-444 which was a multicentre open label single arm trial with a primary objective to evaluate the safety and efficacy of adalimumab in 32 patients aged 2 to 4 years and patients older than 4 years weighing less than 15 kg. As the Assessment Group had done, AbbVie discussed the available data for the effectiveness of adalimumab in people with uveitis. AbbVie also stated it was inappropriate to compare the data from the 4 trials of abatacept, adalimumab, etanercept and tocilizumab.

5 Patient experience

5.1 A patient expert described her experience of having JIA following a diagnosis of systemic JIA at 2 years of age. She explained that their JIA was very aggressive and because the treatment options were limited at that time they developed joint damage early on. She also experienced pain which was so severe they were prescribed medicine to help her sleep. She said that the prednisolone treatment they received had a bad taste and methotrexate caused her to have nausea. She commented that intra-articular corticosteroid injections can be very effective but also can be painful and evasive. Furthermore she had experienced complications of long-term (15 year) steroid use. She further explained that the condition affected their schooling because of numerous hospital appointments. It also affected her social interactions because of tiredness and not being able to do physical activities. JIA further affected her self-esteem because of having a feeling of being different, having to wear orthopaedic shoes and calipers and feeling the need to wear clothing to cover up swollen joints. The patient expert said that as an adult, she is now in remission, but have joint deformities caused by the aggressive JIA in childhood. She said that she still needs surgery, has gastro-oesphageal reflux and her mental health has been affected. The patient expert stated that the most important outcome is avoiding joint damage. The patient expert emphasised that JIA can have a large impact not only on the patient, but on the family too because of hospital visits, interruption to schooling and the emotional impact of having a child in distress.

6 Cost-effectiveness evidence

6.1 2 of the companies submitted a cost analysis, 1 a cost effectiveness analysis and 1 stated that because of the data limitations they considered it inappropriate to do so. The nature of the analyses were:

- BMS (abatacept) presented a cost minimisation analysis of the costs (drug and resource) of abatacept, adalimumab, etanercept and

tocilizumab for people starting treatment at 12 years and continuing until 18 years (longer time horizons of 10 and 20 years were assessed in scenario analyses). A cost minimisation approach assumes the clinical effectiveness and utility associated with each technology is the same and models only the costs.

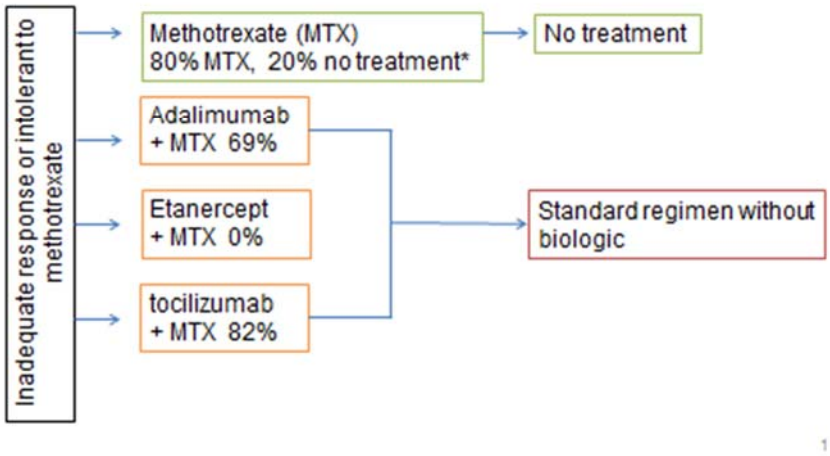
- AbbVie (adalimumab) did not present any cost analyses because it considered the available data would not allow it to carry out a robust cost effectiveness analysis. It described what it considered to be the key factors to be addressed when carrying out a cost effectiveness analysis
- Pfizer (etanercept) did not present a cost effectiveness analysis, but presented an analysis of the drug costs for adalimumab, etanercept and tocilizumab.
- Roche (tocilizumab) presented an economic model which it used to estimate the cost effectiveness of tocilizumab compared with adalimumab only

In this document, the Assessment Group model and results are presented in sections 6.2-6.12; a comparison of the Assessment Group's model and the companies' assumptions and modelling results is presented in sections 6.13-6.18. The companies' discussions of the limitations of carrying out a cost-effectiveness analysis are presented in section 6.19.

6.2 The Assessment Group developed 2 Markov models. In the first, the Assessment Group modelled a population with JIA who had had an inadequate response to, or did not tolerate, methotrexate; this represented people who would receive their first biologic option ("**1st biologic model"**). The Assessment Group deemed it necessary to have a second model because the marketing authorisation for abatacept states that abatacept should be taken **after** an anti-TNF inhibitor. In the "**2nd biologic model"**, the Assessment Group modelled a population with JIA who had and inadequate response to, or did not tolerate, methotrexate and who had previously received a TNF alpha inhibitor (etanercept); this

represented people who would receive their 2nd biologic option. The Assessment Group stated that the RCT and registry data used to inform the modelling came from mixed populations with predominantly polyarticular course JIA and there was insufficient evidence to model enthesitis-related and psoriatic subtypes of JIA separately. In both models, the average age of the modelled population was 11 (to reflect the clinical trials [see section 4.2-4.11]). The Assessment Group modelled the population's height and weight to be the same as the general UK population. The models had a 30 year time horizon to capture the costs and benefits of treating paediatric patients, given that there is uncertainty surrounding how well patients with JIA do during adulthood. The Assessment Group tested shorter and longer time horizons in sensitivity analyses. Consistent with the NICE reference case, the model used a discount rate of 3.5% and the perspectives were those of the NHS and personal social services. The model cycle length was 3 months.

1st biologic model



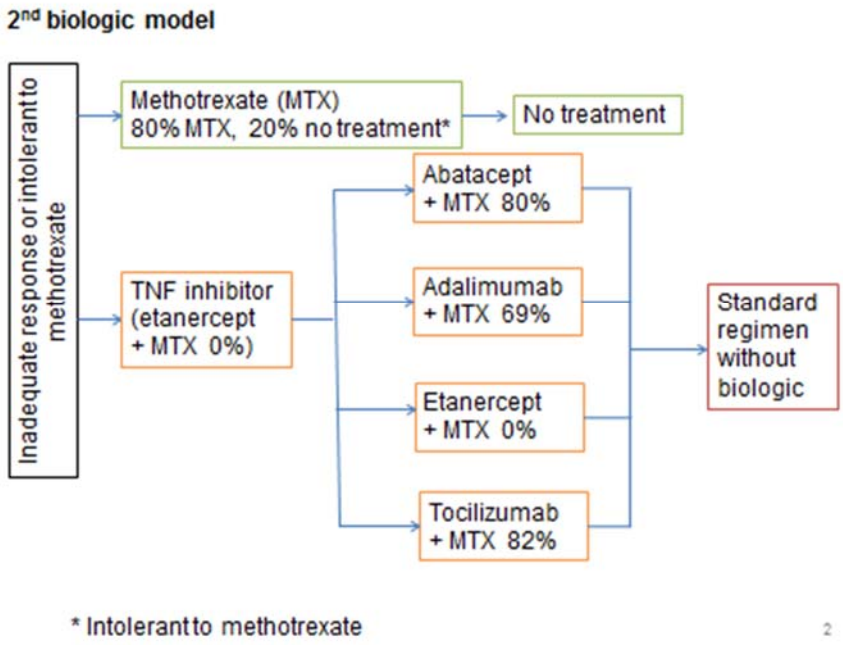


Figure 2, treatment sequences modelled by assessment group

6.3 To determine the costs and benefits for people taking their first biological treatment, the Assessment Group used the **1st biologic model** to compare adalimumab, etanercept and tocilizumab to methotrexate or to no treatment (for 20% people assumed intolerant to methotrexate). In the base case the Assessment Group assumed that when people stop their first biological treatment they do **not** switch to another biological treatment. The Assessment Group used the **2nd biologic model** to determine the costs and benefits of abatacept, adalimumab, etanercept, tocilizumab and methotrexate for people who had already had an anti-TNF inhibitor (assumed to be etanercept based on clinical advice to the Assessment Group). After their second biological treatment, the Assessment Group again assumed that people do **not** switch to another biological treatment. The Assessment Group explored a sequence of 3 biologic treatments in sensitivity analyses. It assumed that 80% of people receiving abatacept, 69% of people receiving adalimumab, 0% of people receiving etanercept and 82% of people receiving tocilizumab had

concomitant methotrexate. The proportions of people receiving methotrexate were based on trial and registry data.

6.4 Both models had 3 health states: "on-treatment", "off-treatment" , and "death". Based on clinical advice the Assessment Group assumed that if people remitted while on-treatment, clinicians would be reluctant to stop the treatment and people would continue to take it. In a sensitivity analysis, the model had an additional health state reflecting "off-treatment remission" to test the effect of stopping treatment on remission, (see section 6.10). People stayed on treatment unless they died or stopped treatment because of adverse effects or loss of drug efficacy. In the short term (3-month cycle) the Assessment Group obtained rates of discontinuation from the open-label lead-in period in each of the 4 RCTs (4.2-4.11). The Assessment Group obtained the discontinuation rates after that time from Tynjala et al. (a retrospective observational study of patients with JIA in Finland taking etanercept or infliximab with a 4-year follow-up). The Assessment Group did not use the discontinuation rates from the RCT phase of the trials because people could stop for reasons other than adverse events of loss of drug efficacy, such as withdrawing consent. The Assessment Group noted that because there were few studies for the biological treatments, it assumed that discontinuation rate were the same for each biological treatment. The Assessment Group assumed that when people stop treatment they switch to a non-biological treatment.

Figure 3 schematic of the Assessment Group model, Assessment report figure 8 page 121

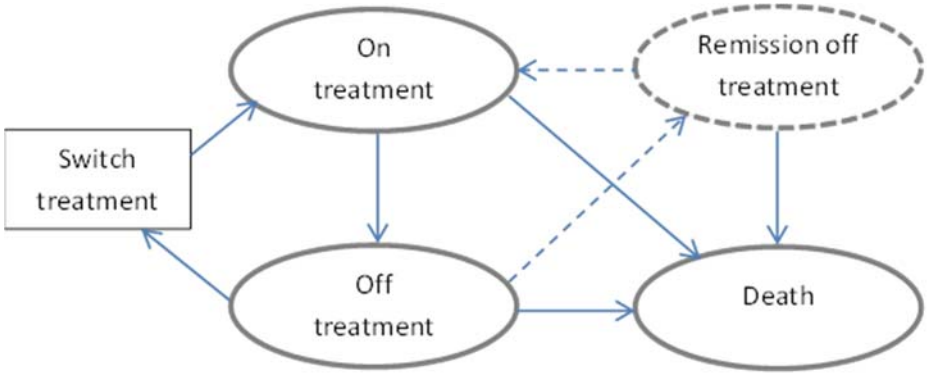


Table 12, discontinuation rates in the model, modified from Table 50 assessment report page 124

1st cycle (3-months) data from open label lead in phase of each trial				
	Abatacept[57]	Adalimumab[61]	Etanercept[42]	Tocilizumab[68]
Adverse events	0.5%	1.8%	1.4%	1.6%
Loss of efficacy	9.5%	3.5%	2.9%	8.0%
Total discontinuation	10.0%	5.3%	4.3%	9.6%
Subsequent cycles				
Adverse events	7% over 4 years			
Loss of efficacy	28% over 4 years			

6.5 In both models, to estimate the risk of flares, the Assessment Group weighted the rate of disease flares for people taking methotrexate from the placebo arms of the abatacept, adalimumab and tocilizumab trials, converting them to a 3 month risk (the Assessment Group excluded the placebo arm of the etanercept trial because no one received methotrexate). Then, to estimate the risk of flare for each biological treatment, the Assessment Group multiplied this average risk of flare on methotrexate by the relative risk for each biological treatment compared with placebo in its respective clinical trial.

Table 13 risk of disease flare, table 49 page 123 of the assessment report

Disease Flare	Risk of flare per cycle	Source

Methotrexate	0.25	Ruperto et al.[57], Lovell et al. 2008[61] Brunner et al.[68]
Abatacept	0.09	Ruperto et al.[57]
Adalimumab	0.14	Lovell et al. 2008[61]
Etanercept	0.09	Lovell et al. 2000[42]
Tocilizumab	0.14	Brunner et al.[68]

6.6 Because none of the 4 RCTs had collected data which the Assessment Group could use to derive utility values, it carried out a systematic review to identify generic (not disease-specific) preference-based health related quality of life studies in people with JIA who received a biological treatment. The Assessment Group obtained utility values from a Dutch study of the ABC registry (Prince et al 2011), which had measured utility with the Health Utility Index-3 (HUI-3). This registry included people with polyarticular course JIA which had not responded to maximum-dose methotrexate. The Assessment Group assumed that the utility value for a person taking methotrexate only or a person who had stopped biological treatment was the same as for a person before taking etanercept in Prince et al. 2011. The Assessment Group assumed that a person's utility value while taking a biological treatment is the same for all biological treatments, and that utility increases over time. The Assessment Group assumed that having a disease flare lowers utility and would recover within 3 months (one-model cycle). When the Assessment Group annualised this disutility, it estimated 0.03 per flare. The Assessment Group did not apply a disutility to adverse events. The Assessment Group acknowledged that people who care for someone with JIA would have a lower quality of life, but noted there were no published data. The Assessment Group did not include a caregiver disutility in its base case, but did explore this in scenario analyses (see section 6.10).

Table 14, utility values, table 51 page 125 assessment report

HRQoL utility values	Per year	Source
No biologic treatment (including people receiving	0.53	Prince *et al.*[123]

methotrexate only and people who have discontinued treatment with a biologic)		
Treatment with first line biologic, 0-3 months	0.53	Prince *et al.*[123]
Treatment with first line biologic, 3-15 months	0.69	Prince *et al.*[123]
Treatment with first line biologic, 15-27 months	0.74	Prince *et al.*[123]
Treatment with first line biologic, 27+ months	0.78	Prince *et al.*[123]
Treatment with second and third line biologic	0.74	Prince *et al.*[123]
Disutility for disease flare	0.03	Assumption

6.7 The drug costs and dosing regimens of the biological treatments are as listed in table 1 of this document. Abatacept and tocilizumab have confidential patient access schemes (PAS). Because of this the Assessment Group provided cost effectiveness results using the NHS list price in its assessment report and provided the results incorporating the PAS for abatacept and tocilizumab in a confidential appendix to its report. Abatacept and tocilizumab had an additional administration cost of £154 because these are administered intravenously rather than subcutaneously. The dose of methotrexate was 10 to 15 mg/m^2 administered subcutaneously or orally once weekly. The Assessment Group assumed that the number and cost of GP and hospital visits and hospital tests, and the resource costs off- and on-treatment (£724 per cycle) were the same irrespective of treatment. The cost of inpatient treatment per disease flare was £429.97. The Assessment Group commented that the most commonly occurring serious adverse events in people with JIA were 'infections and infestations'. The Assessment Group estimated an inpatient cost of £1,533 for treating infections from averaging across health resource group codes. The proportion of people having adverse events in the 1st cycle is given in table 55 page 129 of the assessment report, and resource use costs are presented in table 54 on page 127.

6.8 The Assessment Group presented the results of its base case for:

- People receiving their first biological treatment after methotrexate
- People receiving a biological treatment after methotrexate and an anti-TNF inhibitor

The Assessment Group presented the deterministic results as pairwise comparisons with methotrexate rather than as a fully incremental analysis. The probabilistic results were similar to the deterministic results (table 73 and 74 on pages 139 and 140 of the assessment report; the with-PAS results are reported in tables 7 and 8 of the confidential appendix, pages 5 and 6).

Table 15 assessment group deterministic base case results , Assessment report tables 58 and 61 pages 130 and 132)

	Costs, £	QALYs	Incremental costs	Incremental QALYs	**List price ICER** (£ per QALY gained) versus methotrexate [a]	**PAS ICER** (£ per QALY gained) versus methotrexate with PAS
Population receiving first biological DMARD after methotrexate						
Methotrexate only	£67,534	9.37				
Adalimumab	£145,047	11.40	£77,513	2.0	£38,127	£38,127
Etanercept	£134,868	11.44	£67,334	2.1	£32,526	£32,526
Tocilizumab	£150,530	11.52	£82,995	2.1	£38,656	[redacted]
Population receiving a biological DMARD after methotrexate and an anti-TNF inhibitor						
Methotrexate only	£67,534	9.37				
Abatacept	£203,276	12.80	£135,742	3.4	£39,536	[redacted]
Adalimumab	£183,387	12.65	£115,853	3.3	£35,284	£35,284
Etanercept	£179,580	12.67	£112,045	3.3	£33,948	£33,948
Tocilizumab	£194,263	12.76	£126,728	3.4	£37,363	[redacted]
[a] Results presented compared to methotrexate; no incremental analysis presented. Note: Abatacept was not included in this analysis as the marketing authorisation is not for first line biologic DMARD						

6.9 The Assessment Group carried out one-way deterministic sensitivity analyses when taking adalimumab, abatacept and tocilizumab as a 1st line biologic and when taking abatacept as a 2nd line biologic (tables 62 to 65

on pages 132 to 135 of the assessment report). For all 4 technologies, the key drivers of the ICERs were the utility values (particularly over the long-term) and the discounting rates.

6.10 The Assessment Group carried out a series of scenario analyses. The Assessment Group presents results from the 1st line model only (with the exception of the scenario changing the starting age in which it presents the results from both models). All of the scenarios decreased the ICER for each biologic treatment compared with methotrexate. The scenarios included:

- People discontinuing because of improvement and entering a 'remission off treatment' health state. In different analyses, the Assessment Group assumed that once in remission, relapse rates were either 67% (Baszis et al 2011) or 40% (Wallace et al 2005). The Assessment Group assumed that no one stops treatment with methotrexate if this is their only treatment, because few patients on methotrexate would be in remission.
- Health state costs. The Assessment Group assumed the health state costs per cycle to be £589.51 and £408.91 for the off-treatment and on-treatment health states respectively (compared to £724 for both in the base case).
- Used the discount rates that had been used in NICE appraisal of etanercept. The previous NICE appraisal of etanercept used a discount rate of 6% for costs and 1% for benefits (which the NICE reference case included at that time; now NICE recommends 3.5% for both).
- Applying a disutility for caregiver burden. The estimates came from Kuhlthau et al. 2010 (which assessed the utility of caregivers of children with activity limitations) and Gani et al. 2008 (which assessed utility of caregivers of people with highly active relapsing remitting multiple sclerosis).
- 3 lines of biologic therapy. The Assessment Group compared a sequence of etanercept --> adalimumab --> tocilizumab and

etanercept-->adalimumab -->abatacept with methotrexate only. The Assessment group stated that these sequences reflected the sequence of treatments used in clinical practice in England.

- Modelled population entered at age 6 rather than 11. This scenario was carried out because people aged 6 are eligible for all 4 biologic treatments.

People with remission can stop treatment (1st biologic model)					
	Remission off treatment (per cycle)	Relapse rate	ICER (£/QALY) versus methotrexate		
			Adalimumab	Etanercept	Tocilizumab (+PAS)
Base case	0.00%		£38,127	£32,526	£38,656 [redacted]
Baszis et al.[160]	7.80%	67%	£33,744	£28,580	£34,214 [redacted]
Tynjala et al.[145]	0.66%	40%	£37,512	£31,970	£38,028 [redacted]
Health state costs from Prince and colleagues (1st biologic model)					
	Assumption	Cost	ICER (£/QALY) versus methotrexate		
			Adalimumab	Etanercept	Tocilizumab
Base case			£38,127	£32,526	£38,656 [redacted]
Prince et al			£35,214	£29.691	£35,767 [redacted]
Disutility for caregiver burden included (1st biologic model)					
	Disutility for caregivers		ICER (£/QALY) versus methotrexate		
	On biologic	Off biologic	Adalimumab	Etanercept	Tocilizumab
Base case	0.000	0	£38,127	£32,526	£38,656 [redacted]
Higher disutility (Kuhlthau et al. 2010)	-0.035	-0.07	£33,436	£28,619	£33,933 [redacted]
Lower disutility (Gani et al. 2008)	-0.010	-0.02	£36,658	£31,305	£37,178 [redacted]
Starting age in models (results given for 1st and 2nd biologic models)					
1st biologic	Age	ICER (£/QALY) versus methotrexate			
		Abatacept	Adalimumab	Etanercept	Tocilizumab
Base case	11	Na	£38,127	£32,526	£38,656 [redacted]
scenario	6	na	£38,124	£26,173	£32,993 [redacted]

2nd biologic					
Base case	11	£39,536 [redacted]	£35,284	£33,948	£37,363 [redacted]
scenario	6	£33,234 [redacted]	£31,383	£38,895	£31,961 [redacted]
Discount rates used in TA35 applied (6% for costs 1% for benefits) 1st biologic model					
			Costs	QALYs	ICER (£/QALY)
Methotrexate			£51,494	12.96	
Etanercept			£107,200	15.53	£21,718
Three lines of biologics					
			Costs	QALYs	ICER (vs. methotrexate)
Methotrexate			£67,534	9.47	-
Etanercept, adalimumab, tocilizumab			£207,565	13.16	£36,982 [redacted]
Etanercept, adalimumab, abatacept			£212,562	13.17	£38,152 [redacted]

6.11 The Assessment Group noted that there is a subgroup of people with JIA and uveitis, but there were insufficient data to consider this subgroup separately in a cost-effectiveness analysis. It noted that the prevalence of uveitis in JIA is between 8-30%, and is particularly common in children with early onset JIA (mean age of onset 3-5 years). The NHS England interim commissioning policy states that infliximab or adalimumab combined with methotrexate are widely used worldwide to treat refractory uveitis, but that etanercept is not used. The Assessment Group noted that the utility data used in its model was derived from the HUI3 generic preference instrument which has a vision domain. However, because the Assessment Group assumed on-treatment utility is the same across biological treatments, the utility value it chose for the model does not capture the effect on uveitis . The Assessment Group stated that if one includes vision loss with JIA, then adalimumab will be more cost effective in JIA patients with uveitis than without uveitis. Also if most of the costs related to uveitis relate to managing it (as stated in the clinical commissioning policy), then any reduction of these costs because of

improving vision would further improve cost effectiveness of adalimumab in the sub-group of patients with uveitis.

6.12 The Assessment Group noted that its model did not account for disease progression in terms of joint damage. Joint damage may lessen physical function and quality of life into adulthood, and may require joint surgery. There were no available data to determine whether abatacept, adalimumab, etanercept and tocilizumab reduce long-term disease compared with methotrexate or each other, but the Assessment Group noted that in recent decades there has been an increase in the use of immunomodulatory agents and a corresponding decrease in end-stage joint damage. The Assessment Group did not have evidence to document that the patients who received the biologicals were the same people who experienced fewer complications. The Assessment Group stated that if biologic treatments reduced long-term damage to a greater extent than methotrexate then the ICERs would be lower.

Company submissions

Roche cost effectiveness model comparing tocilizumab with adalimumab.

6.13 Roche used a Markov model. The model had a 6 month cycle length with half-cycle correction and runs over a 25 year time horizon. Roche applied a discounting rate of 3.5% per annum. Roche assumed the study population was the same as the trial population in CHERISH which compared tocilizumab with placebo (see sections 4.2-4.11), with a starting age of 11 years. The model had 3 health states “uncontrolled disease or off-treatment”, “on treatment” and “dead”. Patients were modelled to start with uncontrolled disease and move on to first line treatment and once patients had exhausted all lines of treatment to move back into the uncontrolled disease health state. Death was the absorbing health state.

6.14 Roche used the model to compare tocilizumab with adalimumab only because 1) it considered that ‘no therapy’ is not an option because biological treatments are the current standard of care in the UK, 2) it

would be unlikely that patients who have already had an inadequate response to methotrexate would be rechallenged with methotrexate; 2) it considered only the trials of tocilizumab and adalimumab are similar enough to compare. In an exploratory analysis, the company compared tocilizumab with etanercept which Roche assumed was equally effective to adalimumab.

6.15 Unlike the Assessment Group's model, the Roche used ACR Pedi response instead of flare as the main measure of clinical effectiveness. The probability of stopping treatment depended on the extent of response. Roche based these rates of stopping treatment on data for etanercept from the Dutch Arthritis and Biologicals in Children (ABC) register. Roche assumed that people with no response (JIA ACR Pedi <30) have a 6-month discontinuation rate of 0.1260; people with a moderate response (JIA ACR Pedi >30 and <70), a 6 month discontinuation rate 0.09; and people with a good response (JIA ACR Pedi ≥70) have a 6 month discontinuation rate 0.042. Roche assumed that 1% of patient die every 6 months.

6.16 Roche used the same time-dependent utility values from Prince et al. 2011 as chosen by the Assessment Group. Roche incorporated a rate of serious infections (based on an average across biological treatments) in the model (2.18% over a 6 month period), and, similar to the Assessment Group, modelled the cost of infections and did not apply a disutility. The costs of administration were similar in the Roche and in the Assessment Group's models.

Table 16 A comparison of the Roche and Assessment Group modelling assumptions

	Roche model	Assessment group model
Model population starting age	11 years	
Time horizon	25 years	30 years

Cycle length	6 months (1/2 cycle correction)	3 months
Discontinuation rates	Dependent on response 12.6%/cycle (worst response); 4% best response	Dependent on treatment Adalimumab 5.3% in 1st cycle; tocilizumab 9.6% in 1st cycle. 7%/ 4 years for adverse events; 28%/4 years for loss of efficacy subsequent cycles
Disease flare rate modelled	No	Yes
Adverse events (infections)	2.18%/cycle	Adalimumab 1.75%/cycle; Tocilizumab 1.60%/cycle
Cost per admin	Adalimumab (SC) £6.10 if child, £3.05 if young person; tocilizumab (IV) £152.24	Adalimumab £0; tocilizumab £154
Cost of adverse events	Average cost per admitted patient £3273	£1533
Resource costs	£1,591/cycle off treatment; £912.33/cycle on treatment	£724/cycle on or off treatment
Cost per flare	n/a	£429.97
Utility values	Time dependent utility values from Prince et al 2011. No disutility for adverse events. Assessment group had disutility for flare.	

6.17 The Assessment Group stated that it corrected some errors in the Roche model by applying the off treatment utility values when patients finished the first-line biologic treatment and assigning the 6-month utility value to each cycle. In addition the Assessment Group reduced the mortality rate to 0.03% per cycle to reflect that of the general population. The company presented its results with and without concomitant methotrexate. The with-methotrexate results are presented in table 17. Tocilizumab was less costly and less effective than adalimumab.

Table 17 A comparison of the Roche and Assessment Group model results

Roche results (adalimumab and tocilizumab taken with methotrexate)		
	adalimumab	tocilizumab
Total QALYs	18.76	18.72
Total costs	£81,827	£70,707

Roche model with assessment group amendments		
Total QALYs	10.10	10.05
Total costs	£95,761	£83,593
Assessment group base case results for adalimumab and tocilizumab 1st biologic model (with PAS)		
Total QALYs	11.40	11.52
Total costs	£145,047	£150,530 ([redacted])

BMS and Pfizer cost analyses

6.18 Both BMS (abatacept) and Pfizer (etanercept) presented analyses of only costs rather than cost effectiveness. BMS presented undiscounted and discounted costs over 6 years (from age 12 to 18), including both drug costs and administration costs. The administration costs were £154 for abatacept and tocilizumab and £3.05 for adalimumab and etanercept. BMS also presented results for a 10 and 20 year time horizon. BMS applied a patient access scheme for abatacept but not for tocilizumab which is confidential (please see BMS submission tables 12, 13 and 16 on pages 45 and 48 of the BMS submission). Pfizer presented the annual costs by age (2 to 17 years) of a person treated with etanercept, adalimumab or tocilizumab. Pfizer assumed that the administration costs of tocilizumab as £178.83 per infusion, but did not state whether it had applied the PAS discount for tocilizumab. Please see table 32 page 157 of the Pfizer submission for these results.

Comments from companies on feasibility of making an economic model to assess the cost effectiveness of abatacept, adalimumab, etanercept and tocilizumab for JIA

6.19 The companies drew attention to the following points:

- **Utility values**. BMS, AbbVie and Pfizer noted the lack of suitable quality of life data (using a preference based measure) in the trials to calculate utility values. They noted that Prince et al. 2011 had collected HUI-3 data and CHAQ (child health assessment questionnaire) data, but mapping this to EQ5D would cause problems because of the small number of patients in Prince et al. 2011(n=46). They also noted that

using data from an adult population or people with rheumatoid arthritis to map utility values has not been validated.

- **Lack of data on long term clinical outcomes and complications**. There are uncertainties around the natural course of the disease. The costs and benefits of avoiding complications such as joint surgery, and eye problems should be taken into account. AbbVie suggested that between 7-28% of patients have joint surgery, and 9-65% have eye surgery. Costs of impaired vision and blindness should also be included in the modelling but data were limited in the UK.
- **Transition between child an adult services and an appropriate time horizon**. Because JIA can continue into adulthood, a time horizon beyond age 17 may be needed. AbbVie noted that there will be administration costs associated with transitioning between child and adult services.
- **Difficulties in comparing the clinical effectiveness of biological treatments with each other.** The companies noted the difficulties in comparing the clinical effectiveness of the biological treatments because of the study sizes, differences in trial populations and the marketing authorisations of the technologies.

Comments from consultees on assessment report

6.20 Roche (tocilizumab) commented that using disease flare as the main measure of clinical effectiveness in the economic modelling was a problem. It noted that disease flare does not provide enough information on severity and JIA's impact on a patient's condition. Using flare as the main outcome will underestimate the benefits of treatments that achieve sustained disease improvement. Roche also noted that the utility a person experiences while having a flare may depend on the severity of the flare rather than there being a fixed disutility associated with a flare as assumed by the Assessment Group. Roche considered that ACRpedi response combined with rates of discontinuing treatment better reflects the impact of each treatment on the patient's condition. AbbVie

(adalimumab) commented that each trial defined disease flare differently. AbbVie further commented that it was not clear where the Assessment Group's obtained the cost of flare (£429.27), and presented alternative estimates based on Health Research Group costs (see table 1 page 9 AbbVie response to assessment report). AbbVie noted that the Assessment Group applied only 1 cost for disease flare, whereas it considered that people may visit a health professional multiple times during a disease flare.

6.21 Several consultees reiterated their concerns about the inappropriateness of an indirect comparison of the biological treatments, given the differences in the trials and concomitant use of methotrexate.

6.22 BMS (abatacept) commented on the treatment sequences assumed in the Assessment Group model. BMS questioned why the Assessment Group chose etanercept before the 2nd biological treatment. BMS noted that the Assessment Group assumed that people who stopped biological treatment 'continue on a standard treatment regimen that does not contain a biologic DMARD', but it was unclear to BMS what treatments this included. BMS noted that the Assessment Group modelled no cost, efficacy, or utility data for people who stopped treatment with methotrexate.

6.23 Pfizer (etanercept) considered it most plausible to include a caregiver benefit and to assume that all people start biological treatment at age 6. Several consultees suggested that the Assessment Group model is conservative. The reasons given included the following:

- The benefits of adalimumab on juvenile idiopathic arthritis have not been incorporated. A consultee (AbbVie) state that there is evidence that adalimumab improves uveitis. Accounting for this would save money and improve quality of life for patients with uveitis receiving adalimumab

- The Assessment Group applied utility values from Prince et al. 2011 in the model at the end of the period in which they were collected Utility data were collected in Prince et al at baseline, and after month 3, 15 and 27. This means, for example, that in its model is the Assessment Group assumed that biologics do not increase utility during the first 3 months of treatment. Consultees (AbbVie, BMS) suggested that the Assessment Group should have used a half cycle correction, or conduct sensitivity analyses. Suggested scenario analyses were 1) applying the utility value collected at the end of the observed period to the start of the modelled cycle (i.e. apply the value at the 3 month observation period for the whole 1st modelled cycle [months 0-3]) or 2) apply a mid-point utility value in each cycle.
- Resource use with methotrexate may have been underestimated and utility values overestimated because the long-term outcomes (joint damage, surgery , visual impairment) because the Assessment Group did not incorporate these in its model
- The Assessment Group did not differentiate between resource use in the biological and methotrexate arms. AbbVie suggested that people continuing to take methotrexate, when it had failed to control disease activity, were likely to have poorer disease control and need more resources
- The cost of disease flare may have been underestimated
- AbbVie considered that wider societal benefits should be incorporated.

7 Equality issues

7.1 During scoping participants noted that there are anecdotal reports of patients with JIA having their treatment discontinued at age 18 because the existing NICE guidance for etanercept (TA35) makes recommendations for adolescents only up to age 17. NICE also heard that previous NICE guidance has not considered adults and unless this multiple technology appraisal covers adults with JIA, then the guidance

may discriminate against this group. Consultees noted that the recommendations in TA35 reflect the wording of the marketing authorisation for etanercept at the time whereas the marketing authorisation for etanercept no longer stipulates a maximum age.

8 Innovation

8.1 Only the manufacturer of etanercept (Pfizer) made a case for innovation for biological treatments, and etanercept in particular. It noted that etanercep that is not associated with neutralising anti-drug antibodies which can affect a drug's efficacy. The company noted that for all the biological drugs, the QALY calculation was unlikely to capture caregiver burden or impact on educational attainment.

9 Authors

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Appendix A: Supporting evidence

Related NICE guidance

- Tocilizumab for the treatment of systemic juvenile idiopathic arthritis. NICE technology appraisal guidance 238 (2011)
- Guidance on the use of etanercept for the treatment of juvenile idiopathic arthritis. NICE technology appraisal guidance 35 (2002).

NICE pathways

- There is a NICE pathway on Musculoskeletal conditions, which is available from http://pathways.nice.org.uk/pathways/musculoskeletal-conditions