NICE National Institute for Health and Care Excellence

NICE guidance

Abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance replaces TA35.

1 Recommendations

1.1 Abatacept, adalimumab, etanercept and tocilizumab are recommended, within their marketing authorisations, as options for treating polyarticular juvenile idiopathic arthritis (JIA), including polyarticular-onset, polyarticular-course and extended oligoarticular JIA. That is:

- for abatacept, people 6 years and older whose disease has responded inadequately to other disease-modifying anti-rheumatic drugs (DMARDs) including at least 1 tumour necrosis factor (TNF) inhibitor
- for adalimumab, people 2 years and older whose disease has responded inadequately to 1 or more DMARD
- for etanercept, people 2 years and older whose disease has responded inadequately to, or who are intolerant of, methotrexate
- for tocilizumab, people 2 years and older whose disease has responded inadequately to previous therapy with methotrexate.

  Abatacept and tocilizumab are recommended only if the companies provide them with the discounts agreed in the patient access schemes for these technologies.

1.2 Adalimumab and etanercept are recommended, within their marketing authorisations, as options for treating enthesitis-related JIA, that is, for people 6 years and older (adalimumab) and 12 years and older (etanercept) whose disease has responded inadequately to, or who are intolerant of, conventional therapy.

1.3 Etanercept is recommended, within its marketing authorisation, as an option for treating psoriatic JIA, that is, in people aged 12 years and over whose disease has responded inadequately to, or who are intolerant of, methotrexate.

1.4 When more than 1 technology is suitable (taking into account extra-articular manifestations) treatment should be started with the least expensive technology, taking into account administration costs, the dose needed and the product cost per dose.

2 Clinical need and practice

2.1 Juvenile idiopathic arthritis (JIA) describes all forms of arthritis that have an unknown cause, an onset younger than 16 years, and joint inflammation that lasts more than 6 weeks. JIA is classified by the number of joints affected. Oligoarticular JIA, also known as oligoarthritis, is diagnosed when 4 or fewer joints are affected over the first 6 months after diagnosis. Polyarticular-onset JIA, also known as polyarthritis, is diagnosed when 5 or more joints are affected over the first 6 months after diagnosis. After 6 months from diagnosis, if 5 or more joints become affected it is then referred to as polyarticular-course JIA. This includes people who are diagnosed with oligoarticular JIA but who then have more joints affected after 6 months (also known as extended oligoarticular JIA). Other subtypes of JIA include systemic, enthesitis-related and psoriatic arthritis. These can have additional symptoms or conditions including:

- systemic JIA: fever, tiredness, rash, loss of appetite and weight loss
- enthesitis-related arthritis: affects entheses (where tendons attach to the bones)
- psoriatic arthritis: psoriasis.

  People with enthesitis-related and psoriatic arthritis can have polyarticular-course JIA, as can people who initially had systemic JIA providing there have been no active systemic symptoms in the previous 6 months.

2.2 About 1,000 children are diagnosed with JIA in the UK per year, and about 10,000 children have the condition. JIA may continue into adulthood, and about a third or more of children with the condition still need treatment in adult life.

2.3 At the onset of JIA, swollen and painful joints can limit movement. Later, progressive joint damage can permanently disable patients and it has been estimated that between 7% and 28% of patients need joint replacements. About 10% to 20% of patients with JIA (mainly those with systemic or polyarticular JIA who need high-dose corticosteroids) have impaired growth. JIA can decrease bone mass and increase the risk of osteoporosis. It is associated with a range of

extra-articular manifestations, notably uveitis (inflammation of the middle layer of the eye); about 30% to 50% of children with JIA have uveitis at diagnosis. Untreated uveitis can be associated with cataracts, glaucoma and macular oedema, and about 50% to 70% of people with severe uveitis develop visual impairment. Children with JIA are screened for uveitis in England.

2.4 NICE issued technology appraisal guidance on the use of etanercept for the treatment of juvenile idiopathic arthritis in 2002. The recommendation states that '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 current multiple technology appraisal reviews this guidance because the marketing authorisation for etanercept now includes children from 2 years with polyarticular JIA, and children and young people with extended oligoarthritis, enthesitis-related arthritis and psoriatic arthritis. Also, abatacept, adalimumab and tocilizumab have all got marketing authorisations for JIA since the previous guidance was issued. This multiple technology appraisal does not include people with systemic JIA because tocilizumab is the only intervention licensed to treat this type of JIA, and because there is already NICE technology appraisal guidance on tocilizumab for the treatment of systemic juvenile idiopathic arthritis recommending tocilizumab for children and young people whose disease has failed to respond to methotrexate. Of note, people with systemic JIA may develop polyarticular-course JIA (see section 2.1), which is covered by this multiple technology appraisal.

3 The technologies

Abatacept

3.1 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 treating moderate to severe active polyarticular juvenile idiopathic arthritis (JIA) in paediatric patients 6 years and older whose disease has responded inadequately to other disease-modifying antirheumatic drugs (DMARDs) including at least 1 tumour necrosis factor (TNF) inhibitor. The summary of product characteristics suggests stopping abatacept if a response to treatment is not seen within 6 months.

3.2 The summary of product characteristics lists upper respiratory tract infections as the only very common (affecting 1 in 10 people or more) adverse reaction for abatacept. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.3 Abatacept costs £302.40 for a 250 mg vial (British National Formulary for Children, accessed September 2015). The dose of abatacept depends on body weight. For children and young people who weigh less than 75 kg, the dose is 10 mg/kg. For young people weighing over 75 kg, the adult dosing regimen applies, up to a total dose of 1,000 mg per administration. Abatacept is given at 2 and 4 weeks after the initial intravenous infusion and then every 4 weeks. The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of abatacept with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

Adalimumab

3.4 Adalimumab (Humira, AbbVie) is an antibody that inhibits 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 JIA in patients 2 years and older whose disease has responded inadequately to 1 or more DMARDs
- treating active enthesitis-related arthritis in patients 6 years and older whose disease has responded inadequately to, or who cannot tolerate, conventional therapy.

The summary of product characteristics suggests stopping adalimumab if a response to treatment is not seen within 12 weeks.

3.5 The summary of product characteristics lists the following very common (affecting 1 in 10 people or more) adverse reactions for adalimumab: respiratory tract infections, low white blood cell count, low red blood cell count, increased blood levels of lipids, headache, abdominal pain, nausea and vomiting, rash, musculoskeletal pain, injection site reactions and increased plasma levels of liver enzymes. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.6 Adalimumab costs £352.14 for a 40 mg prefilled pen or prefilled syringe and for a 40 mg/0.8 ml vial (British National Formulary for Children, accessed September 2015). The dose of adalimumab depends on body surface area. For children younger than 13 years, the dose is 24 mg/m2, up to a maximum single dose of 20 mg in children aged 2 to 4 years and 40 mg in children aged 4 to 12 years. It is given every other week. For young people 13 years and older, the dose is 40 mg every other week regardless of body surface area. Costs may vary in different settings because of negotiated procurement discounts.

Etanercept

3.7 Etanercept (Enbrel, Pfizer) is a human tumour necrosis factor receptor p75 Fc

fusion protein that inhibits TNF. It is administered by subcutaneous injection. It is indicated for:

- treating polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and young people 2 years and older whose disease has responded inadequately to, or who cannot tolerate, methotrexate
- treating psoriatic arthritis in young people 12 years and older whose disease has responded inadequately to, or who cannot tolerate, methotrexate
- treating enthesitis-related arthritis in young people 12 years and older whose disease has responded inadequately to, or who cannot tolerate, conventional therapy.

  The summary of product characteristics suggests stopping etanercept if a response to treatment is not seen within 12 weeks.

3.8 The summary of product characteristics lists the following very common (affecting 1 in 10 people or more) adverse reactions for etanercept: injection site reactions, upper respiratory tract infections, and bladder and skin infections. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.9 Etanercept costs £35.75 for a 10 mg vial and £89.38 for a 25 mg vial (British National Formulary for Children, accessed September 2015). The dose of etanercept is either 0.4 mg/kg given twice weekly up to a maximum of 25 mg per dose or 0.8 mg/kg given once weekly up to a maximum of 50 mg per dose. Costs may vary in different settings because of negotiated procurement discounts.

Tocilizumab

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

- treating juvenile idiopathic polyarthritis (rheumatoid factor positive or

negative, and extended oligoarthritis) in patients 2 years and older whose disease has responded inadequately to methotrexate

- treating active systemic JIA in patients 2 years and older whose disease has responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs and systemic corticosteroids.

  The summary of product characteristics suggests stopping tocilizumab if a response to treatment is not seen within 12 weeks.

3.11 The summary of product characteristics lists the following adverse reactions affecting 5 people in 100 or more for tocilizumab: upper respiratory tract infections, nasopharyngitis, headache, hypertension and abnormal liver function tests. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.12 Tocilizumab costs £102.40 for an 80 mg vial, £256.00 for a 200 mg vial and £512.00 for a 400 mg vial (British National Formulary for Children, accessed September 2015). The dose of tocilizumab is 8 mg/kg once every 4 weeks in patients weighing 30 kg or more or 10 mg/kg once every 4 weeks in patients weighing less than 30 kg. The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of tocilizumab with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

4 Evidence and interpretation

The Appraisal Committee considered evidence from several sources.

Clinical effectiveness evidence

4.1 The Assessment Group carried out a systematic review of published studies on the clinical effectiveness of the technologies and supplemented this review with data provided by the company submissions from Bristol-Myers Squibb for abatacept, AbbVie for adalimumab, Pfizer for etanercept and Roche for tocilizumab. The Assessment Group also took into account submissions from the British Society for Paediatric and Adolescent Rheumatology, the National Rheumatoid Arthritis Society and the Royal College of Pathologists. The key clinical trials identified by the Assessment Group review included:

- randomised controlled trial data for abatacept, adalimumab, etanercept and tocilizumab in which the populations included people with polyarticular juvenile idiopathic arthritis (JIA) which may have included people with polyarticular JIA, extended oligoarticular JIA, polyarticular psoriatic arthritis and polyarticular enthesitis-related JIA, and people who had systemic arthritis initially who went on to have polyarticular JIA (see section 2.1)
- open label extensions of the randomised controlled trials (for adverse events)
- single-arm studies for people with enthesitis-related JIA and psoriatic arthritis, which informed the regulatory decisions for adalimumab and etanercept.

Abatacept, adalimumab, etanercept and tocilizumab for polyarticular JIA

4.2 The Assessment Group review identified 1 randomised placebo-controlled trial in polyarticular-onset or polyarticular-course JIA for each of the 4 biological treatments (abatacept, adalimumab, etanercept and tocilizumab). These were AWAKEN (abatacept), Lovell et al. (2008; adalimumab), Lovell et al. (2000;

etanercept) and CHERISH (tocilizumab). All 4 trials were multicentre and international, but only the tocilizumab CHERISH trial included patients 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. However, only people with a 30% decrease in disease activity (measured by the American College of Rheumatology Paediatric [ACR Pedi] 30% response criteria) by the end of this phase entered the double-blind withdrawal phase of the trial and were randomised to either continue on the biological treatment or switch to 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.

The trials also differed in the background medication permitted in either the placebo or intervention arms. Most people in the trials had methotrexate in addition to the study drug or placebo. The exception was the etanercept trial, which did not allow treatment with methotrexate at the same time as with etanercept.

4.3 The trial populations differed between studies and sometimes between arms of each trial. Key differences were:

- How long patients had JIA before entering the trial (from between 3.4 years and 4.7 years across trial arms in the tocilizumab trial to between 5.3 years and 6.4 years in the etanercept trial).
- Previous treatments people had before entering the study. About 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 number of people who had received a prior biological treatment in the etanercept trial was unknown.
- The relative proportions of people with different subtypes of JIA also differed

although the Assessment Group noted that the publications from the trials did not always report the proportions of people who had polyarticular JIA with systemic onset or enthesitis-related or psoriatic arthritis.

- The mean age of people included in the trials varied from around 7.5 years to 13.0 years.

4.4 The primary outcome for all 4 trials was 'disease flare'. The definitions of disease flare were broadly consistent between the studies, namely, a worsening of at least 30% or more in at least 3 of the 6 core (ACR Pedi) criteria for JIA, and an improvement of 30% or more in no more than 1 of the criteria. Some studies also defined 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 statistically significantly lower with the biological treatment than with placebo ($p<0.05$).

4.5 All 4 studies reported ACR Pedi 30, 50 and 70 responses (a 30%, 50% and 70% decrease in disease activity), with all but the etanercept study also reporting ACR Pedi 90 response (a 90% decrease in disease activity). The abatacept and tocilizumab studies also reported values for the proportion of people with inactive disease over the course of the double-blind withdrawal phase. In all 4 trials, in people randomised to the biological treatments, there was a better response (across all response cut-offs measured in each trial) than in those randomised to placebo. P values were not reported for all comparisons (including ACR Pedi 50 and 70 in the etanercept trial and ACR Pedi 90 and inactive disease in the tocilizumab trial). When reported, the p values were less than 0.05, except ACR Pedi 30 in the abatacept trial (when $p=0.1712$).

4.6 For health-related quality of life, only the abatacept trial reported 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).

4.7 For 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 studies, pain improved more with biological treatment than with placebo, but the difference was statistically significant only in the tocilizumab study (p=0.0076). For additional outcomes listed in the final scope issued by NICE, none of the studies reported on whether the biological treatments reduced the use of corticosteroids, the incidence of uveitis or affected height and body weight.

4.8 The trials results included adverse event rates that occurred in the placebo-controlled and open-label extension periods. In the placebo-controlled period, people in the biological treatment and placebo arms had similar rates of adverse events:

- In the abatacept trial, the most common class of adverse events in both treatment groups was 'infections and infestations' (44% to 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 73 events in 4.0 patient-years; placebo 57 events in 3.8 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). One person in each study arm had injection-site reactions.
- In the tocilizumab trial, the most 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; 12.3 per 100 patient-years for etanercept and 11.1 per 100 patient-years for tocilizumab. The Assessment Group stated that 7 serious adverse events had occurred in the extension phase of the adalimumab trial but the length of follow-up was unclear. AbbVie, the marketing authorisation holder for adalimumab, presented a figure of 4.6 serious adverse events per 100 patient-years (using data from its STRIVE registry of people having adalimumab).

4.9 The Assessment Group indirectly compared abatacept, adalimumab, etanercept and tocilizumab for people with JIA with a polyarticular course using data from the 4 randomised controlled trials and using placebo as a common comparator. 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 which did not include tocilizumab. The Assessment Group identified several limitations with the evidence, which compromised the indirect comparison. These included having data from only 1 trial for each drug and differences across the trials, as highlighted in sections 4.2 and 4.3 (including the proportion with each subtype of JIA, time with JIA and prior treatments before enrolling on study, use of concomitant methotrexate, age, and duration of the double-blind randomised phase of the studies). The results showed that there were no statistically significant differences between the 4 treatments in flare and ACR Pedi response. 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 patients could not receive methotrexate and had had JIA for a longer time than other trials), the proportion who experienced flares in the placebo arm was 81% compared with 48% to 65% in the other trials. The Assessment Group, advised by a clinical advisor, concluded that the results showed that the 4 technologies had similar short-term effectiveness and any differences in effects of each technology, if they exist, have not yet been captured by current trial data.

Etanercept for enthesitis-related JIA, extended oligoarticular JIA and psoriatic arthritis

4.10 The assessment group identified 1 study of etanercept in the further subtypes of JIA, the CLIPPER trial. The CLIPPER trial was a single-arm open-label multicentre trial with 2 parts: 12 weeks of treatment until the primary outcome was measured, and a 96-week extension phase. The trial included children and young people with:

- extended oligoarticular JIA (n=60, 2 to 17 years), enthesitis-related arthritis (n=38, 12 to 17 years) or psoriatic arthritis (n=29, 12 to 17 years)
- 2 or more active joints (swollen or limited motion with pain or tenderness)

- a history of intolerance or unsatisfactory disease response to at least a 3-month course of 1 or more DMARDs
- only for enthesitis-related arthritis, unsatisfactory disease response to at least a 1-month course of 1 or more NSAIDs (that is, 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 corticosteroid and 1 NSAID at the same time as etanercept. Etanercept was given at a dosage of 0.8 mg/kg once weekly (maximum dose 50 mg/kg).

4.11 The primary outcome at week 12 was ACR Pedi 30, which was seen in 83% of patients with enthesitis-related JIA, 93% of patients with psoriatic arthritis and 90% of patients with extended oligoarthritis. The proportion with inactive disease at week 12 was 17% in the enthesitis-related arthritis group, 7% in the psoriatic arthritis group and 12% in the extended oligoarthritis group. The proportion having inactive disease was greater at week 96, when 29% of patients in both the enthesitis-related arthritis and psoriatic arthritis groups and 37% of patients in the extended oligoarthritis group had inactive disease. All subtypes showed improvement from baseline in the Child Health Assessment Questionnaire (CHAQ, a measure of quality of life), degree of 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).

Adalimumab for enthesitis-related arthritis

4.12 The Assessment Group noted an ongoing trial of adalimumab in people with enthesitis-related arthritis that has only been published in abstracts. The European Medicines Agency used data from this trial to extend the marketing authorisation 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 to 17 years old) with moderate enthesitis-related arthritis.

Patients were randomised to receive either adalimumab or placebo every other week for 12 weeks. The double-blind period was followed by an open-label period in which patients received adalimumab for up to an additional 192 weeks. There were 31 people in the adalimumab arm and 15 people in the placebo arm of the trial. After 12 weeks of treatment, people randomised to adalimumab showed greater improvement in the primary outcome of active joint count than people randomised to placebo (a 62.6% reduction from before treatment compared with 11.6% reduction), p=0.039.

TNF inhibitors for uveitis

4.13 The Assessment Group discussed the evidence for the effect of the technologies on uveitis. It noted 2 systematic reviews by Simonini et al. (2014) and Cordero-Coma et al. (2013) and commented that these reviews mainly included observational studies relating to using adalimumab, etanercept and infliximab. The Assessment Group reported that the authors concluded that adalimumab was associated with better outcomes than etanercept, but considered these conclusions to be highly uncertain because the data came from observational studies rather than controlled studies. 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 trials (SYCAMORE and ADJUVITE) assessing adalimumab in patients with JIA and uveitis. The SYCAMORE trial was due to report in 2020 but closed early because of a benefit with adalimumab compared with placebo. ADJUVITE is ongoing and due to report in 2016.

Cost-effectiveness evidence

4.14 Two of the companies submitted cost analyses, 1 submitted a cost-effectiveness analysis and 1 stated that, because of the data limitations, it considered it inappropriate to submit evidence. The nature of the submissions were:

- Bristol-Myers Squibb (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 years 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.

4.15 The Assessment Group developed 2 Markov models. In the first, the Assessment Group modelled a population with JIA whose disease had responded inadequately to, or who did not tolerate, methotrexate; this represented people who would receive their first biological treatment option ('1st biologic model'). The Assessment Group considered it necessary to build a second model because the marketing authorisation for abatacept states that abatacept should be administered after a TNF inhibitor. In the '2nd biologic model', the Assessment Group modelled a population with JIA whose disease had responded inadequately to, or who did not tolerate, methotrexate and who had previously received a TNF-alpha inhibitor (etanercept); this represented people who would receive their second biological treatment option. The Assessment Group stated that the randomised controlled trial and registry data used to inform the modelling came from mixed populations with predominantly polyarticular-course JIA and that it did not have sufficient evidence to model enthesitis-related and psoriatic subtypes of JIA separately. In both models, the average age of the modelled population was 11 years (to reflect the clinical trials in people with polyarticular JIA [see section 4.2]). 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 JIA in paediatric patients. 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.

4.16 To determine the costs and benefits for people having their first biological treatment, the Assessment Group used the '1st biologic model' to compare adalimumab, etanercept and tocilizumab with methotrexate or with no treatment (for 20% of people assumed to be 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 a TNF inhibitor (assumed to be etanercept based on clinical advice to the Assessment Group). The Assessment Group again assumed that people do not switch to another biological treatment after their second biological treatment. It assumed that 80% of people receiving abatacept, 69% of people receiving adalimumab, 0% of people receiving etanercept and 82% of people receiving tocilizumab took methotrexate at the same time in both models. The Assessment Group based the proportions of people receiving methotrexate on trial and registry data (see section 4.2).

4.17 Both models had 3 health states: 'on-treatment', 'off-treatment' and 'death'. Based on clinical advice, the Assessment Group assumed that, if disease goes into remission while on-treatment, clinicians would be reluctant to stop treatment and people would continue. In a sensitivity analysis, the model had an additional health state reflecting 'off-treatment remission' to test the effect of stopping treatment during remission (see section 4.22). People stayed on treatment unless they died or stopped treatment because of adverse events or because the drug no longer worked. In the first 3-month cycle of the model, the Assessment Group obtained rates of stopping treatment from the open-label lead-in period in each of the 4 randomised controlled trials (see section 4.2). The Assessment Group obtained the stopping rates after 3 months from Tynjala et al. (2009; a retrospective observational study of patients with JIA in Finland having etanercept or infliximab with a 4-year follow-up). The Assessment Group did not use the rates of stopping treatment from the randomised controlled phase of the trials because people could stop for reasons other than adverse events or loss of drug efficacy, such as if consent was withdrawn. The Assessment Group noted that, because there were few studies for the biological treatments, it assumed that stopping rates were the same for each biological treatment. The Assessment

Group assumed that when people stop treatment they had methotrexate alone.

4.18 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 (see section 4.2), 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 technology treatment, the Assessment Group multiplied this average risk of flare with methotrexate by the relative risk for each technology compared with placebo from each clinical trial.

4.19 The 4 randomised controlled trials did not collect data that the Assessment Group could use to derive utility values, so 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 got 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 46 people with polyarticular-course JIA that had not responded to maximum-dose methotrexate who had started to have etanercept. Quality of life was measured before starting etanercept and over 27 months while taking etanercept. The Assessment Group assumed that a person's utility value while having a biological treatment would be the same for all biological treatments. The utility values applied in the model were 0.53 for baseline, for the first 3 months and for people who stopped biological treatment, 0.69 for months 3 to 15, 0.74 for months 15 to 27 and 0.78 thereafter. People who had a second or third biological treatment were assumed to have a utility value of 0.74. The Assessment Group assumed that having a disease flare lowers utility and that people would recover within 3 months (one-model cycle). When the Assessment Group annualised this disutility, it was estimated to be 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 about this. The Assessment Group did not include a caregiver disutility in its base case, but did explore this in scenario analyses (see section 4.22).

4.20 Abatacept and tocilizumab had an administration cost of £154 because they are administered intravenously rather than subcutaneously. The dose of

methotrexate was 10 to 15 mg/m2 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 £430. The Assessment Group commented that the most commonly occurring serious adverse events in people with JIA were infections. The Assessment Group estimated an inpatient cost of £1,533 for treating infections by averaging across health resource group codes.

4.21 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 a TNF inhibitor.

The Assessment Group presented the deterministic results as pairwise comparisons with methotrexate rather than as a fully incremental analysis. It stated that a robust comparison of the clinical evidence could not be done so it could not assess the cost effectiveness of the biological treatments relative to each other (see section 4.9). 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. Additionally, for this reason, the results for the comparisons of abatacept and tocilizumab compared with methotrexate are presented within a £10,000 per quality-adjusted life year (QALY) gained range to prevent back calculation of the confidential discounts. See the results in table 1.

Table 1 Results from the Assessment Group's '1st and 2nd biologic models'

–	Incremental QALYs	ICER versus methotrexate with PAS
'1st biologic model' Adalimumab	2.0	£38,127
'1st biologic model' Etanercept	2.1	£32,526

–	Incremental QALYs	ICER versus methotrexate with PAS
'1st biologic model' Tocilizumab	2.1	£30,000 to £40,000
'2nd biologic model' Abatacept	3.4	£30,000 to £40,000
'2nd biologic model' Adalimumab	3.3	£35,284
'2nd biologic model' Etanercept	3.3	£33,948
'2nd biologic model' Tocilizumab	3.4	£30,000 to £40,000

Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjust life year.

4.22 The Assessment Group carried out one-way deterministic sensitivity analyses. For all 4 technologies in both models, the key drivers of the ICERs were the utility values (particularly over the long term) and the discounting rates. The Assessment Group carried out a series of scenario analyses. The Assessment Group presented results from the '1st biologic model' only (except the scenario that included changing the starting age, in which it presented the results from both models). All the scenarios decreased the ICER for each biological treatment compared with methotrexate (see table 2). The scenarios included:

- **People stopping treatment because of improvement and entering a 'remission off treatment' health state:** in different analyses, the Assessment Group assumed a rate of remission per cycle of 7.8% and a relapse rate of 67% (Baszis et al. 2011), or a rate of remission of 0.66% per cycle and a relapse rate of 40% (Tynjala et al. 2009).
- **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 with £724.00 for both in the base case).

- **Using 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 the utility of caregivers of people with highly active relapsing-remitting multiple sclerosis. In Kuhlthau et al. the disutility was −0.035 on treatment and −0.07 off treatment; in Gani et al. the disutility was −0.010 on treatment and −0.02 off treatment.
- **Three lines of biological therapy:** the Assessment Group compared sequences of etanercept, then adalimumab, then tocilizumab and of etanercept, then adalimumab, then abatacept with methotrexate only. The Assessment Group stated that these 2 sequences reflect the sequence of treatments used in clinical practice in England.
- **Modelled population entered at 6 years rather than 11 years:** This scenario was carried out because children aged 6 years are eligible for all 4 biological treatments.

Table 2 Results from the Assessment Group's scenario analyses showing ICER (£ per QALY) versus methotrexate

–	Adalimumab	Etanercept	Tocilizumab (+PAS)
People with remission who can stop treatment ('1st biologic model') Baszis et al. (2011)	£33,744	£28,580	£20,000 to £30,000
People with remission who can stop treatment ('1st biologic model') Tynjala et al. (2009)	£37,512	£31,970	£30,000 to £40,000
Health state costs from Prince et al. 2011 ('1st biologic model')	£35,214	£29,691	£20,000 to £30,000

–	Adalimumab	Etanercept	Tocilizumab (+PAS)	
Disutility for caregiver burden applied Higher disutility (Kuhlthau et al. 2010)	£33,436	£28,619	£20,000 to £30,000	
Disutility for caregiver burden applied Lower disutility (Gani et al. 2008)	£36,658	£31,305	£30,000 to £40,000	
Discount rates from NICE technology appraisal 35 applied	–	£21,718	–	
Starting age in models 6 years not 11 years **'1st biologic model'**	£38,124	£26,173	£20,000 to £30,000	
Starting age in models 6 years not 11 years **'2nd biologic model'**	Abatacept (+PAS)	Adalimumab	Etanercept	Tocilizumab (+PAS)
Starting age in models 6 years not 11 years **'2nd biologic model'**	£20,000 to £30,000	£31,283	£28,895	£20,000 to £30,000

Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year.

4.23 The Assessment Group noted that, because of lack of data, it was unable to model the cost effectiveness of the treatments for the subgroup of people with JIA and uveitis separately. It noted that the prevalence of uveitis in JIA is between 8% and 30%, and is particularly common in children with early onset JIA (mean age of onset 3 to 5 years). The Assessment Group noted that the NHS England interim commissioning policy states that adalimumab combined with methotrexate is widely used to treat refractory uveitis, but that etanercept is not generally used. The Assessment Group stated that, if it had modelled the costs and benefits of the vision loss associated with JIA, then adalimumab would have been more cost effective in JIA patients with uveitis than without uveitis. Also, if most of the costs related to uveitis related to managing it (as stated in the clinical commissioning policy), then any reduction of these costs because of improving

vision would have further improved the cost effectiveness of adalimumab in the subgroup of patients with uveitis.

4.24 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 lead to the need for joint surgery. There were no available data to determine whether abatacept, adalimumab, etanercept and tocilizumab reduce long-term joint damage compared with methotrexate or each other. However, 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 biological treatments were the same people who experienced fewer complications. The Assessment Group stated that, if biological treatments reduced long-term damage to a greater extent than methotrexate, the ICERs compared with methotrexate would be lower.

Roche cost-effectiveness model comparing tocilizumab with adalimumab

4.25 Roche developed a Markov model. The model had a 6-month cycle length with a half-cycle correction. It ran over a 25-year time horizon with a starting age of 11 years. Roche applied a discounting rate of 3.5% per annum. Roche assumed that the real-life population was the same as the trial population in CHERISH, which compared tocilizumab with placebo (see section 4.2). 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.

4.26 Roche used the model to compare tocilizumab with adalimumab only because it considered that 'no therapy' is not an option because biological treatments are the current standard of care in the UK. Roche felt it would be unlikely that patients whose disease has already responded inadequately to methotrexate would have further treatment with methotrexate. Moreover, Roche considered

that only the trials of tocilizumab and adalimumab were similar enough to compare. In an exploratory analysis, the company compared tocilizumab with etanercept, which Roche assumed was equally effective to adalimumab.

4.27 Roche's model used ACR Pedi response as the main measure of clinical effectiveness (unlike the Assessment Group's model, which used flare). 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 whose disease does not respond (JIA ACR Pedi less than 30) have a 6-month stopping rate of 0.126
- people whose disease has a moderate response (JIA ACR Pedi more than 30 and less than 70) have a 6-month stopping rate of 0.090
- people whose disease has a good response (JIA ACR Pedi the same as or more than 70) have a 6-month stopping rate of 0.042.

Roche assumed that 1% of patients die every 6 months.

4.28 Roche used the same time-dependent utility values from Prince et al. (2011) as chosen by the Assessment Group (see section 4.19). 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 Assessment Group's models.

4.29 In the Roche model, when taken with methotrexate, adalimumab was associated with 18.76 QALYs and tocilizumab with 18.72 QALYs. Adalimumab was associated with higher total costs than tocilizumab (£81,827 compared with £70,707). 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 biological 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 Assessment Group amendments reduced the QALYs for adalimumab to 10.10 and for tocilizumab to 10.05. The amendments increased the total costs to £95,761 for adalimumab and £83,593 for tocilizumab.

Company comments on the feasibility of an economic model to assess the cost effectiveness of abatacept, adalimumab, etanercept and tocilizumab for JIA

4.30 The companies drew attention to the following points:

- **Utility values.** Bristol-Myers Squibb, 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 data, but mapping this to EQ-5D would cause problems because of the small number of patients in Prince et al. (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% and 28% of patients have joint surgery, and between 9% and 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 and adult services and an appropriate time horizon.** Because JIA can continue into adulthood, models reflecting JIA may need a time horizon to reflect this. AbbVie noted that there will be administration costs associated with transitioning between child and adult services.
- **Difficulties in comparing the clinical effectiveness of the technologies with each other.** The companies noted the difficulties in comparing the clinical effectiveness of the technologies because of the study sizes, differences in trial populations and the marketing authorisations of the technologies.

Comments from consultees on the assessment report

4.31 Roche (tocilizumab) commented that using disease flare as the main measure of clinical effectiveness in the economic modelling was problematic. It noted that disease flare does not provide enough information on severity and the impact of JIA 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 and this was not captured in the utility values used in the Assessment Group model. Roche considered that ACR Pedi response combined with rates of stopping 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 obtained the cost of flare (£430), and presented alternative estimates based on Health Research Group costs. AbbVie noted that the Assessment Group applied a single cost for disease flare, whereas it considered that people may visit a health professional multiple times during a disease flare.

4.32 Bristol-Myers Squibb (abatacept) commented on the treatment sequences modelled by the Assessment Group. It questioned why the Assessment Group chose etanercept before the second biological treatment. It 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 the company what treatments this included. Bristol-Myers Squibb noted that the Assessment Group modelled no cost, efficacy, or utility data for people who stopped treatment with methotrexate.

4.33 Several consultees suggested that the Assessment Group's model is conservative and that it overestimated the ICERs. The reasons given included the following:

- The benefits of adalimumab on JIA have not been incorporated. A consultee (AbbVie) stated 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 months 3, 15 and 27. This means, for example, that in its model the Assessment Group assumed that biological treatments do not increase utility in the first 3 months of treatment. Consultees (AbbVie, Bristol-Myers Squibb) suggested that the Assessment Group should have used a half-cycle correction, or conducted sensitivity analyses. Suggested scenario analyses were:
  - applying the utility value collected at the end of the observed period to the start of the modelled cycle (that is, applying the value at the 3-month observation period for the whole first modelled cycle [months 0 to 3]); or
  - applying a mid-point utility value in each cycle.
- Resource use with methotrexate may have been underestimated and utility values overestimated because the Assessment Group did not incorporate the long-term outcomes (joint damage, surgery, visual impairment) in its model.
- The Assessment Group did not differentiate between resource use when receiving a biological treatment or methotrexate. AbbVie suggested that people continuing to take methotrexate, when it had failed to control disease activity, were likely to have poorer disease control and to need more resources.
- The cost of disease flare may have been underestimated.

Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of abatacept, adalimumab, etanercept and tocilizumab having considered evidence on the nature of polyarticular-onset JIA, polyarticular-course JIA, enthesitis-related JIA and psoriatic JIA. It also considered the value placed on the benefits of abatacept, adalimumab, etanercept and tocilizumab by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.34 The Committee discussed the natural history of JIA and the associated comorbidities and complications. It heard from a clinical expert that, in the absence of treatment, JIA is a progressive inflammatory condition and that duration of uncontrolled disease is associated with joint damage and growth impairment. Joint damage can lead to children and young people needing joint surgery, including joint replacement. If children have joint replacement, it is likely they will need multiple revisions over the course of their lives. The Committee was also aware that uveitis is common in people with JIA, and an estimated 30% to 50% of people have uveitis at diagnosis. A patient expert highlighted that children and young people with JIA in England are screened for uveitis because it is an asymptomatic condition that can lead to blindness if untreated. A clinical expert explained that the symptoms of JIA can resolve naturally, and do so in about half of people with JIA (depending on the subtype). The Committee agreed that JIA is a progressive condition that is associated with significant comorbidities and complications, which have a large impact on the lives of people with JIA. It concluded that treatments that reduce joint damage and disease activity were important to patients and for the clinical management of the condition.

4.35 The Committee discussed which measures were commonly used in UK clinical practice to monitor disease activity. It was aware of the American College of Rheumatology paediatric measure (ACR Pedi), which brings together several individual measures of disease activity into 1 score. A clinical expert stated that the individual measures of disease activity that make up the ACR Pedi are also used to monitor disease activity in clinical practice. It heard from a clinical expert that disease flare was an important, but incomplete, measure of disease activity. The Committee concluded that ACR Pedi scores and flare were important clinical outcomes.

4.36 The Committee discussed the treatment pathway for JIA. It heard from clinical experts that the aim of treatment for all JIA subtypes is to achieve remission (that is, to attain no disease activity in any joints). The clinical experts stated that diagnosing and starting treatment early in the course of disease is associated with better outcomes. The Committee heard that clinicians first offer patients intra-articular or systemic corticosteroids. If there is still active inflammation, then subcutaneous (rather than oral) methotrexate would be used. A clinical expert stated that people taking methotrexate are reviewed at 6 weeks and if the

disease has not improved, clinicians would offer a biological treatment that is, abatacept, adalimumab, etanercept or tocilizumab. A clinical expert stated that, after 6 months of treatment, if the disease does not respond, the patient switches biological treatments. However, if at 6 months there is a modest decrease in disease activity (such as an ACR Pedi 30 or 60), clinicians might encourage the patient to persist longer with the biological treatment and add corticosteroids. The Committee heard that clinicians continue to prescribe methotrexate in combination with a biological treatment (despite a person's disease not responding to methotrexate alone) because biological treatments work better with than without methotrexate. If a patient does not improve on 1 biological treatment, then the patient is switched to another biological treatment. There are now more than 10 years of experience of using biological treatments for JIA. The Committee heard that they have reduced the need for systemic corticosteroids with the associated short- and long-term adverse effects including, but not limited to, problems with dysglycaemia, sleep and generalised immunosuppression.

4.37 The Committee discussed how clinicians choose between the biological treatments. It was aware:

- that the NHS England interim guidelines suggest a TNF inhibitor as the first biological treatment, followed by abatacept and tocilizumab
- that the marketing authorisation for abatacept stipulates that abatacept should be administered only after a TNF inhibitor
- from the clinical experts, that they and their clinical colleagues consider the biological treatments to be:
  - of similar effectiveness to each other in clinical practice
  - similarly effective across the subtypes of JIA for which they are indicated
- that the choice of biological treatment takes into account patient preference after a discussion with the patient and carers about how, and how often, the drugs are administered.

The Committee concluded that biological treatments are used interchangeably in clinical practice, taking into account patient

characteristics, preference and previous treatments.

4.38 The Committee considered when patients start and stop biological treatments in English clinical practice. It was aware that, for all 4 technologies, the marketing authorisations stipulate which previous treatment(s) patients must have had. The Committee understood that the previous treatment must have been associated with an inadequate response or with intolerance. The Committee noted that the summaries of product characteristics for the technologies include different treatment durations at which a response would be expected: 6 months for abatacept, 16 weeks for adalimumab, 12 weeks for etanercept and 12 weeks for tocilizumab. One clinical expert stated that, if the biological treatment brought a patient's JIA into remission (meaning no disease activity), they would consider stopping treatment if remission were maintained for 1 to 2 years. One clinical expert stated that, in her experience, of people who stopped biological treatment because of remission, around half restarted it. The Committee was aware that JIA can resolve naturally and therefore there was uncertainty as to whether sustained improvement would be because of the treatment, the underlying natural history of the disease, or both. The Committee concluded that the technologies should be started and stopped in line with their marketing authorisations, and that some people stop treatment because of sustained remission.

4.39 The Committee listened to a patient expert's experience of having JIA as a child and the longer-term consequences of the condition. She said that JIA negatively impacted her daily activities because of pain, sleep disturbances and fatigue. They recounted frequent hospital visits and disrupted schooling because of clinic visits and because of absences when they felt too unwell to go to school. The patient expert explained that having had JIA as a child affects her life as an adult. Specifically, they said that the joint replacements they had in her teens have needed several revision surgeries. The patient experts explained that JIA impacts carers and family because people with JIA need extra help with day-to-day activities and numerous hospital visits. The Committee heard that the impact of JIA on quality of life is rarely captured in clinical trials but is improved by effective treatments. The Committee concluded that effective treatments improve quality of life for patients with JIA. It further concluded that JIA not only affects the quality of life of the child or young person with the disease but can affect the quality of life of their carers and family. The Committee also concluded that

caregiver utility should be taken into account when appraising the cost effectiveness of the biological treatment for JIA.

Clinical effectiveness

4.40 The Committee discussed the clinical effectiveness of abatacept, adalimumab, etanercept and tocilizumab for polyarticular JIA. The Committee was aware that 4 randomised placebo-controlled trials of the 4 technologies included populations with polyarticular-onset and polyarticular-course JIA, including extended oligoarthritis. The Committee considered that, in all the trials, the technologies were clinically effective compared with placebo in reducing disease activity (as measured by disease flare rate and ACR Pedi responses). The Committee also noted that the drugs had an acceptable safety profile.

4.41 The Committee considered differences between the clinical trials of abatacept, adalimumab, etanercept and tocilizumab for polyarticular JIA. It heard from a clinical expert that the proportion of people taking methotrexate with each biological treatment, and the length of time patients had JIA before entering the trials, would affect the clinical outcomes. It further heard that changes in clinical practice since the trials were carried out may affect the generalisability of the clinical trials to clinical practice in England. In particular, the Committee heard from 1 of the clinical experts that, because etanercept was the first biological treatment marketed for JIA, patients in the etanercept trial had JIA for a longer duration before enrolment than did patients in the other trials. Furthermore, the patients did not receive concomitant methotrexate because the benefits of continuing methotrexate use were not known at that time. Therefore, the clinical effectiveness of etanercept in clinical practice in England may be greater than reported in the clinical trials. The marketing authorisation holder for etanercept confirmed that the marketing authorisation does not contraindicate concomitant methotrexate, and that etanercept is administered as either monotherapy or with methotrexate in clinical practice. One clinical expert stated that taking concomitant methotrexate would likely affect trial outcomes because continuing to take methotrexate reduces the chance of an immune response against the biological treatment. Duration of JIA before entering the trial would also affect the outcome because it has been demonstrated in clinical practice that starting treatment early in the disease course is associated with better outcomes. The

Committee agreed with the Assessment Group that carrying out an indirect comparison of the technologies was problematic because differences between each trial may have affected the clinical effectiveness estimates and because there was only a single trial for each technology. The Committee further concluded that it was not possible to quantify the extent that differences between the trials affected the clinical-effectiveness estimates.

4.42 The Committee noted that the results of the network meta-analysis showed no statistically significant differences between the treatments and the confidence intervals around the relative risk for each comparison were wide. In addition, because the Committee had not been presented with evidence or clinical experience to suggest that there would be a difference in effectiveness between the 4 technologies, it considered it reasonable to conclude that the effectiveness of abatacept, adalimumab, etanercept and tocilizumab for polyarticular JIA were similar.

4.43 The Committee discussed the clinical effectiveness of adalimumab and etanercept for treating enthesitis-related JIA and etanercept for treating psoriatic JIA. The Committee noted that people had an ACR Pedi response in both trials, and that the response exceeded placebo in the adalimumab randomised controlled trial. It noted that the CLIPPER trial which had assessed etanercept for enthesitis-related and psoriatic JIA was a single-arm open-label trial. The Committee heard from the clinical experts that it was possible to generalise results for the effectiveness of etanercept and adalimumab for treating adult forms of enthesitis-related JIA and psoriatic JIA because the immunological effect of these treatments would be expected to be the same in adults and children. A clinical expert further stated that in her experience there was no evidence to suggest that adalimumab and etanercept would be any less effective in reducing disease activity in people with enthesitis-related JIA (or for etanercept in reducing disease activity in psoriatic JIA) than when using these technologies for polyarticular JIA. The Committee concluded that adalimumab and etanercept were clinically effective for treating enthesitis-related JIA and etanercept was clinically effective for treating psoriatic JIA. The Committee further concluded that the clinical effectiveness of etanercept and adalimumab for reducing disease activity in these subtypes was expected to be similar to the clinical effectiveness of these technologies for reducing disease activity in polyarticular JIA.

Cost effectiveness

4.44 The Committee discussed the structure of the Assessment Group's '1st biologic model' and '2nd biologic model'.

- The Committee noted that the structure and assumptions in the models were broadly similar, except that, in the '1st biologic model', people started treatment with a biological treatment immediately after methotrexate whereas, in the '2nd biologic model', people switched to a second biological treatment after etanercept. The Committee considered that it was appropriate to develop a '2nd biologic model' because abatacept is licensed only for use after a TNF inhibitor and because people switch from 1 biological treatment to another in clinical practice. However, it noted that the results for etanercept from this '2nd biologic model' would not reflect clinical practice because people would switch to another biological treatment rather than stay on etanercept if their JIA did not respond.
- The Committee noted that the Assessment Group chose to model a population based on people included in the randomised controlled trials of polyarticular JIA. It considered that the results of the model were generalisable to people with enthesitis-related JIA and psoriatic JIA because it heard from clinical experts that the biological treatments indicated for these JIA subtypes are similarly effective across all subtypes of JIA (see section 4.43).
- The Committee noted that JIA is not associated with a reduced life expectancy, nor did the Assessment Group model a survival benefit from biological treatments. Furthermore, the Committee noted that the Assessment Group ran the model over a 30-year horizon rather than a lifetime, noting limited data over the long term. The Committee accepted this approach as reasonable and noted that Roche had assumed a similar time horizon in the cost-effectiveness model it had submitted for this appraisal.

  The Committee concluded that the structures of the Assessment Group's models were appropriate to model the cost effectiveness of abatacept, adalimumab, etanercept and tocilizumab where indicated in the treatment pathway and across all indications covered by their marketing authorisations for JIA.

4.45 The Committee discussed whether the Assessment Group's model captured the clinical benefits of abatacept, adalimumab, etanercept and tocilizumab for treating JIA.

- It noted that the main clinical outcome in the Assessment Group's model was disease flare, which the Assessment Group assumed would last 3 months. The Committee, however, heard from the clinical experts that flare lasts for around 6 months. The Committee considered that including disease flare in the model was appropriate, but that it did not reflect all the factors taken into account by clinicians nor did it capture all the potential benefits of biological treatment. For example, the Committee noted that the Assessment Group had not additionally modelled response to treatment (such as ACR Pedi response). The Committee considered that the effect of the 4 technologies on controlling disease activity and duration (including flare, response and remission) was an important benefit, but that the Assessment Group's model did not fully capture this.
- The Committee considered how the model accounted for disease remission. It understood that treatment could lead to remission and that JIA could resolve naturally (see section 4.34). It noted that, in the base case, the Assessment Group's model had not taken disease remission into account, but a sensitivity analysis had tested this.
- The Committee discussed the modelling of comorbidities and complications associated with JIA. It noted that the Assessment Group stated that, because of sparse data, it had not modelled the effect of the technologies on uveitis and vision complications, or on joint damage and joint surgery. The Committee considered that clinical trial data suggested that people receiving adalimumab may have a lower risk of uveitis and fewer visual complications, and that all 4 technologies may decrease the risk of joint surgery because joint damage is associated with prolonged disease activity.
- The Committee discussed the impact of biological treatments on corticosteroid use. The Committee noted that the Assessment Group's model had not modelled corticosteroid use. The Committee was aware that prolonged use of systemic corticosteroids is associated with complications, and reducing systemic corticosteroid use was beneficial. The Committee was aware that the availability of biological treatments would be expected to reduce the need for systemic corticosteroids for JIA.

The Committee concluded that the model had captured some, but not all, of the benefits of the biological treatments in controlling disease activity. It further concluded that additional possible clinical benefits of the technologies, such as treating uveitis, preventing long-term joint damage, avoiding surgery and minimising the adverse effects of corticosteroids, had not been captured in the model. However, it concluded that it was not possible to estimate the extent of these benefits.

4.46 The Committee discussed how quality of life was modelled. It had heard from patient experts that achieving disease control improved quality of life both in the short and long term.

- It was aware from the Assessment Group report and the company submissions that there were limited data available. It noted that both the Assessment Group and Roche had used utility data from Prince et al. (2011), which reported that a person's quality of life increases over time while having a biological treatment for JIA.
  - The Committee heard from a clinical expert that it was plausible that quality of life would increase as JIA begins to respond to the biological treatment.
  - One clinical expert stated that response to etanercept and adalimumab starts after 4 weeks and improves over time and said clinicians and patients expect a response and better quality of life by 6 months with all the biological treatments, which would improve further over the first year.
  - Despite limitations of the data, the Committee considered that improving utility by around 50%, from 0.53 before starting treatment with a biological treatment to 0.78 after 27 months of treatment, seemed plausible.
- The Committee considered the utility values of people whose JIA did not respond to methotrexate but who continued to receive it. The Committee understood that quality of life would likely decrease over time because JIA is not adequately controlled, but that the model did not include a decrease in utility for this situation. The Committee considered the utility of people whose JIA did not respond to treatment had not been fully addressed in the

modelling.

- The Committee discussed the inclusion of a flare disutility in the model. It considered there was a risk of double counting as some people in Prince et al. may have had disease flares. Therefore, it considered that there was uncertainty around whether flares may have been taken into account twice by using utility values from Prince et al. and applying a separate disutility for disease flare.

- The Committee noted that the Assessment Group had not included caregiver utility in its base case, but had tested 2 values (1 for carers of children with impaired mobility, and 1 for carers of adults with multiple sclerosis) in sensitivity analyses. The Committee considered it appropriate to include a disutility for caregivers of people with JIA, but was unclear which value to use.

  The Committee concluded that there was considerable uncertainty surrounding the utility values used in the model because of the lack of data, but that the utility should improve over time if disease control is achieved. The Committee also concluded that it was relevant to include caregiver utility in the modelling.

4.47 The Committee considered the resource costs used in the model. The Committee considered that the resource costs in the Assessment Group model came from reasonable sources, being National NHS reference costs or from the Personal Social Services Research Unit. However, it heard from a clinical expert that the reference cost for disease flare seemed low. The Committee noted that the Assessment Group had assumed that resource costs on and off a biological treatment were the same. It heard from consultees and a clinical expert that this seemed implausible because people not having a biological treatment would be expected to have worse disease control and poor disease control would need more resources. The Committee concluded that the source of resource costs used by the Assessment Group was appropriate, but the impact of the biological treatments on resource costs had not been fully explored by the Assessment Group.

4.48 The Committee noted that the Assessment Group had presented pairwise comparisons of each of the 4 technologies with methotrexate rather than a fully

incremental analysis in its base case. The Committee considered other biological treatments, and not methotrexate, would be the most clinically relevant comparator if biological treatments continued to be available in clinical practice. However, if biological treatments were not available, methotrexate would be the only treatment option available to patients. The Committee agreed that differences between the clinical trials for the 4 technologies prevented a robust comparison between the technologies in the indirect treatment comparison. Moreover, the Committee noted that it had not been presented with evidence of a difference in the clinical effectiveness of the biological treatments in clinical practice. For these reasons the Committee considered the pairwise comparisons of cost effectiveness between each technology and methotrexate appropriate for its decision-making. The Committee noted that taking into account the patient access schemes for abatacept and tocilizumab resulted in base-case ICERs of around £30,000 to £40,000 per QALY gained for adalimumab, etanercept and tocilizumab compared with methotrexate in the '1st biologic model' and around £30,000 to £36,000 per QALY gained for abatacept, adalimumab, etanercept and tocilizumab compared with methotrexate in the '2nd biologic model'. The Committee considered the Assessment Group's scenarios tested in the '1st biologic model': assuming that people with remission stop treatment; assuming that the health resource costs differ when on methotrexate or a biological treatment; assuming that caregivers experience a decrease in quality of life; and assuming a younger starting age in the model; the Committee considered all these more plausible than the Assessment Group's base-case analysis. Applying these assumptions individually resulted in lower ICERs for all 3 technologies (adalimumab, etanercept and tocilizumab) compared with methotrexate than the base case. The Committee agreed that the discounting rates in the current NICE reference case should be applied in the model. The Committee also noted that, in the '2nd biologic model', the only assumption the Assessment Group had tested was around the younger starting age, which decreased the ICER for all 4 technologies compared with methotrexate in this model. It considered that this scenario was more plausible than the Assessment Group's base case in the '2nd biologic model'. The Committee concluded that the Assessment Group's scenario assumptions (except a scenario that used a different discount rate to the current NICE methods guide) were appropriate and should be applied.

4.49 The Committee discussed the cost-effectiveness evidence submitted by the companies. It noted that only Roche, the marketing authorisation holder for

tocilizumab, had submitted a cost-effectiveness model. The Committee considered that the Roche model had a structure similar to the Assessment Group model and had used the same source of utility values. It noted that the models differed mainly in that the Roche model did not model flare but rather ACR Pedi, and that whether a patient stopped treatment depended on a person's ACR Pedi response. The Committee also noted that Roche had presented results only for a comparison between tocilizumab and adalimumab rather than for all 4 biological treatments compared with each other or with methotrexate. The Committee considered that, despite the differences in the models, the results of Roche's model were consistent with the results of the Assessment Group's '1st biologic model' for tocilizumab and adalimumab. The Committee concluded that these data, and information provided by the other companies, supported the results from the Assessment Group's model.

4.50 The Committee discussed whether abatacept, adalimumab, etanercept and tocilizumab were innovative and whether they had substantial, demonstrable and distinctive benefits adequately captured in the modelling of the QALYs. The Committee noted that, when introduced years ago, these technologies were a step change compared with non-biological treatments for treating JIA. It heard from the clinical experts that biological treatment options were critically important when treating JIA. The Committee were aware that, because of data limitations, there were outcomes that had not been included in the modelling. It considered this meant that the benefits of the technologies may not have been fully captured in the modelling. The Committee concluded that, even though abatacept, adalimumab, etanercept and tocilizumab are not new to the market, they remain a step change in the treatment of JIA, and that there were demonstrable and distinctive benefits of the technologies that had not been captured in the QALY calculations. The Committee further concluded that the technologies were innovative and this should be taken into account in its decision-making.

4.51 The Committee considered whether it should take into account the consequences of the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism, when appraising abatacept, adalimumab, etanercept and tocilizumab. It noted that neither the Assessment Group nor the companies had made a case for its relevance in this appraisal. The Committee noted NICE's position statement in this regard, and accepted the

conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The Committee heard nothing to suggest that there is any basis for taking a different view on the PPRS to this appraisal of abatacept, adalimumab, etanercept and tocilizumab. It therefore concluded that the PPRS payment mechanism was not applicable when considering the cost effectiveness of these technologies.

4.52 The Committee discussed factors that the Assessment Group had not included in its models and how each may have impacted the ICER had they been included. The Committee considered factors that it would expect to increase the ICER for the biological treatments compared with methotrexate (in both models) including:

- starting treatment with a biological treatment earlier in people with milder JIA
- double counting the disutility associated with disease flare and
- assuming that, in a proportion of people, JIA resolves naturally.

Factors that would be expected to decrease the ICER for biological treatment compared with methotrexate in both models were:

- corticosteroid sparing
- a lower risk of impaired growth
- decreasing utility over time for people with inadequately managed JIA
- a lower risk of joint damage and joint surgery and
- a positive effect of biological treatment on uveitis and vision complications.

The Committee concluded that, taking into account its preferred assumptions from the Assessment Group's scenario analyses plus the likely impact of factors not included in the modelling, the Assessment Group's base case was likely to overestimate the most plausible ICERs for abatacept, adalimumab, etanercept and tocilizumab compared with methotrexate. It further concluded that, taking into account the innovative nature of abatacept, adalimumab, etanercept and tocilizumab, it was reasonable to consider that these technologies were a cost-effective use of NHS resources. The

Committee concluded that abatacept, adalimumab, etanercept and tocilizumab be recommended, within their marketing authorisations, as options for treating polyarticular (onset and course), enthesitis-related and psoriatic JIA.

4.53 The Committee noted that each technology's marketing authorisation stipulates inadequate, insufficient or no response to a specific treatment. However, the Committee noted that the marketing authorisations did not define inadequate, insufficient or no response. The Committee discussed whether it needed to define starting criteria in its recommendations. It noted that NHS England, in its interim commissioning guidance, had defined critical criteria response and treatment failure, but that this guideline would be superseded by NICE guidance. The Committee considered that it was not necessary to define inadequate, insufficient or no response because the clinical experts had not presented this as an issue in clinical practice, and determining response appeared to be widely understood by clinicians.

4.54 The Committee noted that each technology's marketing authorisation suggests the time point at which stopping treatment should be considered because of no response to treatment (see section 3). The Committee considered whether a stopping rule was necessary to include in its recommendations.

- The Committee noted that, in the Assessment Group's model, people stopped treatment if the treatment did not work, but the Assessment Group did not apply the specific stopping criteria suggested in the summary of product characteristics for each of the technologies.
- The Committee noted that, for the first 3 months of treatment, the rates of stopping treatment in the Assessment Group's model were based on the proportion of people whose disease had not responded to treatment in the randomised controlled trials.
- The Committee noted that it had not been presented with any evidence to suggest the rates of non-response to treatment would be greater in clinical practice than in the clinical trials.
- It also heard from clinical experts that, because there were 4 biological treatment options, people would switch biological treatment if their disease

had not responded (that is, people would not continue to take an ineffective biological treatment).

- The Committee therefore considered that the Assessment Group's model reflected the length of time people would continue to take a biological treatment if it was not working in clinical practice. The Committee recognised that taking biological treatments for a shorter time than that modelled would improve the cost effectiveness of each of the technologies.

  The Committee concluded that it was not necessary to define stopping criteria in its recommendations because this was defined in the marketing authorisations and the Committee was satisfied that treatment duration with abatacept, adalimumab, etanercept and tocilizumab in clinical practice was unlikely to exceed the treatment duration on which the cost-effectiveness estimates and its recommendations were based.

4.55 The Committee noted the potential equality issue raised by consultees during scoping. The consultees noted that the recommendations in NICE's previous technology appraisal guidance on the use of etanercept for the treatment of juvenile idiopathic arthritis stipulated that etanercept was recommended for children aged 4 years to 17 years, and that this may restrict access to etanercept for people who may need on-going treatment after 17 years. The Committee heard that, at the time of this guidance, the recommendation reflected the marketing authorisation. The Committee was aware that the marketing authorisation of etanercept has changed since then and no longer includes an upper age limit. The Committee noted that the recommendations refer to the ages covered by each technology's marketing authorisations.

5 Implementation

5.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has juvenile idiopathic arthritis and the healthcare professional responsible for their care thinks that abatacept, adalimumab, etanercept or tocilizumab is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Recommendations for further research

6.1 The Committee noted a paucity of data on the effect of biological treatments for JIA on long-term outcomes and quality of life. It noted that continued collection of data on long-term outcomes and quality of life would improve the evidence base for juvenile idiopathic arthritis.

7 Appraisal Committee members, guideline representatives and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Amanda Adler (Chair)
Consultant Physician, Addenbrooke's Hospital

Professor Ken Stein (Vice Chair)
Professor of Public Health, University of Exeter Medical School

Dr Ray Armstrong
Consultant Rheumatologist, Southampton General Hospital

Dr Jeff Aronson
Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

Mr Matthew Campbell-Hill
Lay member

Mr Mark Chapman
Health Economics and Market Access Manager, Medtronic UK

Dr Peter Crome
Consultant, Geriatrics

Dr Neil Iosson
Locum General Practitioner

Mrs Anne Joshua
NHS 111 Pharmacy Lead, Patients and Information, NHS England

Dr Sanjay Kinra
Reader in Clinical Epidemiology and Honorary Consultant in Paediatrics, London School of Hygiene and Tropical Medicine and University College London NHS Hospitals Trust

Mr Christopher O'Regan
Head of Health Technology Assessment & Outcomes Research, Merck Sharp & Dohme

Professor Stephen Palmer
Professor of Health Economics, Centre for Health Economics, University of York

Dr Sanjeev Patel
Consultant Physician & Senior Lecturer in Rheumatology, St Helier University Hospital

Dr John Pounsford
Consultant Physician, Frenchay Hospital, Bristol

Dr Nicky Welton
Senior Lecturer in Biostatistics and Health Technology Assessment, University of Bristol

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project

manager.

Dr Mary Hughes
Technical Lead

Eleanor Donegan
Technical Adviser

Jeremy Powell
Project Manager

8 Sources of evidence considered by the Committee

The assessment report for this appraisal was prepared by the Southampton Health Technology Assessments Centre:

- Shephard J, Cooper K, Harris P et al., The clinical and cost-effectiveness of abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis: a systematic review and economic evaluation, July 2015

The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, assessment report and the appraisal consultation document. Companies, professional or expert and patient or carer groups, and other consultees, were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

Companies:

- AbbVie
- Bristol-Myers Squibb
- Pfizer
- Roche Products

Professional or expert and patient or carer groups:

- British Society for Paediatric and Adolescent Rheumatology
- National Rheumatoid Arthritis Society
- Primary Care Rheumatology Society
- Royal College of Paediatrics & Child Health
- Royal College of Pathologists
- Royal College of Physicians

Other consultees:

- Department of Health
- NHS England
- Welsh Government

Commentator organisations (without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland

The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on abatacept, adalimumab, etanercept and tocilizumab by attending the initial Committee discussion and/or providing a written statement to the Committee. They are invited to comment on the appraisal consultation document.

- Dr Hana Alachkar, Consultant Immunologist, nominated by the Royal College of Pathologists – clinical expert
- Dr Kate Armon, Consultant Paediatric Rheumatologist, nominated by the British Society for Paediatric and Adolescent Rheumatology – clinical expert
- Helen Berger, nominated by the National Rheumatoid Arthritis Society – patient expert
- Ailsa Bosworth, Chief Executive Office of the National Rheumatoid Arthritis Society, nominated by the National Rheumatoid Arthritis Society – patient expert

Representatives from the following companies attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- AbbVie
- Bristol-Myers Squibb
- Pfizer

- Roche Products

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