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Bristol-Myers Squibb (BMS) abatacept submission for NICE Multiple Technology Appraisal (MTA) ID738:

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

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Abbreviations

Abbreviation	Definition
ACR	American College of Rheumatology
ACR Pedi	American College of Rheumatology paediatric response criteria
ACR Pedi 30	American College of Rheumatology paediatric response ≥30%
Admin	Administration
AEs	Adverse events
APC	Antigen-presenting cells
bDMARD(s)	Biological disease modifying anti-rheumatic drug(s)
CHAQ	Childhood Health Assessment Questionnaire
CHQ	Child Health Questionnaire
CI	Confidence interval
CSHQ	Children's Sleep Habits Questionnaire
DB	Double-blind
DMARDs	Disease-modifying anti-rheumatic drugs
DNA	Deoxyribonucleic acid
ESR	Erythrocyte sedimentation rate
HRQL	Health-related quality of life
IL	Interleukin
IR	Incidence rate
JIA	Juvenile idiopathic arthritis
LTE	Long-term extension
MTX	Methotrexate
MHC	Major histocompatibility complex
MIMS	Monthly Index of Medical Specialties
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSAID	Non-steroidal anti-inflammatory drug
OLE	Open-label extension
PAS	Patient access scheme
Pers. Comm.	Personal communication
PhS	Physical
PPD	Purified protein derivative
PSA	Probabilistic sensitivity analysis
PsS	Psychosocial
QALYs	Quality-adjusted life years
RF	Rheumatoid factor
RR	Relative risk
SAEs	Serious adverse events
SD	Standard deviation
TB	Tuberculosis
TCR	T-cell receptor
TNF	Tumour necrosis factor
VAS	Visual analogue scale

1 Executive summary

Juvenile idiopathic arthritis (JIA) is the umbrella term for all forms of arthritis of unknown aetiology that persist for at least 6 weeks and begin in patients younger than 16 years of age.[1] JIA is characterised by persistent joint swelling, pain and limitation of movement and has an estimated incidence in the UK of 1 per 10,000 children and a prevalence in the order of 1 per 1,000 children.[2]

JIA is initially treated with disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate. Patients with inadequate response to methotrexate are subsequently treated with the tumour necrosis factor (TNF) inhibitor, etanercept (Enbrel®, Pfizer). However, patients with polyarticular JIA who also have an inadequate response to a TNF inhibitor have very limited treatment options.[2,3] Biologic therapies with an alternative mode of action could provide additional treatment options for this patient group.

Intravenous abatacept (Orencia®, Bristol-Myers Squibb) in combination with methotrexate is indicated for the treatment of moderate-to-severe active polyarticular JIA in paediatric patients 6 years of age and older who have had an insufficient response to other DMARDs, including at least one TNF inhibitor.[4] Abatacept exerts its effects earlier in the immune cascade than TNF inhibitors. By preventing T-cell activation, abatacept inhibits a pivotal point in the immune cascade that is associated with both inflammation and joint destruction.[5]

The efficacy of abatacept was demonstrated in paediatric patients in a Phase III, double-blind, randomised, controlled, withdrawal trial involving 190 paediatric patients (6-17 years) with active JIA and an inadequate response or intolerance to at least one DMARD (the AWAKEN study).[6] The study consisted of three periods: an open-label lead-in period, a double-blind withdrawal period and an OLE period. The primary endpoint was time to flare of JIA. Flare was defined as worsening of 30% or more in at least three of the six American College of Rheumatology (ACR) core-response variables for JIA, and at least 30% improvement in no more than one variable during the double-blind period. After an initial 4-month open-label lead-in period, patients who had improved according to the ACR paediatric response criteria (ACR Pedi) definition were randomly assigned (1:1) to receive either abatacept or placebo for the double-blind period of 6 months. During the 6-month, double-blind withdrawal phase, the time to flare was shorter for patients given placebo than for those given abatacept (p=0.0002). Patients who were randomly assigned to receive abatacept were only about a third as likely to experience flare of JIA as those given placebo (hazard ratio 0.31, 95% confidence interval [CI] 0.16–0.59).[6]

The secondary endpoints were assessed at the end of the 6-month double-blind period and included the proportion of patients who had flare of JIA, changes from baseline in each of

the six ACR core variables and the assessment of safety and tolerability. Flare of JIA occurred in 53% (33/62) of patients in the placebo group during the double-blind period, compared with only 20% (12/60) of the patients in the abatacept group (p=0.0003).[6]

Unless they had discontinued due to safety reasons, all patients who completed the study or had a flare during the double-blind period, or were non-responders in the open-label period, were offered entry into the open-label extension (OLE). The OLE assessed long-term safety and efficacy for up to 7 years of total follow-up. Clinical efficacy was maintained in patients that continued abatacept treatment during the OLE. Additionally, some patients who did not achieve an ACR paediatric response ≥30% (ACR Pedi 30) in the open-label lead-in period but remained on abatacept therapy achieved clinical improvements [redacted] with continued therapy.[7,8]

In terms of safety, abatacept was well tolerated throughout the first two phases of the AWAKEN study, with low rates of adverse events (AEs), serious adverse events (SAEs) and infusional events as well as a high degree of patient retention . There were no incidences of opportunistic infections, tuberculosis or pneumonia during the study. The presence of anti-abatacept antibodies was not associated with significant efficacy or safety concerns. One case of lymphocytic leukaemia was reported (on Day 89 [open-label lead-in period]), but no other malignancies related to the study drug were observed.[6] Additional long-term exposure to abatacept in the OLE did not result in an increased safety risk when compared to short-term exposure.[7]

Along with etanercept and abatacept, other biological disease modifying anti-rheumatic drugs (bDMARDs) used in the treatment of JIA include the TNF inhibitor adalimumab (Humira®, AbbVie) and the IL-6 inhibitor tocilizumab (RoActemra®, Roche). There have been no head-to-head clinical trials conducted comparing bDMARDs in patients with JIA. However, a Bucher indirect comparison has indicated that etanercept, adalimumab and abatacept have comparable short-term efficacy for preventing disease flare after response to treatment in patients with polyarticular JIA, with p values for the relative risks varying from 0.16 to 0.85.[9] Our extension of this analysis to include tocilizumab[10] indicated that the four bDMARDs have similar short-term efficacy for this outcome. To investigate if there were any differences in the incidence of SAEs on the bDMARDs compared to placebo, we assessed the SAEs during the double-blind phase of the trials for abatacept[6], adalimumab[11], etanercept[12] and tocilizumab[10], using Fisher's exact test. We found that SAEs on bDMARDs were not significantly different than SAEs on placebo, with p values of 0.24, 0.49, 0.50 and 1 for etanercept, adalimumab, abatacept and tocilizumab, respectively. As the p values were all insignificant, we concluded that the incidence of SAEs on bDMARDs were similar to the

SAEs on placebo, and hence (in the absence of head-to-head studies), the incidence SAEs on bDMARDs were likely to be similar to each other.

Considering the similar safety and efficacy data between the bDMARDs, a cost-minimisation model was developed to assess the economic impact of using bDMARDs (in combination with methotrexate) in polyarticular JIA. In the base case, where patients received bDMARDs between the age of 12 (the starting age of the AWAKEN study)[6] and 17, abatacept was the least costly option, saving between [redacted] and [redacted] compared to other bDMARDs. When the time horizon was increased under the assumption that patients may continue treatment into adulthood, the savings resulting from abatacept treatment increased substantially. If patients continued treatment for 20 years, use of abatacept saved between [redacted] and [redacted] compared to other bDMARDs.

In addition to the immediate improvement in patient health, abatacept treatment has demonstrated socioeconomic advantages. The number of school days missed due to JIA are reduced by abatacept treatment and fewer work days may be missed by their parents or carers.[13] Abatacept treatment also leads to fewer restrictions in daily activities and reduces the need for carer/parental support.[13]

With its novel mechanism of action, good efficacy and tolerability and additional socioeconomic benefits, abatacept represents an alternative treatment for JIA in patients who have failed on TNF inhibitor therapy. Given the limited treatment alternatives for these patients, the clinical benefits of abatacept far outweigh the potential disadvantages of treatment, which mainly are concerned with the well-recognised and easily managed common side effects. Compared to alternative bDMARDs, abatacept is the least expensive treatment option, saving up to [redacted] depending on the treatment duration and comparator.

2 Background

2.1 Disease overview

JIA encompasses all forms of arthritis of unknown aetiology that persist for at least 6 weeks and begin in patients younger than 16 years.[1] JIA comprises several heterogeneous subtypes (oligoarthritis, polyarthritis, systemic, psoriatic, enthesitis-related and undifferentiated), all presenting with different clinical signs and symptoms.[1,3,14] Overall, JIA is characterised by persistent joint swelling, pain and limitation of movement and has an estimated incidence in the UK of 1 per 10,000 children and a prevalence in the order of 1 per 1,000 children.[2] Polyarticular JIA (classifiable as polyarthritis [rheumatoid factor-positive or -negative]) is characterised by arthritis affecting five or more joints during the first 6 months of the disease[1,3,14,15], and it affects 13%–37% of patients with JIA.[3]

JIA causes functional impairment due to joint and back pain, heel pain, swelling of joints and morning stiffness, contractures, pain and anterior uveitis leading to blindness.[16] This leads to suboptimal health-related quality of life (HRQL) in patients and parents or carers alike.[17,18] Moreover, as JIA patients reach adulthood, they face possible continuing disease activity, medication-associated morbidity, life-long disability and the risk of emotional and social dysfunction.[16]

2.2 Management of juvenile idiopathic arthritis

Management typically involves the use of non-steroidal anti-inflammatory drugs (NSAIDs) during diagnosis, while other arthritis causes are excluded.[2,3] Patients with a diagnosis of polyarticular JIA that is refractory to intra-articular steroids can be considered for treatment with DMARDs, the most widely used of which is methotrexate.[2,3] It is recommended that patients with polyarticular JIA whose condition has not responded adequately to a DMARD, such as methotrexate, should receive the TNF inhibitor etanercept.[2,3] Where patients with polyarticular JIA fail to achieve an adequate response after receiving treatment with a TNF inhibitor, subsequent treatment options can be limited. Biologic therapies with an alternative mode of action, such as abatacept or tocilizumab[4,19] could increase the treatment options for this patient group.

2.3 Role of T-cells in pathogenesis of juvenile idiopathic arthritis

T-cells are believed to have a crucial role in initiating the immune response cascade in JIA. Increased numbers of activated CD4+ and autoreactive CD8+ T-cells are found in the circulation and the synovium of polyarticular JIA patients.[20] No specific antigens that trigger

T-cell activation have been identified, but there are two major hypotheses on potential autoantigen groups. These include heat shock proteins and epitopes from the components of joint tissue found in the inflamed synovium. The synovial fluid from patients with polyarticular JIA contains higher levels of cytokines (including interleukin [IL]-12) and chemokines that upregulate the immune response.[20] Activated oligoclonal T-cells that originate in the blood are concentrated in the synovial fluid in larger numbers in JIA.[21] IL-17, produced by subsets of CD4+ cells in the synovium, was recognised to induce further local production of cytokines by synoviocytes, especially IL-6, IL-8 and matrix metalloproteinases that enhance joint destruction. IL-17 also suppresses regulatory T-cell (Treg, CD4+ CD25+) activity. Tregs have an important role in the process of autoimmune disease prevention and have been found in decreased numbers in patients with polyarticular JIA compared to patients with persistent oligoarthritis.[22]

2.4 Overview of abatacept

Abatacept in combination with methotrexate is indicated for the treatment of moderate-to-severe active polyarticular JIA in paediatric patients 6 years of age and older who have had an insufficient response to other DMARDs, including at least one TNF inhibitor.[4]

The recommended dose of abatacept for polyarticular JIA patients aged 6 to 17 years (who weigh less than 75kg) is 10mg/kg, calculated based on the patient's body weight at each administration. Paediatric patients weighing 75kg or more should follow the abatacept adult dosing regimen and should not exceed a maximum dose of 1,000mg. Abatacept should be administered as a 30-minute intravenous infusion. Following the initial administration, abatacept should be given at 2 and 4 weeks after the first infusion, and every 4 weeks thereafter.[4] The safety and efficacy of abatacept has not been evaluated in children under 6 years of age; abatacept is therefore not recommended for use in children under 6 years.

2.5 Abatacept mode of action and pharmacology

Abatacept has a different mode of action compared with the alternative bDMARDs available. Abatacept prevents T-cell activation, thus down-regulating the immune response of inflammatory disease. Therefore, abatacept exerts its effects earlier in the immune cascade than TNF inhibitors (Figure 1).[5]

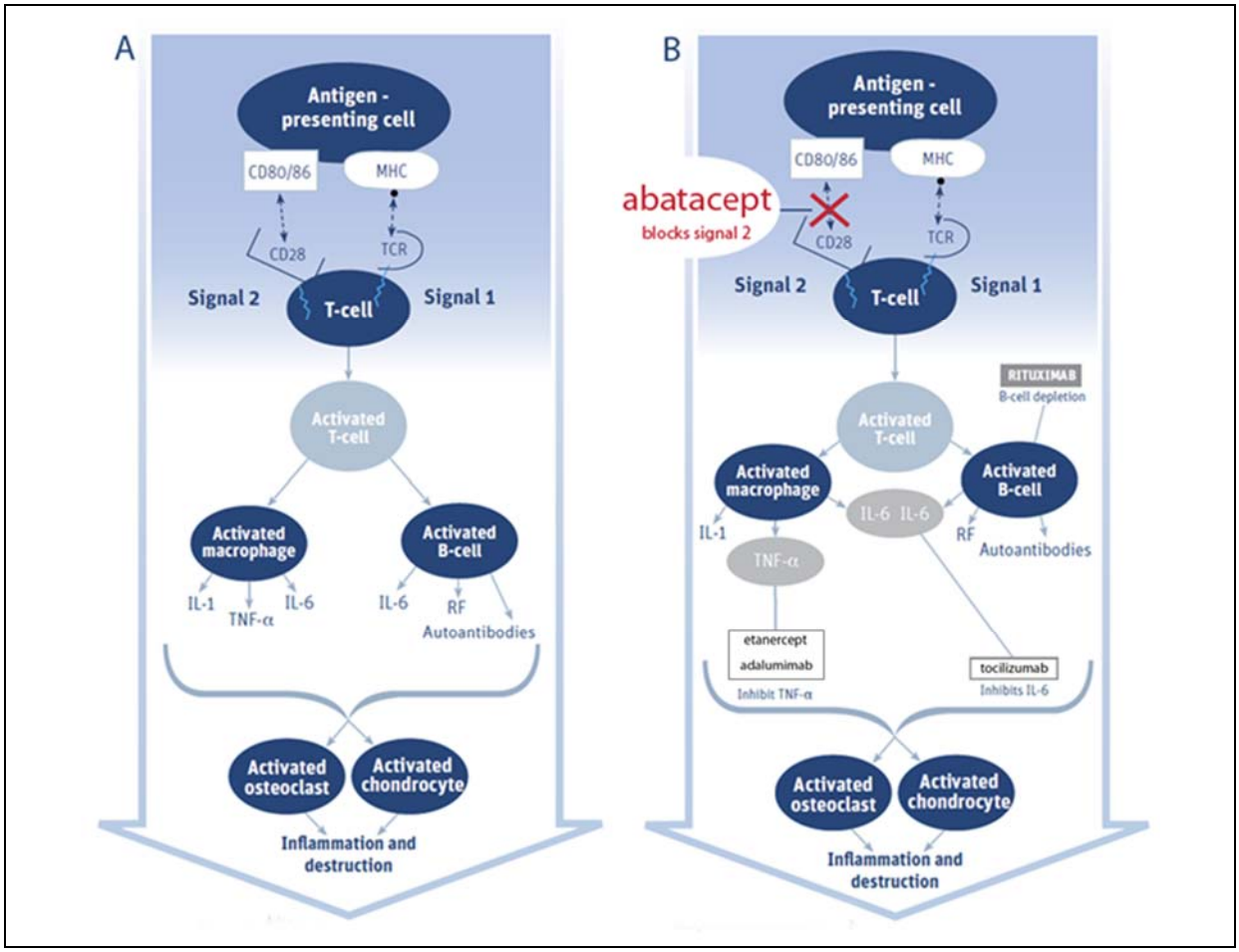
As previously mentioned, T-cells are believed to play a crucial role in initiating the immune response cascade in JIA.[20] Full T-cell activation requires the interaction of T-cells with antigen-presenting cells (APCs), which causes two signals that result from receptor interactions (Figure 1):[5]

- Signal 1: An APC internalises a relevant antigen, making it possible for the major histocompatibility complex (MHC) to bind and display antigen fragments on the cell surface. The MHC/antigen combination then binds to receptors on appropriate T-cells.
- Signal 2: This is generated by the co-stimulatory interaction of the CD80 and CD86 antigens on the surface of APCs with the CD28 antigen on T-cells.

Under normal conditions, a pathogen-derived peptide would lead to full T-cell activation. Over time, a regulatory protein, CTLA-4, is subsequently up-regulated on T-cells and binds to CD80 and CD86 with a much higher affinity than CD28. Unlike CD28, CTLA-4 blocks activation. This homeostatic mechanism keeps the immune system 'in check'. In the absence of CTLA-4, the activated T-cells continue to stimulate macrophages and B-cells to produce a variety of cytokines, which ultimately lead to the inflammation and destruction associated with JIA.

Abatacept is a fusion protein that consists of an 'active' extracellular CTLA-4 domain linked to a 'modified' Fc region of human immunoglobulin. Abatacept is a T-cell co-stimulation modulator with a unique mechanism of action, based on a naturally occurring pathway for immune regulation. By selectively modulating the CD80/CD86:CD28 co-stimulatory signal required for full T-cell activation, abatacept works at an earlier stage in the immune response cascade than the TNF inhibitors, etanercept and adalimumab, and the IL-6 inhibitor, tocilizumab (Figure 1). Abatacept binds to CD80 and CD86 and prevents the co-stimulatory signal (Signal 2) required for full T-cell activation, which restores immune homeostasis by modulating (but not depleting) T-cell activity, thereby reducing inflammatory cytokines towards normal physiologic levels. This subsequently prevents the downstream events that lead to joint damage and bone erosion, including the activation of rheumatoid factor (RF)-producing B-cells, macrophage activation and the production of inflammatory cytokines, such as TNF and interleukins (IL-1 and IL-6).[5]

Figure 1: Rheumatoid arthritis immune cascade and abatacept mechanism of action



Key: IL, interleukin; MHC, major histocompatibility complex; RF, rheumatoid factor; TCR, T-cell receptor; TNF, tumour necrosis factor.
Notes: Adapted from Choy 2009.[5]

Given that T-cell activation occurs at a pivotal point in the immune cascade of rheumatoid arthritis, influencing both inflammation and joint destruction, there is a strong rationale for therapies that target T-cell activity.[5] With its unique mode of action, which utilises a naturally occurring pathway of immune regulation, abatacept offers a novel alternative treatment for JIA patients who have failed on TNF inhibitor therapy, a population for whom therapeutic options are extremely limited.

2.6 Decision problem

The decision problem and approach for abatacept is summarised in Table 1.

Table 1: Decision problem approach

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	People with the following forms of JIA: polyarthritis (rheumatoid factor-positive, rheumatoid factor-negative and extended oligoarthritis, both onset and course) enthesitis-related arthritis psoriatic arthritis	Abatacept (Orencia®, Bristol-Myers Squibb) in combination with methotrexate for the treatment of moderate-to-severe active polyarticular JIA in paediatric patients 6 years of age and older who have had an insufficient response to other DMARD, including at least one TNF inhibitor.[4]	Aligned population with license wording.
Interventions being assessed	Etanercept (Enbrel®, Pfizer), abatacept, adalimumab (Humira®, AbbVie) and tocilizumab (RoActemra®, Roche), within their licensed indications.	Abatacept, a selective co-stimulation modulator that prevents T-cell activation and is administered intravenously.[4]	Abatacept is the product of interest in this submission.
Comparator(s)	DMARDs (such as methotrexate), if DMARDs can be tolerated Best supportive care, if DMARDs are not tolerated Etanercept, abatacept, adalimumab and tocilizumab should be compared with each other within their licensed indications where appropriate Biosimilars are not expected to be in established NHS practice at the time of appraisal and are not included as comparators	Etanercept, a recombinant TNF inhibitor that is administered subcutaneously.[23] Adalimumab, a recombinant TNF inhibitor that is administered subcutaneously.[24] Tocilizumab, a humanised monoclonal antibody that inhibits the cytokine interleukin-6; it is administered by intravenous infusion.[19]	As per the label, patients will have had an insufficient response to other DMARDs, including at least one TNF inhibitor; therefore, we consider the most relevant comparators for abatacept to be alternative bDMARDs.
Outcomes	The outcome measures to be considered include: • disease activity • disease flares • physical function,	The outcome measures to be considered include: treatment response (ACR Pedi) time to flare of JIA HRQL (CHQ)	Outcome measures used in clinical development of abatacept in JIA, most of which are aligned with those outlined in the scope.

	• joint damage • pain • corticosteroid-reducing regimens • extra-articular manifestations (such as uveitis) • body weight and height • mortality • adverse effects of treatment • HRQL	pain (CHAQ) sleep (CSHQ) participation in daily activities adverse effects of treatment	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account.	A cost minimisation model has been developed for the analysis, and hence, the model does not estimate QALYs. The time horizon for the base case is 6 years, which is sufficiently long to account for the differences in costs. Costs are considered from an NHS and Personal Social Services perspective. The PAS for abatacept is taken into account. The PAS discount for tocilizumab is confidential, and hence, a scenario analysis is conducted considering different discount levels for tocilizumab.	The indirect comparisons and Fisher's exact test suggested similar efficacy and safety for the bDMARDs. However, these comparisons are limited by small sample size and differences in both outcome measures and study population; therefore, developing a cost-effectiveness model was not considered appropriate due to the high level of uncertainty. In addition, since resource use is likely to be the only differentiator between the bDMARDs, a cost minimisation model was developed.
Subgroups to be considered	None	None	N/A

Key: ACR Pedi, American College of Rheumatology paediatric response criteria; CHAQ, Childhood Health Assessment Questionnaire; CHQ, Child Health Questionnaire; CSHQ, Children's Sleep Habits Questionnaire; bDMARDs, biological disease-modifying anti-rheumatic drugs; HRQL, health-related quality of life; JIA, juvenile idiopathic arthritis; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PAS, patient access scheme; QALYs, quality-adjusted life years; TNF, tumour necrosis factor.

2.7 Data issues

Limited data were available from controlled trials on the assessment of the clinical effectiveness and cost effectiveness of each of the interventions compared with potential comparators (and the other interventions) in patients with JIA.[9] There are no head-to-head clinical trials that have been conducted comparing bDMARDs in patients with JIA and no known published meta-analysis. Although the studies for etanercept, adalimumab and tocilizumab were similar in design, the paediatric population enrolled into the abatacept study was a broader population and included different JIA subtypes compared to the paediatric populations in the other trials. The abatacept study included patients with an age range of 6–17 years only, whereas the comparator trials included patients who were younger. In addition, the primary outcome of the abatacept study (time to flare of JIA[6]) was different from the etanercept, adalimumab and tocilizumab studies (proportion of patients experiencing a flare[10-12]).

3 Clinical efficacy

3.1 AWAKEN study methods

3.1.1 Introduction

Abatacept has been studied in JIA in a single Phase III, double-blind, withdrawal trial, (the AWAKEN study) that evaluated the efficacy and safety of abatacept in 190 paediatric patients (6-17 years) with active JIA with an inadequate response to, or intolerance to, at least one DMARD, including biologic agents such as etanercept, infliximab and adalimumab.[6]

After an initial 4-month open-label period, patients who had improved according to the ACR Pedi definition were randomly assigned (in a 1:1 ratio) to receive either abatacept or placebo for the 6-month double-blind period.[6] Unless they had discontinued due to safety reasons, all patients who completed, or had a flare during the double-blind period, or were non-responders in the open-label period, were offered entry into the OLE, which assessed long-term safety and efficacy, with up to 7 years of total follow-up.

3.1.2 Study objective

To assess the clinical efficacy and safety of abatacept in combination with methotrexate vs. placebo in combination with methotrexate in children and adolescents who had active JIA and either an inadequate response, or intolerance to, at least one DMARD, including some patients who had failed TNF inhibitor treatment.[6]

The primary endpoint was time to flare of JIA.

- Flare was defined as worsening of 30% or more in at least three of the six ACR core-response variables for JIA, and at least 30% improvement in no more than one variable during the double-blind period.
- If a global assessment by either physician or parent was used, flare was defined as a worsening of 20mm or more on the 100mm visual analogue scale (VAS).
- If the number of active joints or joints with limited range of motion was used for assessment, it was defined as worsening in two or more joints.

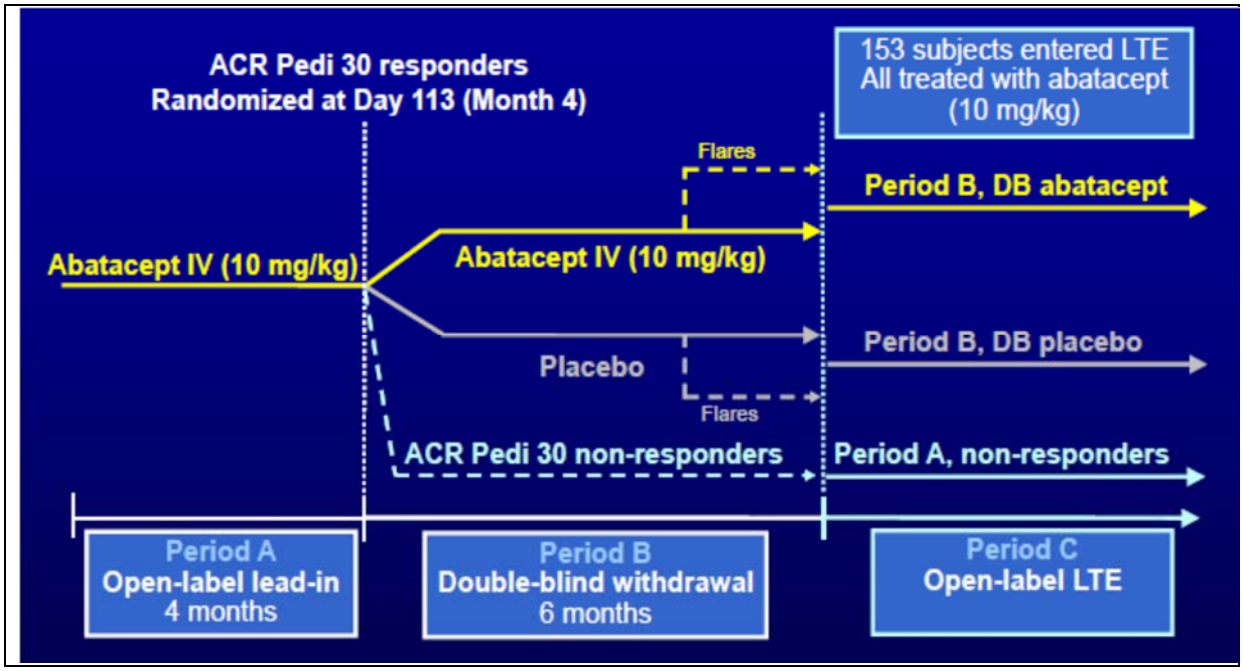
Secondary objectives assessed at the end of the 6-month double-blind withdrawal period included the proportion of patients who had disease flare, changes from baseline in each of the six ACR core variables and the assessment of safety and tolerability.

- Improvement was defined as an improvement of 30% or more in at least three of the six ACR core-response variables, and at least 30% worsening in not more than one variable.
- The level of improvement was determined by exploratory assessments of ACR Pedi, for response rates of 30%, 50%, 70% and 90%, which were conducted throughout the study.
- Disease status was also monitored, where inactive disease was defined as no joints with active arthritis, a normal erythrocyte sedimentation rate (ESR) of 20mm per hour or less, and a physician's global assessment of disease activity of less than 10mm on a 100mm VAS.

3.1.3 Study design

The AWAKEN study consisted of three periods: an open-label lead-in period, a double-blind withdrawal period and an OLE period (Figure 2).[6] A detailed description of the AWAKEN study methodology is given in Appendix 1.

Figure 2: AWAKEN study schematic overview



Key: ACR Pedi 30, American College of Rheumatology Paediatric response ≥30%; DB, double-blind; LTE, long-term extension; IV, intravenous.
Source: Ruperto 2008.[6]

3.1.4 Patient population

Eligible patients aged 6–17 years were enrolled from 45 paediatric rheumatology centres in Europe, Latin America and the USA. Enrolment criteria included at least five active joints (those with swelling or, in the absence of swelling, limited range of motion, accompanied by either pain or tenderness) and active disease (at least two active joints and two joints with a limited range of motion). Patients had JIA extended oligoarticular, polyarticular positive or negative for rheumatoid factor, or systemic onset with a polyarticular course but without systemic manifestations.[6] Only those patients who had an inadequate response, or intolerance, to at least one DMARD (including biological agents such as etanercept, infliximab and adalimumab) were enrolled. All DMARDS, except methotrexate, were withdrawn and prohibited during the trial.

Patients were excluded if they had active uveitis, major concurrent medical conditions, or were pregnant or lactating. All were asked to practice effective contraception as part of their consent to participate. Live vaccines were prohibited within 3 months of the first dose of study medication and throughout the study. All patients were evaluated for tuberculosis with a purified protein derivative (PPD) test during screening. Those with a positive PPD test result at the time of screening were not eligible for the study if they had evidence of active tuberculosis. Patients who had an isolated positive PPD test result were allowed to enter the study if they had completed at least 4 weeks of therapy for latent tuberculosis and had negative results of chest radiography at the time of enrolment.

3.1.5 Clinical assessments

Clinical assessments preceded drug administration at all visits. Patients were primarily assessed based on an ACR Pedi 30[25], using the following ACR Pedi variables[6]: the number of active joints; the number of joints with limited range of motion; a physician's global assessment of disease severity (100mm VAS); the parents' global assessment of patient's overall wellbeing (100mm VAS); functional ability with the validated translated version of the Childhood Health Assessment Questionnaire (CHAQ) disability index (0–3 point scale); and ESR.

For all components excluding ESR, assessments were collected at screening, baseline and each dosing visit in the 4-month open-label lead-in period (Days 1, 15, 29, 57, 85, 113) and the 6-month double-blind period (Days 29, 57, 85, 113, 141, 169). The ESR was collected at screening, Days 1 and 113 in the 4-month open-label lead-in period, and at all dosing visits in the 6-month double-blind period.

To minimise the variability in the assessment of joints, each participating centre had at least two certified joint assessors who underwent specific and standardised joint assessment training as mandated by the US Food and Drug Administration. Responder and flare status were determined by independent blinded evaluators at the coordinating centres of the Paediatric Rheumatology International Trials Organisation and the Paediatric Rheumatology Collaborative Study Group.

Patients were monitored for AEs, vital signs and laboratory assessments at each study visit. All AEs, SAEs and changes in vital signs for a minimum of 1 hour from the start of each infusion were recorded. Acute infusional events were defined as those reported within 1 hour of the start of the infusion.

3.1.6 Health-related quality of life assessments

In addition to the clinical assessments conducted during the AWAKEN study, health-related quality of life (HRQL) was assessed at baseline, in the open-label lead-in period and in the double-blind period.[13]

The parent-administered 50-item Child Health Questionnaire (CHQ) was used to assess physical, emotional and social aspects of HRQL in the children.[26] The questionnaire contains 15 separate domains (global health, physical function, physical role/social limitations, emotional role/social limitations, pain/discomfort, behaviour, global behaviour, mental health, self-esteem, general health, change in health, parental emotional impact, parental time impact, family activity and family cohesion). The higher the CHQ scores in each concept, the better the HRQL.

As well as the CHQ assessments, parents/caregivers rated how much average JIA-related pain they thought their child had experienced in the past week using the CHAQ.[26] Pain was measured by a 100mm VAS, with a higher score indicating more severe pain.[27] In addition, patients' sleep quality was measured using the Children's Sleep Habits Questionnaire (CSHQ), which includes 33 items grouped into eight subscales representing key clinical sleep symptoms: bedtime resistance, sleep-onset delay, sleep duration, sleep anxiety, night waking, parasomnias, sleep-disordered breathing and daytime sleepiness.[28] Finally, participation in daily activities for the child and the parent were assessed by a questionnaire focusing on the number of school days missed and the number of usual activity days missed by the parent per month.

3.2 AWAKEN study: results

3.2.1 Patient disposition

In the 4-month lead-in period, 190 patients were enrolled and given open-label treatment. Detailed baseline characteristics of the study population are presented in Table 2.

The overall mean number of active joints at baseline was 16.2 (SD 12.7) with 24 of 190 (13%) patients having between two and five active joints. Almost a third of patients had previously discontinued TNF inhibitor therapy. The distribution of the types of JIA was similar regardless of whether patients had received previous TNF inhibitor therapy. At randomisation, the number of active joints and joints with limited range of motion did not differ in the two treatment groups.[6]

Of the 190 enrolled patients, 90% completed the open-label lead-in period (Figure 3); 17 of the 20 patients who withdrew before randomisation did so because the treatment was not effective.[6]

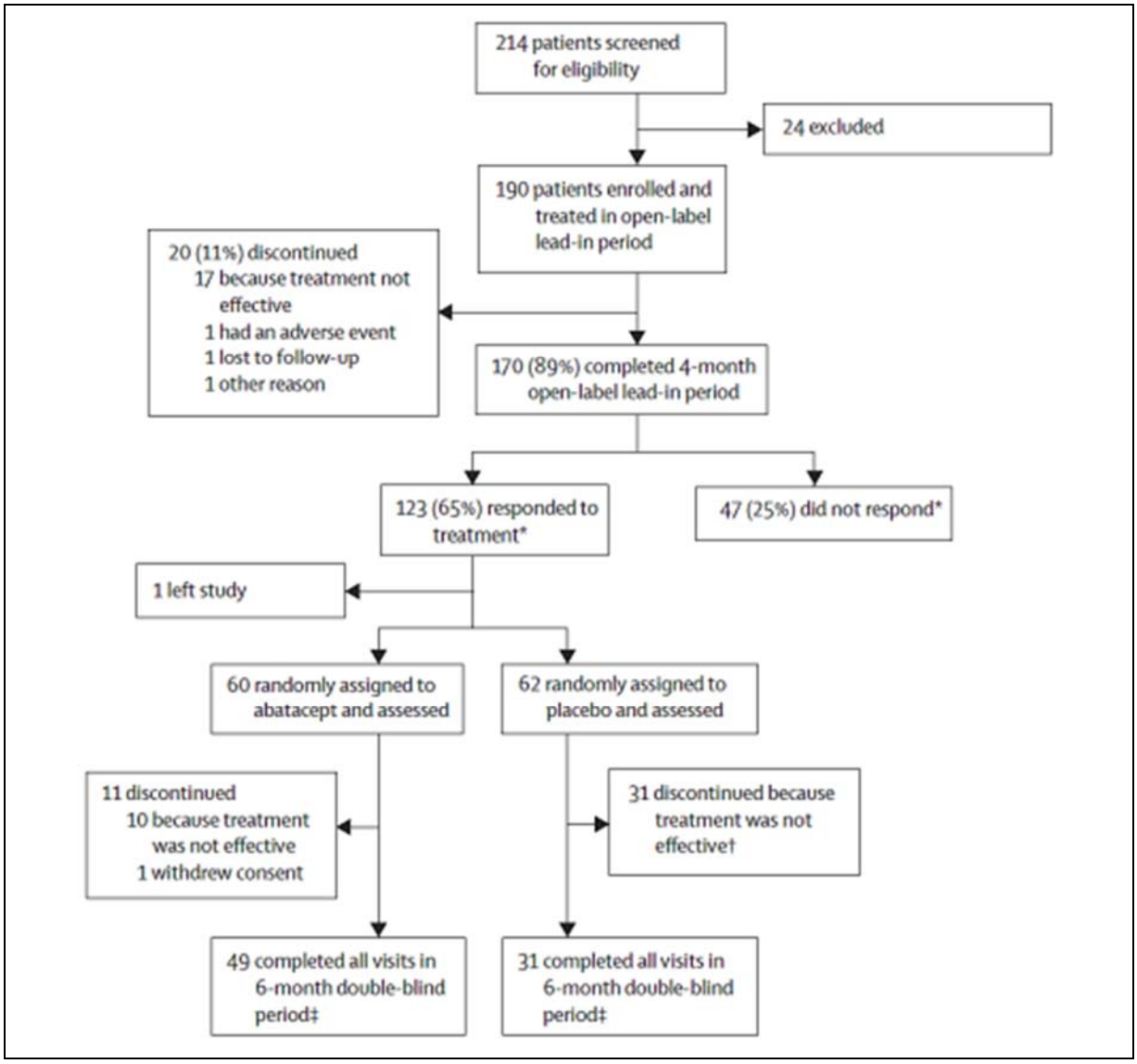
Table 2: Baseline patient demographics and clinical characteristics

Variable	4-month open-label lead-in period	6-month double-blind period	
	Abatacept N=190	Abatacept N=60	Placebo N=62
Age [years] – mean (SD)	12.4 (3)	12.6 (3)	12.0 (3)
Sex [female]	137 (72%)	43 (72%)	45 (73%)
Ethnic origin – n (%)			
White	147 (77%)	46 (77%)	49 (79%)
Black	15 (8%)	5 (8%)	4 (7%)
Other	28 (15%)	9 (15%)	9 (15%)
Duration of JIA [years] – mean (SD)	4.4 (3.8)	3.8 (3.7)	3.9 (3.5)
Number of active joints – mean (SD)	16.2 (12.7)	18.2 (11.5)	14.7 (12.8)
Fewer than five active joints – n (%)	24 (13%)	4 (7%)	8 (13%)
Five or more active joints – n (%)	166 (87%)	56 (93%)	54 (87%)
Number of joints with limited range of motion – mean (SD)	16.3 (14.5)	17.3 (13.2)	14.3 (13.7)
CHAQ disability index[a] – mean (SD)	1.3 (0.8)	1.3 (0.7)	1.2 (0.8)
Parent Global Assessment[b] – mean (SD)[*]	44.5 (24.6)	41.8 (22.5)	39.9 (24.7)
Physician Global Assessment[b] – mean (SD)[*]	54.2 (20.3)	53.5 (17.8)	52.7 (21.1)
JIA subtype – n (%)			
Persistent oligoarthritis	3 (2%)	0	2 (3%)

Variable	4-month open-label lead-in period	6-month double-blind period	
	Abatacept N=190	Abatacept N=60	Placebo N=62
Extended oligoarthritis	27 (14%)	9 (15%)	7 (11%)
Polyarthritis (positive for rheumatoid factor)	38 (20%)	14 (23%)	12 (19%)
Polyarthritis (negative for rheumatoid factor)	84 (44%)	26 (43%)	28 (45%)
Systemic	37 (20%)	11 (18%)	12 (19%)
Erythrocyte sedimentation rate [mm/h] – mean (SD)	32 (26.8)	30.8 (26.9)	31.4 (27.7)
C-reactive protein [mg/L] – mean (SD)	0.32 (0.44)†	0.29 (0.46)	0.27 (0.34)‡
Rheumatoid factor – n (%)			
Negative	149 (78%)	41 (68%)	50 (81%)
Positive	41 (22%)	19 (32%)	12 (19%)
Antinuclear antibodies – n (%)			
Missing	6 (3%)	3 (5%)	2 (3%)
Negative	129 (68%)	40 (67%)	39 (63%)
Positive	55 (29%)	17 (28%)	21 (34%)
Anti-double-stranded DNA – n (%)			
Missing	5 (3%)	3 (5%)	1 (2%)
Negative	159 (84%)	50 (83%)	50 (81%)
Positive	26 (14%)	7 (12%)	11 (18%)
Methotrexate dose [mg/m^2 per week] – mean (SD)	13.2 (4.7)§	13.5 (4.5)**	12.9 (4.0)††
Previous TNF inhibitor therapy discontinued – n (%)	57 (30%)	8 (13%)	13 (21%)
Because treatment ineffective	51 (27%)	7 (12%)	11 (18%)
For financial reasons	4 (2%)	1 (2%)	2 (3%)
Because family member had TB	1 (0.5%)	0	0
Unknown reason	1 (0.5%)	0	0

Key: CHAQ, Childhood Health Assessment Questionnaire; DNA, Deoxyribonucleic acid; JIA, Juvenile idiopathic arthritis; SD, Standard deviation; TB, Tuberculosis; TNF, Tumour necrosis factor.
Notes: [a] CHAQ scale of 1-3; [b] Visual analogue scale 0-100; * n=187, † n=189, ‡ n=61, § n=140, ** n=48, †† n=46.
Source: Ruperto 2008.[6]

Figure 3: AWAKEN study patient disposition



Notes: *Response according to the American College of Rheumatology definition of improvement.
†Two patients in the placebo group who discontinued because the treatment was not effective had no arthritis flare.
‡One patient in the treatment group and two in the placebo group had a flare on the last visit during the double-blind period.[6]

3.2.2 Open-label lead-in period

The ACR Pedi response rates after 4 months of open-label abatacept treatment in the lead-in period are presented in Figure 4.[6] At the end of the open-label treatment period (Day 113), 65% of the 190 enrolled patients had improved by 30% or more according to ACR Pedi.

Similar proportions of patients with different disease subtypes improved by 30% or more:

- 19 (63%) of 30 with oligoarticular extended disease
- 26 polyarticular (68%) of 38 who were positive for rheumatoid factor

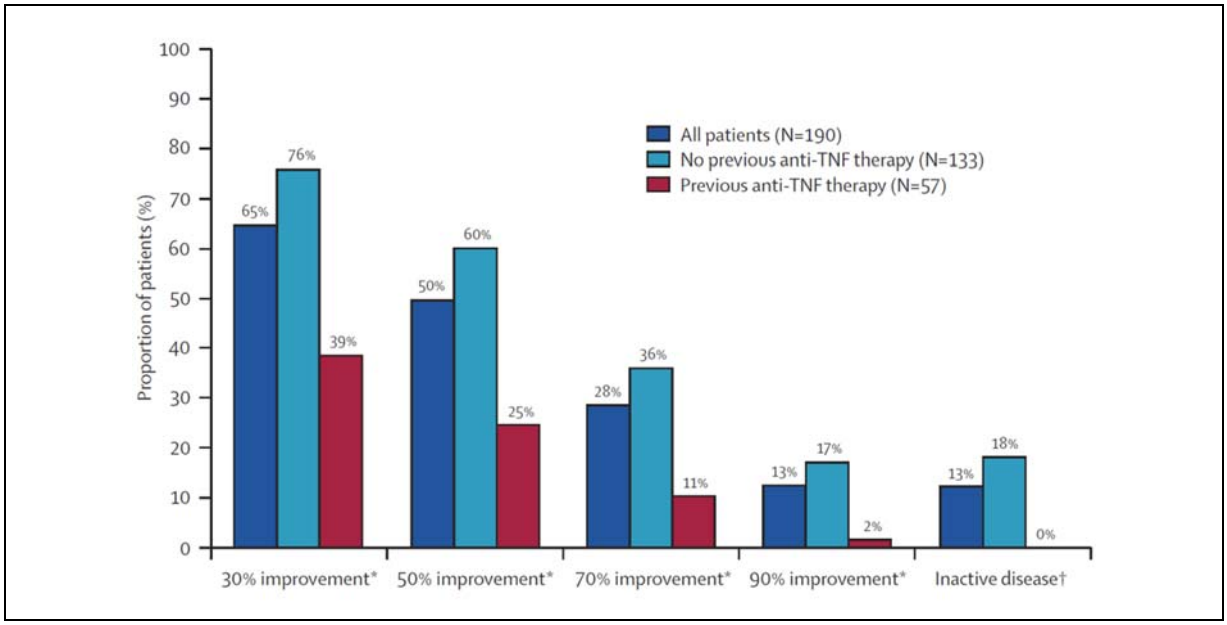
- 54 (64%) of 84 who were negative for polyarticular-rheumatoid factor
- 24 (65%) of 37 with systemic disease (p=0.969)

In the overall population (n=190), after 4 months of open-label treatment:

- 95 (50%) patients had improved by 50% or more,
- 54 (28%) patients had improved by 70% or more and
- 24 (13%) patients had improved by 90% or more.

Moreover, 24 patients (13%) had inactive disease status at Day 113.

Figure 4: Proportion of patients who had ACR Pedi response rates of 30%, 50%, 70% and 90% after 4 months of open-label treatment in the lead-in period



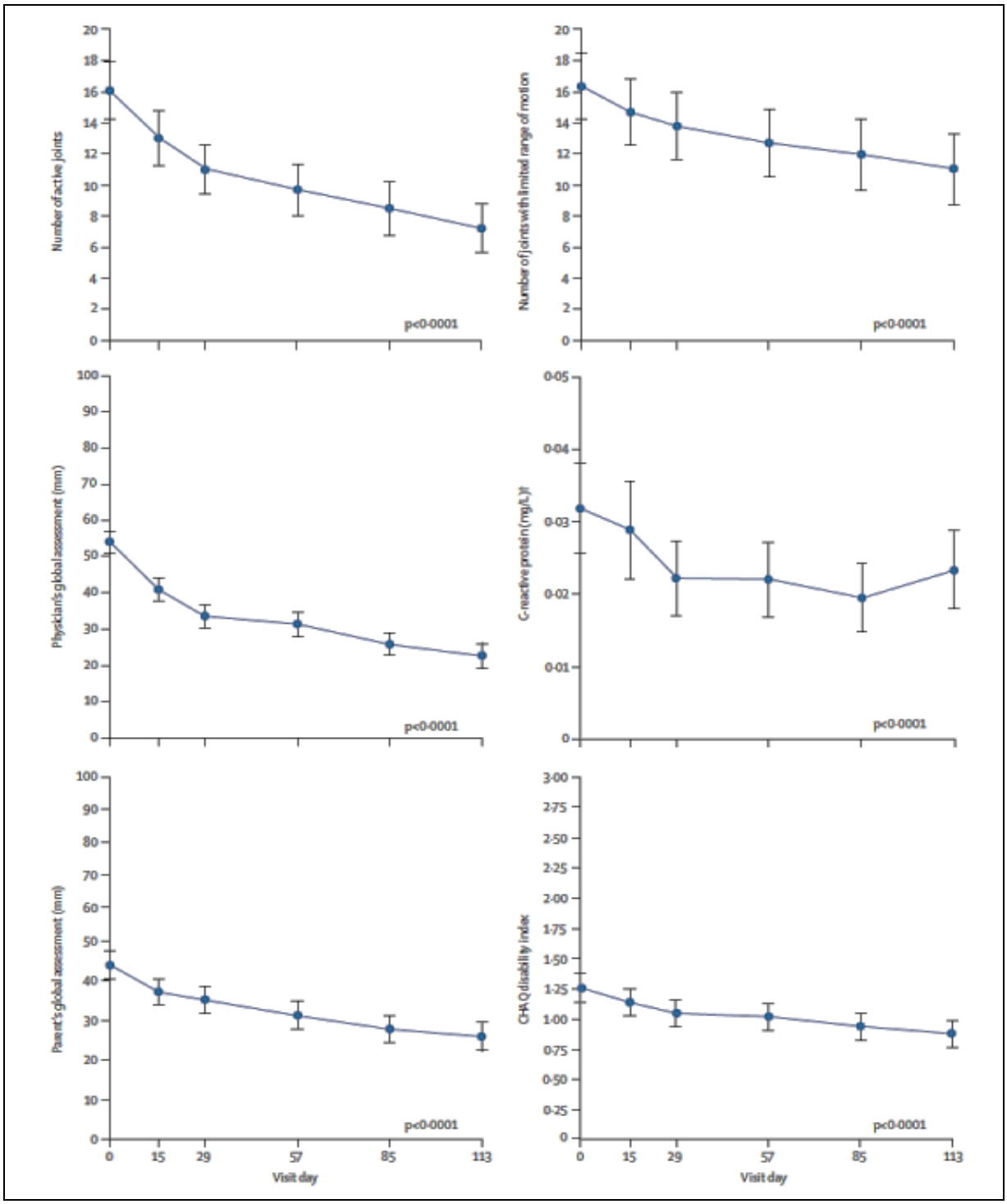
Key: ACR Pedi, American College of Rheumatology paediatric response criteria.
Notes: *According to the ACR Pedi responses. †Inactive disease defined as no joints with active arthritis, a physician's assessment of 10mm or less on a 100mm visual analogue scale and a normal erythrocyte sedimentation rate.[6]

Of the 133 (70%) patients who had not received previous TNF inhibitor therapy, 101 (76%) had an improvement of 30% or more after 4 months of open-label abatacept, compared with 22 (39%) of the 57 patients who had received previous TNF inhibitor therapy.

Furthermore, all 190 patients experienced significant improvements in the six ACR Pedi core-response variables (all p<0.0001) during the open-label lead-in period (Figure 5).[6]

Of the 47 patients who did not respond to abatacept during the lead-in period, 36 were given follow-up treatment in the OLE with abatacept, and 32 were assessed for ACR Pedi at Day 282: Of these 32 patients, 16 (50%) had an improvement of 30% or more, 10 (31%) had an improvement of 50% or more, 6 (19%) had an improvement of 70% or more, 2 (6%) had an improvement of 90% or more, and 1 (3%) had inactive disease.

Figure 5: Core-response variables during the 4-month open-label lead-in period in all 190 patients



Key: CHAQ, Childhood Health Assessment Questionnaire.
Notes: Data are mean (95% CI). p values represent the comparison of means over time. *According to the American College of Rheumatology Paediatric responses. †C-reactive protein, which was measured at all visits, is provided instead of erythrocyte sedimentation rate, which was captured only on Days 1 and 113, when clinical decisions had to be made.[6]

3.2.3 Double-blind period

Time to flare of JIA

Flare of JIA occurred in 33 (53%) of 62 patients in the placebo group during the double-blind period, compared with only 12 (20%) of the 60 patients given abatacept (p=0.0003).

Patients who were randomly assigned to receive abatacept were only about a third as likely to experience a flare of JIA as those given placebo (hazard ratio 0.31, 95% CI 0.16–0.59). Forty-two patients discontinued during the double-blind period (31 in the placebo group and 11 in the abatacept group); all but 1 (abatacept-treated patient) did so because the treatment was not effective.

The median time to flare of JIA in the placebo group was 6 months, and an insufficient number of events occurred in order to be able to calculate the inter-quartile range. An insufficient number of flare events occurred in the abatacept group for median time to flare to be calculated; however, there was a significant difference in the time to flare compared with placebo (p=0.0002; log-rank test; Figure 6).

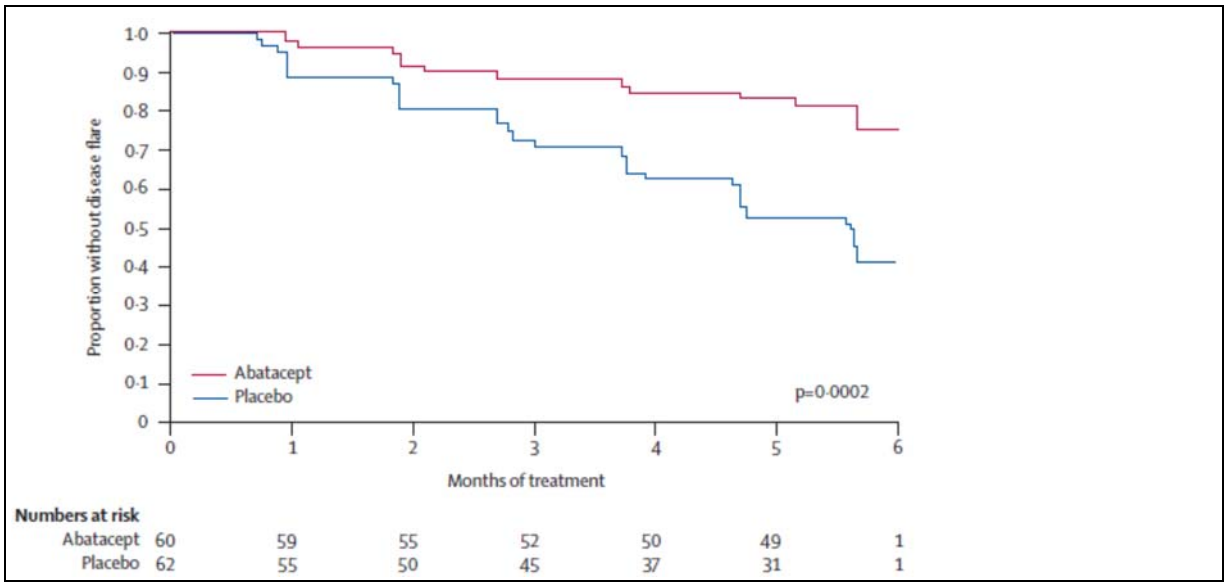
Disease activity improved or stabilised in patients who had abatacept in the double-blind period, as measured by the ACR Pedi, whereas it worsened in the placebo group (Figure 7).

After 6 months of treatment in the double-blind period, or at the time of flare for patients who did not complete this period:

- 49 (82%) patients in the treatment group improved by 30% or more, compared with 43 (69%) controls (p=0.1712)
- 46 (77%) patients given abatacept improved by 50% or more, compared with 32 (52%) controls (p=0.0071)
- 32 (53%) patients given abatacept improved by 70% or more compared with 19 (31%) controls (p=0.0185)
- 24 (40%) patients in the treatment group improved by 90% or more, compared with 10 (16%) controls (p=0.0062)

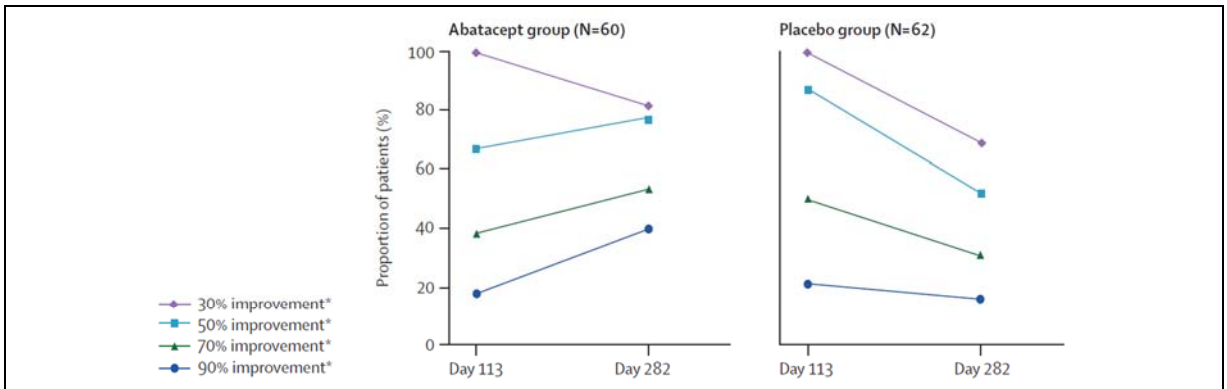
Inactive disease status was recorded for 18 (30%) patients given treatment, compared with 7 (11%) controls (p=0.0195).

Figure 6: Proportion of patients without disease flare during the 6-month double-blind period



Notes: Kaplan–Meier analysis of the time to disease flare during the double-blind withdrawal period. p value represents the comparison of the time to disease flare between the abatacept and placebo groups.[6]

Figure 7: Response rates and core variables during the 6-month double-blind period



	Abatacept group		Placebo group		p value†
Core-response variable	Day 113	Day 282	Day 113	Day 282	
Number of active joints	5·4 (5·5)	4·4 (7·0)	3·9 (5·9)	6·0 (5·8)	0·0245
Number of joints with limited range of motion	8·8 (10·7)	8·8 (12·8)	7·4 (12·6)	8·6 (12·0)	0·0128
Physician's global assessment	15·9 (12·5)	14·7 (18·9)	12·5 (12·5)	23·2 (21·8)	0·0004
Parent's global assessment	17·2 (16·2)	17·9 (22·2)	17·1 (16·8)	23·9 (21·6)	0·6992
CHAQ disability index	0·8 (0·8)	0·8 (0·9)	0·7 (0·6)	0·8 (0·7)	0·0388
Erythrocyte sedimentation rate (mm per hour)	22·2 (20·8)	25·1 (26·4)	23·1 (25·0)	30·7 (30·1)	0·9562
C-reactive protein (mg/L)	0·17 (0·24)	0·16 (0·25)	0·18 (0·33)	0·29 (0·54)	0·0255

Key: CHAQ, Childhood Health Assessment Questionnaire.
Notes: Data are mean (SD). We used the last-observation-carried-forward method. CHAQ=Childhood Health Assessment Questionnaire. *Improvement assessed according to the American College of Rheumatology Paediatric response criteria. †p value based on the difference in the adjusted mean percentage change from Day 113 to Day 282. Adjustment based on an ANCOVA model with treatment as the factor and baseline value as the covariate.[6]

3.2.4 *Open-label, long-term extension period*

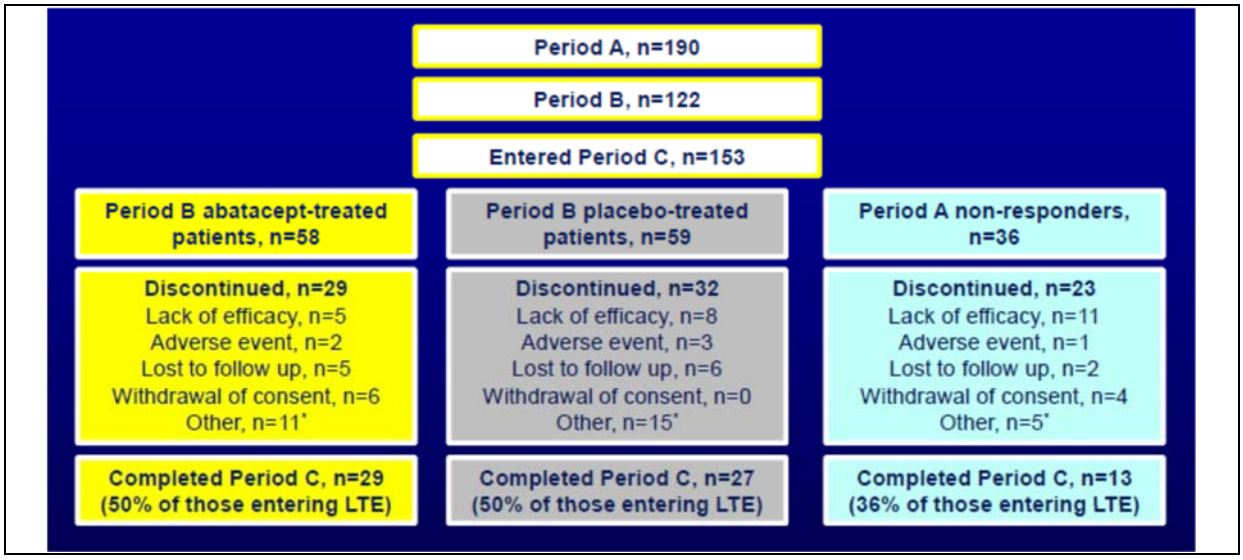
Data from the AWAKEN study's OLE period has been reported, including ≥56 months of the long-term extension (LTE) period and up to 7 years of total follow-up.[7] The patient disposition during the OLE is presented in Figure 8.

A total of 153 patients entered the OLE: 58 abatacept-treated patients from the double-blind period, 59 placebo-treated patients from the double-blind period and 36 non-responder patients from the initial open-label lead-in period. The mean exposure to abatacept for all groups combined ranged from 41.1 (SD 27.0) to 62.1 (SD 20.9) months. The cumulative exposure was 606.2 years.

The ACR Pedi for the combined abatacept- and placebo-treated groups is shown in Figure 9. The analysis was pre-specified and the data are for patients with disease measures available at the visit of interest (as observed).

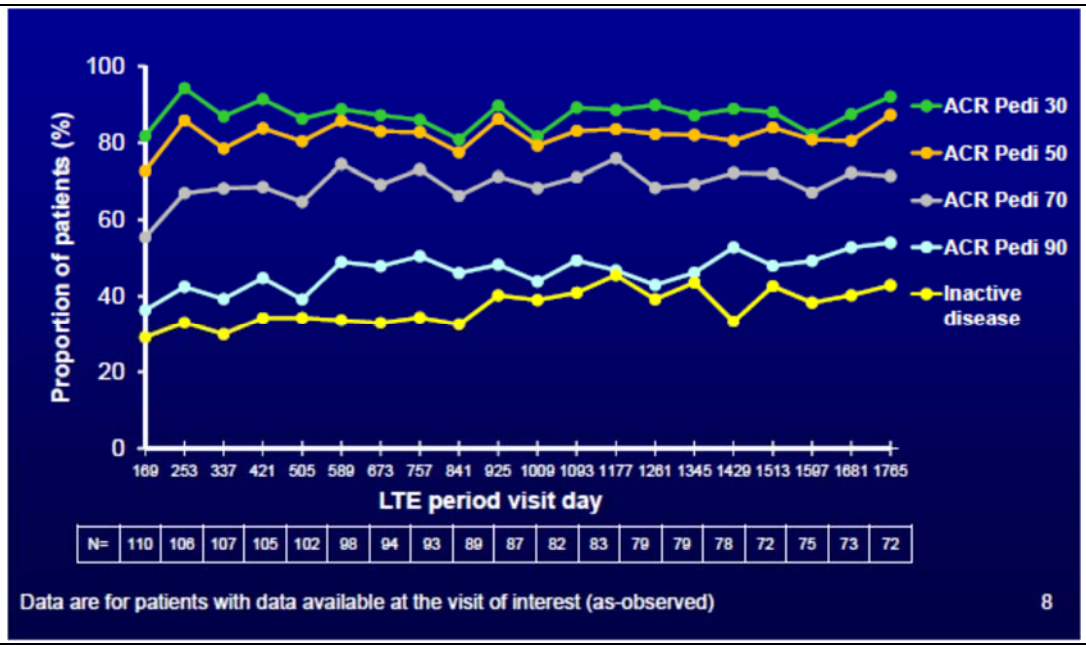
The OLE data show that abatacept provided clinical benefits that were maintained or increased over time. After withdrawal and then re-initiation of abatacept therapy, efficacy was restored. During the OLE, treatment with abatacept resulted in sustained clinical efficacy with continued long-term use. Some patients who did not achieve an ACR Pedi 30 in the open-label lead-in period and remained on abatacept therapy also achieved clinical improvements [redacted] with continued therapy.

Figure 8: Patient disposition of the AWAKEN study open-label, long-term extension



Key: LTE, Long-term extension.
Notes: *Other discontinuations included those related to institutional review board ethical decisions, patient choice and physician recommendations. Period A = open-label lead-in period; Period B = double-blind period; Period C = open-label, long-term extension period.[7]

Figure 9: American College of Rheumatology paediatric responses through the open-label extension for the open-label lead-in period responders



Key: ACR Pedi, American College of Rheumatology paediatric response criteria; LTE, Long-term extension.
Notes: ACR Pedi 30/50/70/90, American College of Rheumatology Paediatric response of ≥30/50/70/90%.[7]

3.2.5 Health-related quality of life findings from the AWAKEN study

Child Health Questionnaire scores

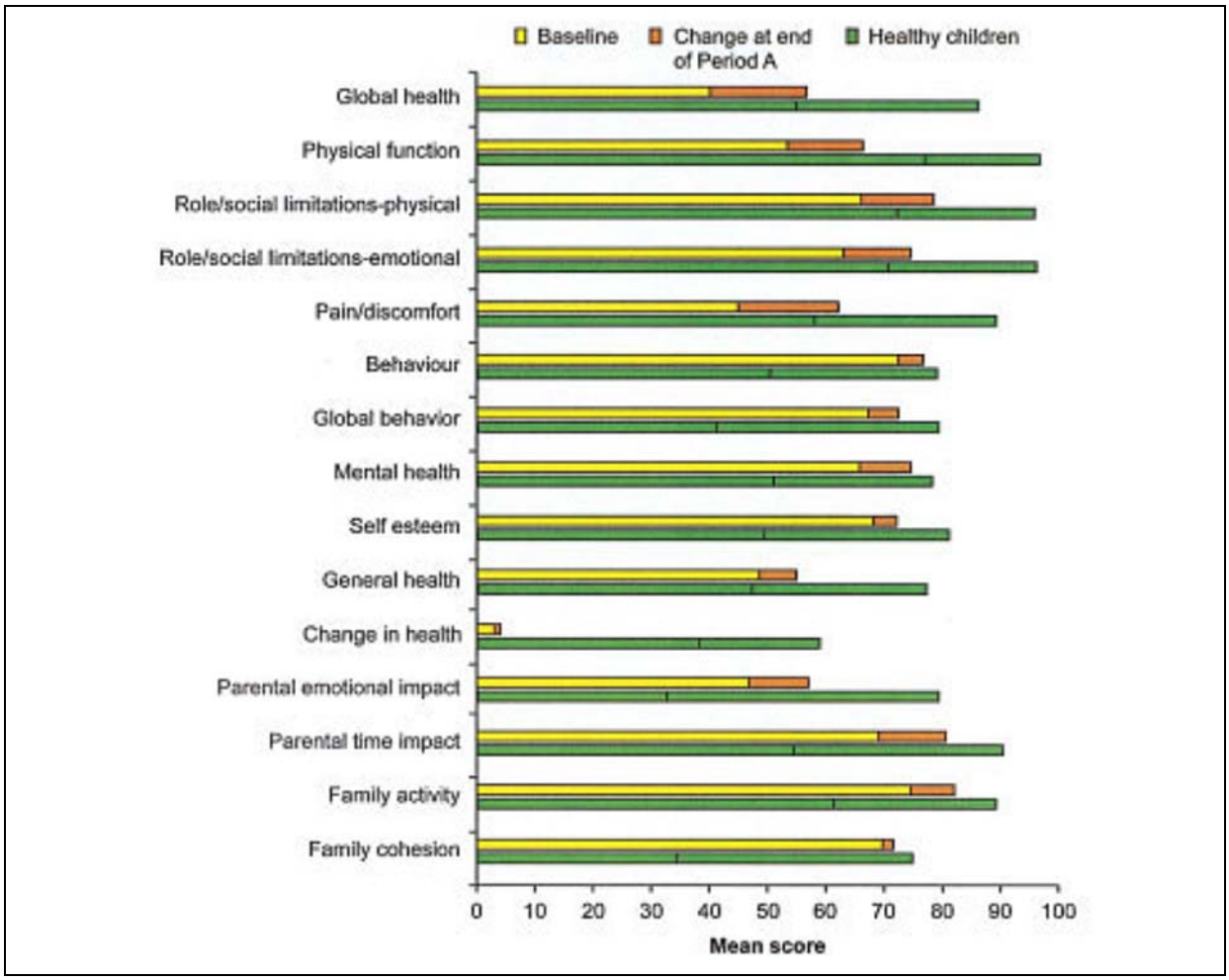
At baseline, patients with JIA had lower CHQ scores than healthy children in all domains. In particular, global health, physical function, emotional role/social limitations, physical role/social limitations and pain/discomfort were more than 2 standard deviations below the mean scores for healthy children. However, after 4 months of abatacept treatment in the open-label lead-in period, substantial improvements were seen across all of the CHQ domains. The domains of global health, emotional role/social limitations, physical role/social limitations and pain/discomfort improved to levels that were within 2 standard deviations of the mean scores for healthy children, with only physical function remaining more than 2 standard deviations below healthy controls (Figure 10).[13]

Moreover, at the end of the 6-month double-blind period, subjects who were randomised to continue on abatacept treatment had further mean improvements in all CHQ domains except for global behaviour. However, subjects randomised to placebo either remained stable or worsened, although differences were not statistically significant between the treatment groups (Figure 11). In both the abatacept and placebo groups, all of the CHQ domain scores were within 2 standard deviations from the mean of healthy controls at the end of the double-blind period.

Child Health Questionnaire physiological and psychosocial summary scores

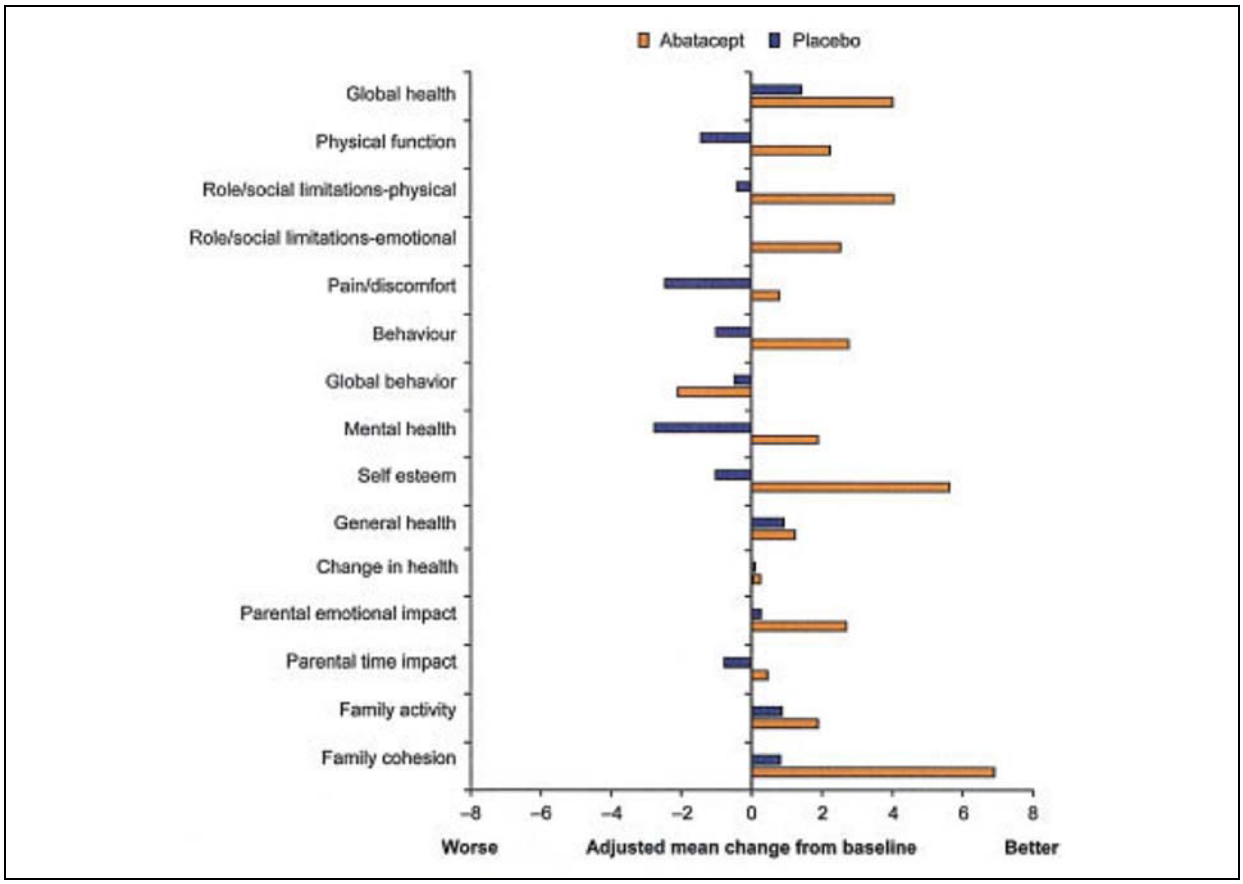
Improvements in the CHQ summary scores (Physical (PhS) and Psychosocial (PsS)) were seen with abatacept treatment in the open-label lead-in period in ACR Pedi 30 responders (from 30.1 to 41.8 for the PhS and from 43.6 to 49.2 for the PsS). The greatest improvements were seen in the PhS, with subjects entering the trial at approximately 2 standard deviations below the standardised mean score of 50 for the normative population, and improving to values within the range of the healthy normative population (mean±SD 50±10). During the double-blind period, improvements in both summary scores were maintained in subjects treated with abatacept (from 42.9 to 43.6 for the PhS and from 49.6 to 51.7 for the PsS), whereas reductions were observed in subjects who were randomised to placebo (p=0.666 for PhS and p=0.056 for PsS).[13]

Figure 10: Change over time in mean individual Child Health Questionnaire domain scores from baseline to the end of the open-label lead-in period.



Notes: The black lines on the green bars show -2 standard deviations. For abatacept-treated patients in the open-label lead-in period, n=172 except for global health (n=161); physical function (n=173); pain/discomfort (n=170); self-esteem and change in health (n=169); and parental time impact, family activity and family cohesion (n=171).[13]

Figure 11: Adjusted mean change from the beginning to the end of the double-blind period for patients who achieved an American College of Rheumatology Paediatric 30 improvement criteria response at the end of the open-label lead-in period.

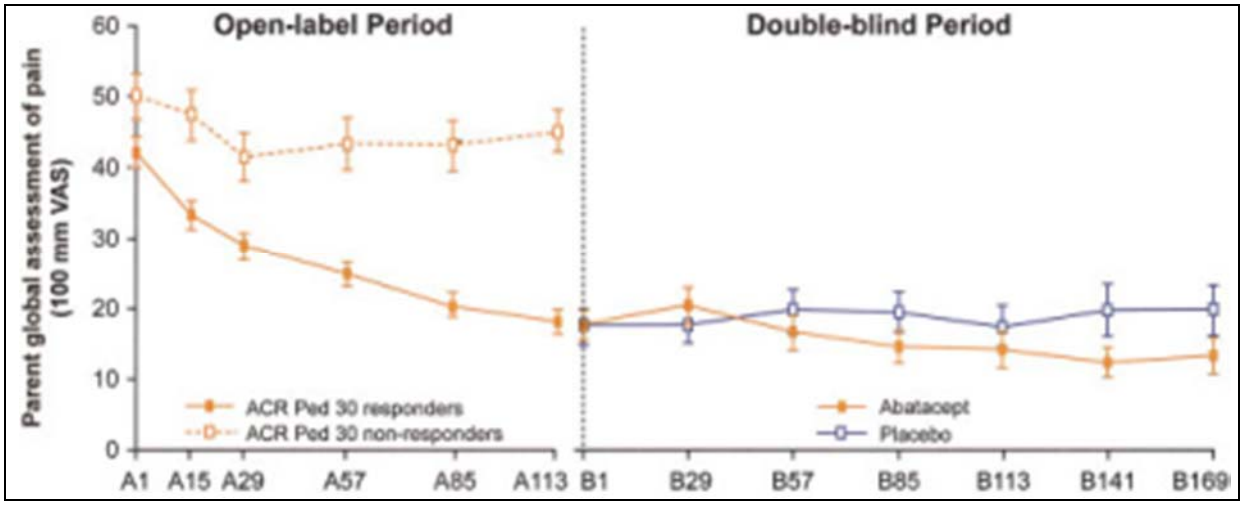


Notes: Sample sizes were n=52 for abatacept and n=34 for placebo, except for parental emotional impact, parental time impact, family activity, family cohesion, change in health and global behaviour (all n=33 for placebo); change in health and global behaviour (n=51 for abatacept); and global health (n=49 for abatacept and n=32 for placebo); p>0.05 for abatacept versus placebo for all subscales. The adjusted mean change in physical role/social limitation from baseline in placebo-treated patients was 0.01.[13]

Parent global assessment of pain

As shown above, a reduction in pain was observed with the CHQ pain/discomfort domain in the open-label lead-in period for all patients (Figure 10), as well as among those continuing on abatacept in the double-blind period (Figure 11). Similarly, in the open-label lead-in period, pain levels assessed by parents/caregivers on a 100-mm VAS as part of the CHAQ were reduced from baseline within 15 days of abatacept treatment in ACR Pedi 30 responders (-8.6) and were further reduced by the end of the period (-23.8). Reductions in pain were also observed in the subjects who did not achieve an ACR Pedi 30 by the end of the open-label lead-in period, although these were of a lower magnitude (reduction of -5.6 from baseline). Over the 6-month double-blind period, pain was further reduced in the abatacept group, whereas pain scores worsened in subjects randomised to placebo (p=0.105 for abatacept versus placebo) (Figure 12).[13]

Figure 12: Change over time in parent global assessment of pain



Key: ACR, American College of Rheumatology; VAS, Visual analogue scale.
Notes: Mean global parent assessment of pain (0–100-mm VAS) scores over open-label Period A for American College of Rheumatology Paediatric 30 (ACR Pedi 30) improvement criteria responders and non-responders, and over double-blind Period B for responders randomised to abatacept or placebo. Abatacept responders are defined as those subjects achieving at least an ACR Pedi 30 response by the end of Period A. Error bars show the standard error of the mean; p=0.105 for abatacept versus placebo at the end of the double-blind period.[13]

Sleep problem index scores

After 4 months of abatacept treatment in the open-label lead-in period, sleep problem index scores had decreased by 2.66 points from baseline in ACR Pedi 30 responders. The elements of sleep problems that showed the greatest improvement were bedtime resistance (-0.51), parasomnias (-0.46) and daytime sleepiness (-1.19).

During the double-blind period, sleep quality improved further in patients randomised to receive abatacept (CSHQ scores decreased by 0.72). The elements of sleep problems that improved the most in the double-blind period were bedtime resistance (-0.36), sleep anxiety (-0.29) and daytime sleepiness (-0.48). In contrast, among patients randomised to placebo, sleep quality deteriorated (CSHQ scores increased by 1.66; p=0.076 for abatacept versus placebo at the end of the double-blind period).[13]

Participation in daily activities

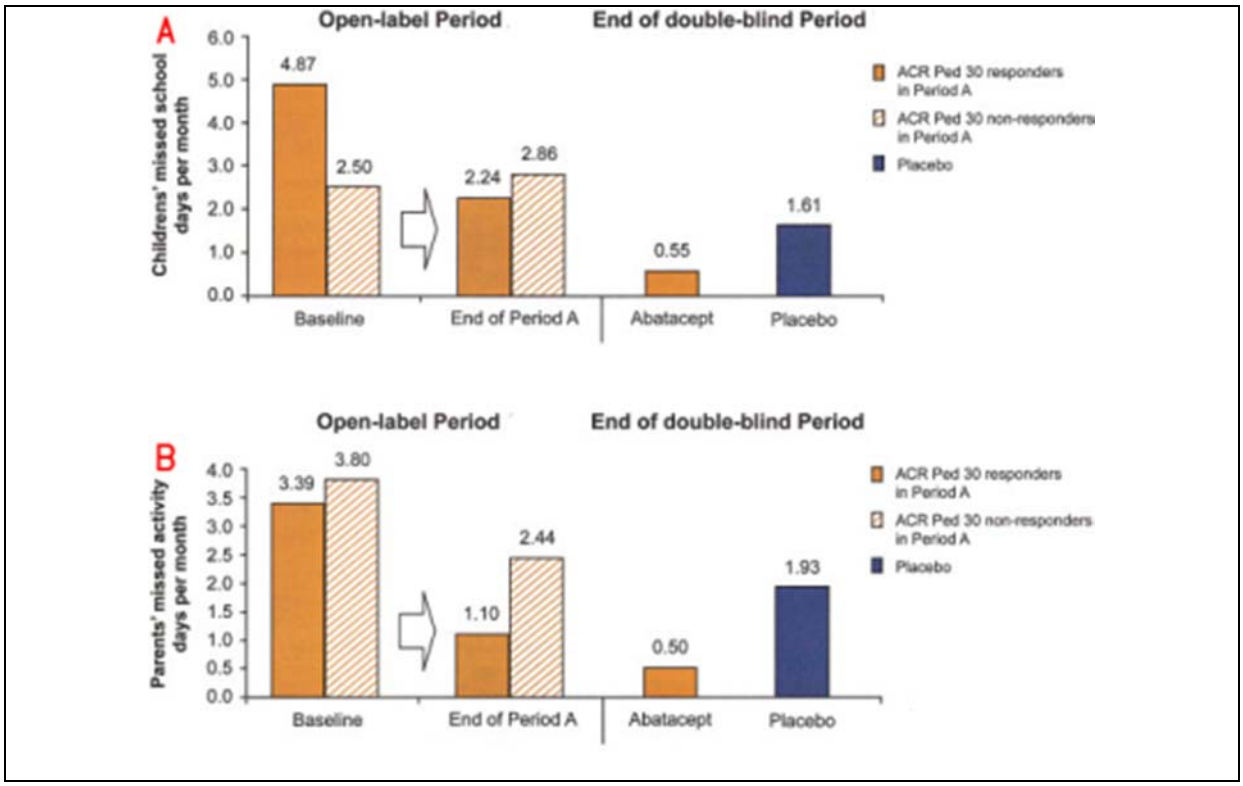
The mean number of missed school days at baseline for the ACR Pedi 30 non-responders was lower when compared with the ACR Pedi 30 responders. By the end of the open-label lead-in period, the number of missed school days per month was reduced by 2.6 days in abatacept-treated ACR Pedi 30 responders (Figure 13A).

The number of days of normal activity per month missed by parents, including work and non-work activities, was reduced by 2.3 days in ACR Pedi 30 responders (Figure 13B). The number of days when paid care was required was reduced by 1.14 days per month with

abatacept treatment in ACR Pedi 30 responders in the open-label lead-in period. Improvements in limitation of daily activities were either not observed or were of a lower magnitude among ACR Pedi 30 non-responders (Figure 13).

In the double-blind period, patients randomised to abatacept experienced a further 4-fold gain in school days (1.9 days); placebo-treated patients also experienced a further gain in school days, but of a lower magnitude than the abatacept group (0.9 days; p=0.033 for abatacept versus placebo). There were also further gains in days of usual activity for parents of patients in the abatacept group (0.2 days). Conversely, parents of patients in the placebo group experienced a loss of days of usual activity (-1.3 days; p=0.109 for the difference between groups). In the double-blind period, the number of days when paid care was required remained stable in both groups.[13]

Figure 13: Reduction in children's missed school days and parents' missed usual activity days



Key: ACR Pedi 30, American College of Rheumatology Paediatric 30 improvement criteria.[12]
Notes: A: mean number of children's missed school days per month at baseline, the end of the open-label lead-in period and the end of the double-blind period (p=0.033 for abatacept versus placebo).
B: mean number of parents' missed usual activity days per month at baseline, the end of the open-label lead-in period and the end of the double-blind period (p=0.109 for abatacept versus placebo).

3.3 Comparative efficacy

No head-to-head clinical trials have been conducted that have compared different bDMARDs in patients with JIA. In addition, no data from randomised controlled studies were available in relation to methotrexate in the treatment of JIA.

In a systematic review[9], efficacy data were retrieved from randomised controlled trials performed in JIA that included bDMARDs. Indirect between-drug comparisons were conducted only if trials were comparable with regard to design and patient characteristics related to treatment outcome.

The systematic review identified three withdrawal trials in patients with resistant polyarticular JIA, with one each for etanercept, adalimumab and abatacept, respectively. These were compared indirectly using the Bucher method.[29] Polyarticular JIA was defined in all trials as JIA with five or more active joints at any time during the disease course and included patients with systemic arthritis with a polyarticular course. In these three trials, the disease duration at baseline varied between 3.8 and 5.8 years, and the mean baseline age ranged from 10.6 to 12.3 years. The proportion of patients with systemic JIA with polyarthritis in the etanercept and abatacept trials was 33% and 19%, respectively; however, the proportion of patients with polyarthritis systemic JIA was not specified in the adalimumab trial. Inclusion of rheumatoid factor-positive patients was similar across all three trials (21–24%). In the abatacept trial, 17% of patients were previously non-responsive to TNF inhibitors, whereas there were none in the etanercept and adalimumab trials. Across the three trials, between 64% and 78% of patients who started treatment in the open-label lead-in phase entered the double-blind phase. Baseline disease characteristics of the patients included in the double-blind phase with regard to the number of joints with arthritis, a physician's assessment of disease activity and CHAQ scores were comparable between the three trials.

Indirect comparisons demonstrated similar short-term efficacy of etanercept, adalimumab and abatacept in preventing disease flare after response to treatment in patients with polyarticular JIA (The authors concluded that, owing to differences between available trials, more analogous trials and head-to-head trials directly comparing bDMARDs are required. Currently, paediatric rheumatologists must make treatment decisions based on indirect comparisons, supplemented by cohort studies and safety, practical and financial arguments (Table 3 and Table 4).[9]

The authors concluded that, owing to differences between available trials, more analogous trials and head-to-head trials directly comparing bDMARDs are required. Currently, paediatric rheumatologists must make treatment decisions based on indirect comparisons, supplemented by cohort studies and safety, practical and financial arguments.[9]

Table 3: Outcomes of polyarticular JIA trials included in the indirect comparison

Study	Comparison(s)	Outcome	Patients included (n)	Patients with outcome in active drug arm (n/N)	Patients with outcome in control arm (n/N)	RR (95% CI) for outcome
Lovell 2000[11]	Etanercept vs placebo	Disease flare	51	7/25	21/26	0.35 (0.18–0.67)
Lovell 2008[10]	Adalimumab (combined)* vs placebo	Disease flare	133	27/68	44/65	0.59 (0.42–0.82)
	Adalimumab (no MTX) vs placebo	Disease flare	58	13/30	20/28	0.61 (0.38–0.97)
	Adalimumab (plus MTX) vs placebo	Disease flare	75	14/38	24/37	0.57 (0.35–0.92)
Ruperto 2008[6]	Abatacept vs placebo	Disease flare	122	12/60	33/62	0.38 (0.22–0.66)

Key: CI, confidence interval; MTX, methotrexate; RR, relative risk.
Notes: *The stratified methotrexate arms were combined.[8]

Table 4: Indirect comparisons between etanercept, adalimumab and abatacept

Indirect comparison	RR (95% CI) of disease flare
Etanercept vs adalimumab (combined)*	0.59 (0.28–1.24)
Etanercept vs adalimumab (no MTX)	0.57 (0.25–1.28)
Etanercept vs adalimumab (plus MTX)	0.61 (0.27–1.38)
Etanercept vs abatacept	0.92 (0.39–2.18)
Adalimumab (combined)* vs abatacept	1.56 (0.81–2.99)
Adalimumab (no MTX) vs abatacept	1.61 (0.78–3.33)
Adalimumab (plus MTX) vs abatacept	1.51 (0.72–3.13)
Adalimumab (no MTX) vs adalimumab (plus MTX)	1.07 (0.55–2.09)

Key: CI, confidence interval; MTX, methotrexate; RR, relative risk.
Notes: *The stratified methotrexate arms were combined.[8] Please note that none of these comparison are significant since each 95%CI contains the value of 1

As the systematic review did not include any trial for tocilizumab, we conducted an indirect comparison to compare the efficacy of tocilizumab in preventing disease flare with the other bDMARDs. The definition of JIA used in the tocilizumab trial was similar to the trials included in the systematic review.[10] The mean baseline age was 11.0 years, and the disease duration at baseline was 4.2 years. Inclusion of rheumatoid factor-positive patients was 29%. The proportion of patients with polyarthritis systemic JIA and the proportion of patients who were previously non-responsive to TNF inhibitors were not reported in the tocilizumab trial. The baseline disease characteristics of the patients included in the double-blind phase with regard to the number of joints with arthritis, physician's assessment of disease activity and the CHAQ scores reported for the tocilizumab trial were comparable to those reported for the trials included in the systematic review. The relative risk of preventing disease flare for tocilizumab versus placebo was 0.53 (95% CI 0.35-0.82).[9] Using placebo as a common comparator, indirect comparisons using the Bucher method[29] demonstrated similar short-term efficacy of tocilizumab and the other bDMARDs in preventing disease flare after response to treatment in patients with polyarticular JIA (Table 5).

Table 5: Indirect comparison between tocilizumab and other bDMARDs

Indirect comparison	RR (95% CI) of disease flare
Adalimumab (combined)* vs tocilizumab	1.10 (0.64–1.91)
Adalimumab (no MTX) vs tocilizumab	1.14 (0.60–2.16)
Adalimumab (plus MTX) vs tocilizumab	1.07 (0.56–2.04)
Abatacept vs tocilizumab	0.71 (0.35–1.43)
Etanercept vs tocilizumab	0.65 (0.30–1.43)

Key: bDMARDs, biological disease modifying anti-rheumatic drugs; CI, confidence interval; MTX, methotrexate; RR, relative risk.
Notes: *The stratified methotrexate arms were combined.[8] Please note that none of these comparison are significant since each 95% CI contains the value of 1

3.4 Clinical safety

3.4.1 Introduction

The AWAKEN study also evaluated the safety of abatacept in 190 paediatric patients (6-17 years) with active JIA and an inadequate response or intolerance to at least one DMARD or TNF inhibitor treatment.[6]

3.4.2 Open-label lead-in period

During the lead-in period, six patients had SAEs: three were related to the patient's underlying JIA (flare in two patients and arthropathy in one). One case each of varicella,

ovarian cyst and acute lymphocytic leukaemia was also recorded. The leukaemia was diagnosed on Day 89; the patient had been anaemic at enrolment, with progressively decreasing haemoglobin concentrations as early as Day 19. No other malignancies were reported.[6]

Adverse events were reported in 133 (70%) patients; 25 had headache (13%), 19 nausea (10%), 17 cough (9%), 17 diarrhoea (9%), 14 upper respiratory tract infection (7%) and 12 pyrexia (6%). Other than upper respiratory tract infection, few infectious AEs were reported; [redacted] All infections had a typical course and resolved with treatment.[8] No opportunistic infections were recorded. Eight (4%) patients had acute infusional AEs; all but one was mild in intensity, and none were serious. Most infusional AEs were reported as single events in one patient each with no recurrences; four patients had headaches and two had dizziness.[6]

3.4.3 Double-blind period

During the double-blind period, no SAEs were reported for patients given abatacept. Three SAEs were reported during the double-blind period for two patients in the placebo group (haematoma in one patient, occurring on Day 108 and deemed unrelated to the study drug by the local investigator; and varicella and encephalitis in the other patient, occurring on Day 27 and deemed possibly related to the study drug; in both cases, the investigator was unaware of which treatment the patient was receiving at the time of the events). All resolved completely without sequelae and without study discontinuation.

No patients developed systemic signs or symptoms (such as fever or rash) or uveitis during the double-blind period. Frequencies of AEs did not differ in patients given abatacept or placebo. The most common system organ class reported was infections and infestations.[6]

Acute infusional AEs were reported in one (2%) patient in the abatacept group and two (3%) patients in the placebo group; all were either mild or moderate in intensity, and none were serious.[6]

No serious infections, serious autoimmune disorders or cases of uveitis or anaphylaxis were reported in either period. Tests of abnormal liver or kidney function or haematological tests showed no positive results.[6]

<u>Autoantibodies</u>

In the 4-month open-label period, 12 of 113 (11%) patients given abatacept who had a negative antinuclear antibody titre at baseline had a positive titre at Day 113. In the 6-month double-blind period, two of 34 (6%) patients given abatacept and one of 25 (4%) controls

who had negative antinuclear antibody titres at baseline had positive titres at Day 169. In the open-label period, nine of 146 (6%) patients who had a negative titre at baseline had anti-double-stranded DNA antibodies at Day 113, as did one of43 (2%) patients in the abatacept group and none in the placebo group at Day 169 of the double-blind period. No clinical manifestations of lupus or other systemic autoimmune disease, or any other consequences associated with the presence of antinuclear or anti-double-stranded DNA antibodies was recorded.[6]

3.4.4 Open-label extension period

Table 6 summarises the long-term safety findings for abatacept from the OLE period.[7] During the OLE period, one death occurred in the group of patients who had been treated with placebo during the double-blind period. This was a motorcycle accident and was determined unrelated to the study treatment.[7] Thirteen patients experienced musculoskeletal or connective tissue disorders: arthritis (n=6), arthralgia (n=3), rheumatoid arthritis (n=2), foot deformity (n=2), juvenile arthritis (n=1), torticollis (n=1) and synovial cyst (n=1).[7] Ten patients experienced serious infections: pyelonephritis, bacterial arthritis and appendicitis (n=2 each); and limb abscess, dengue fever, herpes zoster, bacterial meningitis, tooth abscess, erysipelas and gastroenteritis (n=1 each).[7] Erythema nodosum and vitiligo occurred in one patient in each treatment group during the OLE period (both moderate in intensity; neither patient discontinued). Seven patients experienced autoimmune events in the OLE period (vitiligo [same patients as in the open-label lead-in period], cutaneous vasculitis, multiple sclerosis, psoriasis, uveitis, type 1 diabetes and Raynaud's phenomenon).[7]

When comparing the short-term period (i.e. the open-label lead-in and double-blind period) to the long-term periods (i.e. the OLE), there was no increase in incidence rates with an increase in exposure to abatacept (Table 7).[7]

Table 6: Safety summary through the open-label extension period according to treatment group

Safety variable, n (%)	Open-label lead-in period non-responders (n=36)	Double-blind period abatacept group (n=58)	Double-blind period placebo group (n=59)	TOTAL All groups combined (n=153)
Death	0	0	1 (1.7)	1 (0.7)
AEs	31 (86.1)	55 (94.8)	54 (91.5)	140 (91.5)
Discontinuation due to AEs	1 (2.8)	2 (3.4)	3 (5.1)	6 (3.9)
SAEs	9 (25.0)	9 (15.5)	12 (20.3)	30 (19.6)

Serious infections	4 (11.1)	3 (5.2)	3 (5.1)	10 (6.5)
Discontinuation due to SAEs	0	1 (1.7)	2 (3.4)	3 (2.0)
Key: AEs, adverse events; SAEs, serious adverse events.				

Table 7: Comparison of abatacept safety in juvenile idiopathic arthritis patients in the short-term period (open-label lead-in/double-blind periods) versus open-label extension

	Short-term period (i.e. open-label lead-in period and double-blind period; n=190)		**Long-term period (i.e. open-label extension period; n=153)**	
	n	**IR (95% CI)**	**n**	**IR (95% CI)**
AEs	145	433.61 (365.91, 510.24)	140	132.39 (111.37, 156.22)
SAEs	6	6.82 (2.50, 14.84)	30	5.60 (3.78, 8.00)
Infections	86	142.40 (365.91, 510.21)	120	64.72 (53.66, 77.39)
Serious infections	1	1.13 (0.03, 6.27)	10	1.72 (0.83, 3.16)
Malignancies	1	1.12 (0.03, 6.27)	0	0
Autoimmune events	2	2.26 (0.27, 8.17)	7	1.18 (0.48, 2.44)
Key: AEs, adverse events; CI, confidence interval; IR, incidence rate (calculated as events per 100 patient-years of exposure); SAEs, serious adverse events.				

3.4.5 Overall safety summary

Abatacept demonstrates an acceptable safety profile in both the short term and the long term, with a low rate of AEs, serious AEs, serious infections and infusional events. There was one case of serious infection in the open-label lead-in period and 10 cases in the long-term period. There were no opportunistic infections, tuberculosis or pneumonias during the study. One case of lymphocytic leukaemia (on Day 89 [open-label lead-in period]) was reported, but no other malignancies related to the study drug were observed.[6] The additional exposure to abatacept in the OLE did not result in an increased safety risk when compared to the short-term experience.[7]

3.4.6 *Comparative safety*

Fisher's exact test was used to compare SAEs during the double-blind phase of the trials for abatacept[6], adalimumab[11], etanercept[12] and tocilizumab[10] to see if there was a difference in the incidence of SAEs for bDMARDs compared to placebo. We found that there was no significant difference (at the 5% significance level; Table 8) and concluded that the incidence of SAEs was likely to be similar between the bDMARDs, although we recognise the lack of statistical power in these comparisons due to the low number of patients and event rates.

Table 8: Comparison of SAEs for bDMARDs against SAEs for placebo using Fisher's exact test

Study	Comparison(s)	Outcome	Patients included (n)	Patients with outcome in active drug arm (n/N)	Patients with outcome in control arm (n/N)	Fisher's exact test p value
Lovell 2000[12]	Etanercept vs placebo	SAEs	51	2/25	0/26	0.24
Lovell 2008[11]	Adalimumab (combined)* vs placebo	SAEs	133	0/68	1/65	0.49
	Adalimumab (no MTX) vs placebo	SAEs	58	0/30	0/28	1.00
	Adalimumab (plus MTX) vs placebo	SAEs	75	0/38	1/37	0.49
Ruperto 2008[6]	Abatacept vs placebo	SAEs	122	0/60	2/62	0.50
Brunner 2014[10]	Tocilizumab vs placebo	SAEs	163	3/82	3/81	1.00

Key: bDMARDs, biological disease modifying anti-rheumatic drugs; MTX, methotrexate; RR, relative risk; SAEs, serious adverse events.
Notes: *The stratified methotrexate arms were combined.[9]

4 Clinical effectiveness

4.1 Overview of clinical need

JIA is a group of chronic arthritides affecting children leading to destructive joint disease, with significant morbidity, disability and cost to society. It is a significant burden for paediatric patients, with serious consequences for not only the young patients suffering from the disease but also their parents, family and carers.

Current treatment regimens for JIA, which primarily include methotrexate and TNF inhibitor therapies, still leave a significant group of patients with an inadequate response. Anti-rheumatics with an alternative, novel therapeutic mode of action are necessary. As a fusion protein capable of preventing T-cell activation, abatacept provides such an alternative and has displayed good efficacy and tolerability, thereby offering a viable treatment for patients with JIA who have failed on TNF inhibitor therapy.

In addition to the classical JIA symptoms, childhood uveitis is responsible for visual impairment in up to 40% of patients with JIA, 10% of whom become blind.[30] Indeed, case study evidence (n=10) has indicated that abatacept provided sustained improvement in severe anti-TNF-resistant JIA-related uveitis.[31,32] However, in another small study (n=21), the majority of patients with JIA-related uveitis failed to achieve a sustained anti-uveitis response with abatacept.[33] Further studies are therefore required to elucidate abatacept's role in the treatment of JIA-related uveitis.

Moreover, although by definition JIA presents before a patient's sixteenth birthday, up to 50% of patients continue to have active disease (or sequelae from previous active disease) well into adult life.[34] Such adults with JIA are prone to pain, depression and anxiety.[35] Although the data available specifically in relation to abatacept are limited, biologic therapies have been shown to be an important treatment option in adults with active JIA.[36]

4.2 Summary of abatacept clinical evidence

Clinical evidence indicates that abatacept is a promising treatment for children and adolescents with JIA. In the 6-month randomised period of the AWAKEN study, abatacept treatment induced improvements in ACR Pedi responses, time to flare of JIA, HRQL, pain, sleep and participation in daily activities in patients with active JIA who had responded to this treatment in the 4-month open-label lead-in phase.[6,13]

Moreover, in the OLE period, abatacept provided clinically significant and durable efficacy in patients with JIA, including those who did not initially achieve an ACR Pedi 30 during the initial open-label lead-in phase. Patients who were continuously treated with abatacept

experienced significant improvements in disease symptoms. Patients with prior exposure to TNF inhibitors and those who were naive for treatment with bDMARDs experienced significant improvements in disease symptoms.[7]

Abatacept was well tolerated throughout the AWAKEN study (short term) and into the OLE period (long term). The presence of anti-abatacept antibodies was not associated with significant efficacy or safety concerns. The high degree of patient retention helps support the conclusion that abatacept treatment was well tolerated.[6,7]

4.3 Implications for clinical practice

Abatacept offers an alternative treatment for those patients who have failed on TNF inhibitor therapy and for whom therapeutic options are extremely limited. Considering the young age of the many JIA patients, any therapy that may help alleviate their condition will be of benefit. In providing an alternative treatment for patients who do not tolerate or do not have an adequate response to TNF inhibitor therapies, abatacept has the potential to have an impact beyond the immediate improvement in patient health. In patients with JIA lacking further therapeutic options, adequate treatment would result in fewer days missed from school (and consequently fewer parental/guardian missed days at work), less restriction in daily activities, less need for carer/parental support, fewer doctor visits and less rescue medication.

Parents or carers may prefer their child's therapy to be administered in a clinical setting, rather than having to take the responsibility themselves. Abatacept's intravenous route of administration requires an outpatient visit, thereby ensuring good patient compliance providing that patients or carers keep their child's appointments at the infusion centre. Conversely, where it would be possible for subcutaneous bDMARDs to be administered at home, there is the chance that doses will be missed due to everyday distractions and the potential for increasing anxiety and distress for both children and family.

4.4 Cost-effectiveness

4.4.1 Existing evidence

The technology assessment report identified two published cost-effectiveness studies for bDMARDs for treating JIA.[37] The study by Ungar et al. used a decision tree framework and defined effectiveness in terms of ACR Pedi 30 and not QALYs.[38] It considered a societal perspective and a short time horizon of only 1 year. The study by Prince et al. directly evaluated costs and QALYs from patient files and electronic records. Costs were collected for 1 year before and 27 months after the start of etanercept treatment. The model was not

designed to extrapolate results.[39] The studies by Ungar et al. and Prince et al. considered Canadian and Dutch settings, respectively. Therefore, we conducted a de novo analysis as the framework of the existing studies could not be used to inform the model.

4.4.2 Model overview

The efficacy and safety of bDMARDs has been shown to be similar, see section 3.3 and section 3.4.6, respectively, but there are limitations with this comparison due to the small samples sizes and differences in both the study outcomes and study population. Therefore, using these outcomes to develop a cost-effectiveness model would lead to uncertainty within the model. Moreover, the utility values estimated in Prince et al. are not defined by health states, and there is insufficient information to perform a mapping of utilities to EQ-5D. As such, any assumption for utilities would introduce uncertainty to a cost-utility model. Since resource use is likely to be the only differentiator between the bDMARDs, a cost minimisation model was developed to compare the costs of abatacept, adalimumab, etanercept and tocilizumab in treating polyarticular JIA.

The abatacept-licensed population is paediatric patients (6 years of age and older) with moderate-to-severe active polyarticular JIA who have had an insufficient response to other DMARDs, including at least one TNF inhibitor.[4]

The model was developed from the perspective of the National Health Service (NHS) and Personal Social Services in England and Wales, as per the 2013 National Institute for Health and Care Excellence (NICE) methods guide.[40] The model therefore considers only direct costs.

In the base case analysis, the starting age of patients was 12 years, which was the mean age at baseline in the abatacept clinical trial[6], and the time horizon was 6 years. Patients older than 18 years exited the model because the population of interest is paediatric (up to 17 years of age).[4] However, scenario analyses were conducted for longer time horizons of 10 and 20 years. For abatacept, etanercept and tocilizumab, doses and consequently costs were dependent on patient weight. For adalimumab and methotrexate, doses were dependent on body surface area; hence, both height and weight mattered. Therefore, treatment costs may differ depending upon the patient height/weight, and hence age. Using longer time horizons accounted for the variation in weight observed for children over time.

The base case discount rate was set in accordance with the 2013 NICE methods guide as 3.5% per year.[39]

4.4.3 Intervention and comparators

The treatments considered for the analysis were abatacept, adalimumab, etanercept and tocilizumab. Abatacept, adalimumab and tocilizumab are licensed to be administered in combination with methotrexate.[4,19,24] Both adalimumab and tocilizumab can be given as a monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.[19,24] In the base case of the model, it was assumed that all patients received bDMARDs in combination with methotrexate as this reflects clinical practice, and additionally, patients who are unable to tolerate methotrexate are not eligible for abatacept. The current NICE protocol for JIA also recommends that methotrexate be given along with etanercept.[37] 'Metoject' methotrexate pre-filled syringes are considered for administration of methotrexate in line with the NICE protocol.[37] The dosing details for abatacept are described in section 2.4. The dosing regimens for other treatments are described in Table 9.

We assumed that all patients treated with etanercept received a dose of 800µg/kg once a week, subject to the other criteria in Table 9. This is a favourable assumption towards etanercept as it reduces the associated administration costs. We assumed that the methotrexate dosing was 13.5mg/m^2, which was the mean dosing for methotrexate in the abatacept clinical trial.[6]

Table 9: Dosing details

	Etanercept	Adalimumab	Tocilizumab	Methotrexate	Reference
Dosage	≥18 years: 50mg 2-18 years: 400µg/kg (max 25mg twice a week) or 800µg/kg, (max 50mg once a week)	≥13 years: 40mg 4-13 years: 24mg/m^2 (max 40mg)	>2 years and <30kg: 10mg/kg >2 years and ≥30kg: 8mg/kg (max 800mg)	3-16 years: 10-15mg/m^2	MIMS
Frequency	400µg/kg: twice a week 800µg/kg: once a week	Every other week	Every 4 weeks	Every week	MIMS
Size available (powder/vial)	10mg, 25mg and 50mg. (Use 10 or 25mg prep only for children)	40mg	80mg, 200mg and 400mg	7.5mg, 10mg, 12.5mg, 15mg, 17.5mg, 20mg, 22.5mg, 25mg, 27.5mg and 30mg	MIMS

Mode of administration	Subcutaneous administration	Subcutaneous administration	Intravenous infusion	Subcutaneous administration	MIMS
Key: MIMS, Monthly Index of Medical Specialties.					

4.4.4 Costs

Drug and administration costs were considered in the model. As etanercept, tocilizumab and methotrexate are available in multiple vial sizes, the vial or combination of vials that were cheapest to administer was used for calculating costs. Abatacept and tocilizumab are administered by intravenous infusion; therefore, there is an additional cost per infusion. Adalimumab and etanercept are administered subcutaneously. Stevenson et al. assumed that a district nurse would be required to administer 10% of the subcutaneous injection treatments.[41] We made the same assumption. The administration costs were taken from Stevenson et al., with £154 for intravenous infusion and £3.05 for subcutaneous administration.[41]

When methotrexate was prescribed in combination with a bDMARD, costs for methotrexate administration were only applied for weeks where it did not coincide with the administration of the bDMARD.

The details for drug costs and administration costs are shown in Table 10. The drug costs were taken from the Monthly Index of Medical Specialities (MIMS).

Table 10: Drug and administration costs

Drug	Abatacept	Adalimumab	Etanercept	Tocilizumab	Metho-trexate	References
List price	£302.4	£352.14	£35.75 to £178.75	£102.4 to £512	£14.85 to £18.95	MIMS[42-46]
Vial size	250mg	40mg	10mg to 50mg	80mg to 400mg	7.5mg to 30mg	MIMS
PAS discount (if any)	[redacted]	-	-	Confidential	-	Pers. Comm.
Admin. Costs	£154	£3.05	£3.05	£154	£3.05	Stevenson et al.[41]
Key: Admin, administration; MIMS, Monthly Index of Medical Specialties; PAS, patient access scheme; Pers. Comm., personal communication.						

The drug dosage and subsequent costs are dependent on the age, height and weight of the patients. However, adalimumab comes only in one vial size of 40mg, which is also the maximum dose. As sharing of vials was not allowed in the model, each patient used one vial

of adalimumab. The data for height and weight for age 4-20 years were taken from the Royal College of Paediatrics and Child Health[47] and interpreted using 'GetData Graph Digitizer v 2.24'. Drug costs were estimated separately for males and females as the charts for males and females were available separately. Costs for an average patient was calculated using the proportion of females in the abatacept clinical trial[6]. The body surface area was calculated using the Mosteller formula[48]:

$$Body\ surface\ area\ (in\ m^2) = (\frac{1}{60}) * \left(Height\ (in\ cm)\right)^{0.5} * \left(Weight\ (in\ kg)\right)^{0.5}$$

4.4.5 Assumptions used in the model:

Table 11: Model assumptions and justifications

Assumption	Justification
1 year is equal to 52 weeks for calculations of costs and for applying discount rates.	Precise calculation would be 52.18 weeks. This is unlikely to impact the results as the approximation constitutes a factor of just 0.35%.
The dosing regimen for methotrexate in patients ≥16 years is the same as for younger patients.	The current licence for 'Metoject' methotrexate pre-filled syringes does not mention anything for patients' ≥16 years.
Height and weight is constant for patients >20 years.	Height and weight are not expected to increase after patients reach 20 years of age.
If the methotrexate dose is above 30mg, one vial of 30mg will be used. For the remaining dose, the same algorithm is used to estimate the least costly vial size as the one for a dose below 30mg.	In the base case, the maximum dose is 25mg. It is very unlikely that the methotrexate dose would be higher than 30mg.
Height and weight are assumed to be normally distributed.	The data source did not provide standard error for height and weight. Hence, it is calculated using the data for the 25th and 75th percentiles.
For runs in PSA simulations, where the sampled starting age in the model using distribution is <6 years, we assume the starting age in the model to be 6 years.	Abatacept is not licensed for patients < 6 years.
For runs in PSA simulations, where the sampled starting age in the model using distribution is >16 years, we assume the starting age in the model to be 16 years.	Disease onset should occur before the age of 16 years[37]
For PSA, the standard error for the percentage of females and the administration costs is assumed to be 10% of the mean.	In the absence of other data, we made this assumption.
It is assumed that sharing vials between patients is not possible.	Different patients are likely to visit at different times.

Assumption	Justification
Key: PSA, probabilistic sensitivity analysis.	

4.4.6 Results

The base case results show that abatacept is the least costly treatment option followed by etanercept. Tocilizumab is slightly cheaper than adalimumab, which is the most expensive. The undiscounted and discounted results for the base case are summarised in Table 12 and Table 13, respectively.

Table 12: Undiscounted results for the base case

Item	Abatacept	Adalimumab	Etanercept	Tocilizumab
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	£13,040	£964	£964	£12,889
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Cost savings with abatacept		[redacted]	[redacted]	[redacted]

Table 13: Discounted results for the base case

Item	Abatacept	Adalimumab	Etanercept	Tocilizumab
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]
Administration costs	£11,797	£871	£871	£11,646
Total costs	[redacted]	[redacted]	[redacted]	[redacted]
Cost savings with abatacept		[redacted]	[redacted]	[redacted]

4.4.7 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was carried out to explore the impact of uncertainty in input parameters on the results. The results were found to be stable with 1000 simulations. Mean costs from 1000 simulations were within 5% of the base case costs, which shows that the model results remain stable. Abatacept was the least costly option in 67% of the simulations, whereas etanercept was the least costly option in the remaining 33% of the simulations.

4.4.8 Scenario analysis

The model base case represents the most plausible value for the input parameters. The scenario analyses were performed to test the sensitivity of results to changes in input parameters. During the evaluation of scenarios, all parameters, except the one on which scenario analysis was being conducted, were set to base case values.

a) Infusion costs
   Infusion time for abatacept is 30 minutes, whereas infusion time for tocilizumab is 60 minutes. In the base case, we assumed the same infusion costs for both abatacept and tocilizumab, as per the NICE Assessment Group (AG) for ID537 assumption.[41] However, the AG acknowledged that this is unfavourable to abatacept. Therefore, we evaluated alternative scenarios with lower infusion costs for abatacept (Table 14).

Table 14: Scenario analysis – infusion costs for abatacept

Infusion costs for abatacept	Cost savings by using abatacept over adalimumab	Cost savings by using abatacept over etanercept	Cost savings by using abatacept over tocilizumab
£77	[redacted]	[redacted]	[redacted]
£92	[redacted]	[redacted]	[redacted]
£108	[redacted]	[redacted]	[redacted]
£123	[redacted]	[redacted]	[redacted]
£139	[redacted]	[redacted]	[redacted]
£154	[redacted]	[redacted]	[redacted]
Note: Infusion costs for abatacept is £154 for the base case.			

b) Starting age in the model

Abatacept is given to patients after they have failed on DMARDs, including at least one TNF inhibitor. In the base case, we assumed that the starting age of patients was 12 years, which was the mean age at baseline in the abatacept clinical trial.[6] The mean age at baseline in the trials for the other bDMARDs was 11 years; however, they included patients younger than 6 years in accordance with their licences.[10-12] We assumed that a starting age of 12 years is likely to be representative of clinical practice and was therefore appropriate for the base case. As abatacept is not licensed for patients younger than 6 years[4] and age of disease onset should be less than or equal to 16 years[37], we varied patients' starting ages in the model from 6 to 16 years. The results varied from etanercept being the least costly option to abatacept being the least costly option (Table 15).

Table 15: Scenario analysis – starting age in the model

Starting age in model	Cost savings by using abatacept over adalimumab	Cost savings by using abatacept over etanercept	Cost savings by using abatacept over tocilizumab
6	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]

c) Time horizon

In the base case, a time horizon of 6 years was used, the starting age of patients in the model was 12 years, and patients exited the model at 18 years.

As the NICE protocol mentions that approximately half of children will have symptoms for at least 10 years and at least one third of children will have polyarthritis continuing into adulthood.[37], we explored alternative scenarios where treatment is continued into adulthood by considering time horizons of 10 and 20 years. Beyond 20 years, the results were not expected to vary.

Response to abatacept was assessed at 6 months[4], but as observed during the OLE, treatment with abatacept resulted in sustained clinical efficacy with continued long-term use.[7]

We also evaluated the impact using shorter time horizons from 6 months to 5 years. For the shorter time horizons, the impact of the additional costs associated with the loading dose of abatacept at 2 weeks was more prominent and affects the results for the economic evaluation (Table 16).

Table 16: Scenario analysis – time horizon

Time horizon	Cost savings by using abatacept over adalimumab	Cost savings by using abatacept over etanercept	Cost savings by using abatacept over tocilizumab
6 months	[redacted]	[redacted]	[redacted]
1 year	[redacted]	[redacted]	[redacted]
2 years	[redacted]	[redacted]	[redacted]
2 years	[redacted]	[redacted]	[redacted]
4 years	[redacted]	[redacted]	[redacted]
5 years	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]
20 years	[redacted]	[redacted]	[redacted]
Assumption: 6 months = 24 weeks; 1 year = 52 weeks.			

d) PAS discount for tocilizumab

As there is a confidential patient access scheme (PAS) discount available for tocilizumab, we conducted a scenario analysis by varying discount levels for tocilizumab from no discount to 50% and using the [redacted] PAS discount for abatacept. With a price discount of [redacted] for tocilizumab, the total costs associated with abatacept and tocilizumab are the same. Therefore, if the PAS discount for tocilizumab is less than [redacted] abatacept is the least costly bDMARD (Table 17).

Table 17: Scenario analysis – PAS discount for tocilizumab

PAS discount on tocilizumab	Cost savings associated with using abatacept over tocilizumab
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Key: PAS, patient access scheme.	

e) Exclude methotrexate in etanercept arm.

The NICE protocol advises that etanercept should be given with methotrexate, as it is likely to be more effective that way.[37] However, the etanercept licence does not state this.[23] For the base case, we assumed that methotrexate is given with etanercept. However, as patients who are treated with etanercept monotherapy may also be considered for treatment with abatacept and methotrexate, we evaluated an alternative scenario, where methotrexate was not provided with etanercept (Table 18). Under this scenario, etanercept is the least costly bDMARD; however, it is likely that etanercept would generally be given with methotrexate.

Table 18: Scenario analysis – excluding methotrexate from the etanercept arm

Include methotrexate cost in etanercept arm	Cost savings associated with using abatacept over etanercept
Yes	[redacted]
No	[redacted]

The product information for tocilizumab and adalimumab state that they are indicated in polyarticular JIA in combination with methotrexate,19,24 but they can also be given as a monotherapy in cases of intolerance to methotrexate or where methotrexate is unsuitable. The product information for abatacept states that it is indicated in combination with methotrexate.4 Since abatacept is not licensed to be given to patients for whom methotrexate is unsuitable or not tolerated, the base case population does not include this group of patients. Although some patients in clinical practice may receive tocilizumab and

adalimumab without methotrexate; the population would be different to that of the abatacept population, and therefore, scenarios in which tocilizumab and adalimumab are given as monotherapy are not presented.

4.4.9 Validation

The model was quality checked internally by a health economist with no involvement in the model development.

4.4.10 Conclusion of economic evidence

In the base case, abatacept is the least costly bDMARD and has similar efficacy and safety to other bDMARDs. These results remain stable for a wide range of scenarios.

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6 Appendix 1

6.1 Detailed methodology for the AWAKEN study

Open-label lead-in period (Days 1-113)

All enrolled children were initially given abatacept (10mg/kg according to weight at each visit, with a maximum dose of 1,000mg) by 30-minute intravenous infusion on Days 1, 15, 29, 57 and 85 of a 4-month open-label period (Days 1–113). In addition to study medication, patients were permitted to continue to take a stable dose of methotrexate and either folinic acid or folic acid. Oral corticosteroids were stabilised 4 weeks before enrolment at 10mg per day or 0.2mg/kg per day prednisone equivalent (whichever was less). NSAIDs or analgesics were permitted for pain control.

Intra-articular corticosteroid injections were not permitted from 4 weeks before enrolment or throughout the trial. Every patient had a wash-out period of at least 4 weeks for any DMARD other than methotrexate, before the first dose of study medication. The wash-out period was 4 weeks for patients on etanercept or anakinra and 60 days for patients on infliximab or adalimumab.

Double-blind period (Days 114-283)

On Day 113, patients who had improved by 30% according to the ACR Pedi definition were randomly assigned (1:1) to receive either abatacept or placebo. During the double-blind period, both abatacept (at doses of 10mg/kg) and placebo were given at randomisation and at about 28-day intervals thereafter for 6 months (Days 114–283), or until an arthritis flare.

Open-label, long-term extension period

Patients eligible to enter the OLE period were those who completed the double-blind period without experiencing an arthritis flare, discontinued participation in the double-blind period due to an arthritis flare, or completed the open-label lead-in period without achieving an ACR Pedi 30 and therefore did not qualify for randomisation. All patients in the OLE were treated with 10mg/kg abatacept, up to a maximum dose of 1,000mg for those weighing >100kg. Patients received 30-minute infusions every 28 days, and the efficacy and safety of abatacept were assessed at each visit.

The dosages of oral steroids (maximum 10mg/day prednisone equivalent or 0.2mg/kg/day, whichever was less) and methotrexate (<30mg/m^2 body surface area/week up to an absolute maximum of 40mg/m^2/week) could be adjusted during the OLE.

The use of NSAIDs or analgesics was permitted in patients experiencing pain that was not adequately controlled by the baseline and study medications. The addition of

hydroxychloroquine, sulfasalazine, or azathioprine was permitted during the OLE, but no other DMARDs were allowed during the study. Up to 2 intra-articular injections of corticosteroids per year were permitted; any injected joint was considered “active” at all subsequent visits, regardless of the actual clinical status of that joint.