

# Systemic juvenile idiopathic arthritis: canakinumab

## Evidence summary

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[nice.org.uk/guidance/esnm36](https://www.nice.org.uk/guidance/esnm36)

## Key points from the evidence

The content of this evidence summary was up-to-date in March 2014. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#), [BNF for children \(BNFc\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

## Summary

In August 2013, the licensed indications for canakinumab were extended to include the treatment of active systemic juvenile idiopathic arthritis in patients aged 2 years and older who have responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. NICE terminated a [single technology appraisal of canakinumab](#) for treating systemic juvenile idiopathic arthritis because no evidence submission was received from the manufacturer. In randomised controlled trials, canakinumab was effective in treating systemic juvenile idiopathic arthritis and allowed children and young people to taper their oral corticosteroid dose. However, risks of treatment include serious infections, neutropenia, leukopenia and thrombocytopenia. Macrophage activation syndrome has also been seen in clinical trials.

<p><b>Effectiveness</b></p> <ul style="list-style-type: none"> <li>• In 1 RCT (n=84), 84% of children and young people had an 'adapted JIA ACR 30 response' at day 15 with a single dose of subcutaneous canakinumab 4 mg/kg compared with 10% of those who had placebo (p&lt;0.0001).</li> <li>• In part 1 of a second RCT (n=177), 57 of 128 (45%) children and young people receiving open-label subcutaneous canakinumab 4 mg/kg every 4 weeks and oral corticosteroids were able to taper their corticosteroid dose.</li> <li>• In part 2 of the second RCT (n=100), the relative risk reduction in time to flare of systemic juvenile idiopathic arthritis was 64% (hazard ratio 0.36; 95% confidence interval 0.17 to 0.75; p=0.003) with subcutaneous canakinumab 4 mg/kg every 4 weeks compared with placebo.</li> </ul>	<p><b>Safety</b></p> <ul style="list-style-type: none"> <li>• Risks of canakinumab include serious infections, neutropenia, leukopenia, and thrombocytopenia. Macrophage activation syndrome has also been seen in clinical trials of canakinumab in children and young people with systemic juvenile idiopathic arthritis.</li> <li>• The full list of safety warnings are included in the <a href="#">summary of product characteristics</a>.</li> </ul>
<p><b>Patient factors</b></p> <ul style="list-style-type: none"> <li>• In the pooled systemic juvenile idiopathic arthritis population, 85% of children and young people receiving canakinumab experienced at least 1 adverse event (most often infections and infestations, gastrointestinal disorders, musculoskeletal and connective tissue disorders and respiratory, thoracic and mediastinal disorders).</li> <li>• For systemic juvenile idiopathic arthritis, canakinumab is given every four weeks by subcutaneous injection.</li> </ul>	<p><b>Resource implications</b></p> <ul style="list-style-type: none"> <li>• The annual cost of canakinumab for a child weighing 20 kg (assuming no wastage) is £68,833 excluding VAT.</li> <li>• The annual cost of tocilizumab for a child weighing 20 kg (assuming no wastage) is £7,987 excluding VAT.</li> </ul>

## Key points

In August 2013, the licensed indications for canakinumab were extended to include the treatment of active systemic juvenile idiopathic arthritis in patients aged 2 years and older who have

responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. For systemic juvenile idiopathic arthritis, canakinumab 4 mg/kg is given every 4 weeks by subcutaneous injection.

This evidence summary is based on 2 randomised controlled trials, the results of which were published in 1 paper ([Ruperto et al. 2012a](#)). One trial was a 29-day, single-dose, placebo-controlled trial. The other was a 2-part study, in which participants received open-label treatment in part 1, and were randomised to placebo or canakinumab in part 2.

In the placebo-controlled, single-dose study, more children and young people in the canakinumab 4 mg/kg group had an 'adapted JIA ACR 30 response' at day 15 (36 out of 43 [84%] compared with 4 out of 41 [10%] respectively;  $p < 0.0001$ ) and day 29 (81% compared with 10% respectively;  $p < 0.001$ ).

In part 1 of the other trial, 57 out of 128 (45%) children and young people who received open-label canakinumab 4 mg/kg every 4 weeks and were taking oral corticosteroids were able to taper their corticosteroid dose (from a mean dose of 0.34 mg per kilogram per day to 0.05 mg per kilogram per day). In part 2 of this trial, there was a statistically significant relative risk reduction in time to flare of systemic juvenile idiopathic arthritis of 64% (hazard ratio [HR] 0.36, 95% confidence interval [CI] 0.17 to 0.75;  $p = 0.003$ ) with canakinumab compared with placebo ( $n = 100$ ).

Particular risks identified with canakinumab for the treatment of systemic juvenile idiopathic arthritis are serious infections, neutropenia, leukopenia and thrombocytopenia. Despite the efficacy of canakinumab, macrophage activation syndrome, a life-threatening disorder, has also been seen in clinical trials with this drug. Clinical safety issues are outlined in full in the [summary of product characteristics](#). In the pooled systemic juvenile idiopathic arthritis population reported in the [European public assessment report for canakinumab](#), 85% of children and young people who received canakinumab experienced at least 1 adverse event. The most frequently affected system organ classes were infections and infestations (71%), gastrointestinal disorders (53%), musculoskeletal and connective tissue disorders (42%) and respiratory, thoracic and mediastinal disorders (38%). Severe adverse events were seen in 17% of this population.

Systemic juvenile idiopathic arthritis is a relatively rare multi-organ disease characterised by arthritis symptoms (persistent joint swelling, pain and limitation of movement), intermittent fever, transient rash, and liver and spleen enlargement. It is estimated that approximately 10% of children diagnosed with juvenile idiopathic arthritis have systemic juvenile idiopathic arthritis.

Tocilizumab and canakinumab are currently the only biological disease-modifying antirheumatic drugs (DMARDs) licensed in the UK for the treatment of active systemic juvenile idiopathic arthritis. Etanercept, abatacept and adalimumab are licensed for the treatment of juvenile idiopathic arthritis, but not specifically for active systemic juvenile idiopathic arthritis.

Specialists have advised that it is important to ensure that standard treatments for systemic juvenile idiopathic arthritis (NSAIDs, oral corticosteroids and methotrexate) have been optimised before canakinumab is considered. Canakinumab may be an option, as tocilizumab is (see NICE technology appraisal guidance on [tocilizumab for the treatment of systemic juvenile idiopathic arthritis](#)), for children and young people aged 2 years and older whose disease has responded inadequately to NSAIDs, systemic corticosteroids and methotrexate. NICE does not recommend tocilizumab for children and young people aged 2 years and older whose disease continues to respond to methotrexate or has not been treated with methotrexate.

The annual cost of canakinumab for a child weighing 20 kg (assuming no wastage) is £68,833 excluding VAT. This is considerably more expensive than tocilizumab, which for a child weighing 20 kg (assuming no wastage) is £7,987 ([MIMS](#), February 2014).

#### Key evidence

Ruperto N, Brunner HI, Quartier P, et al. (2012) [Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis](#). *New England Journal of Medicine* 367: 2396–406

### *About this evidence summary*

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance**.

### Relevance to NICE guidance programmes

NICE terminated a [single technology appraisal of canakinumab](#) for treating systemic juvenile idiopathic arthritis because no evidence submission was received from the manufacturer (Novartis).

NICE guidance on [tocilizumab for the treatment of systemic juvenile idiopathic arthritis](#) (NICE technology appraisal guidance 238) was published in 2011. Tocilizumab is recommended for the

treatment of systemic juvenile idiopathic arthritis in children and young people aged 2 years and older whose disease has responded inadequately to non-steroidal anti-inflammatory drugs (NSAIDs), systemic corticosteroids and methotrexate if the manufacturer makes tocilizumab available with the discount agreed as part of the patient access scheme.

NICE guidance on [etanercept for the treatment of juvenile idiopathic arthritis](#) (NICE technology appraisal guidance 35) was published in 2002. Etanercept is recommended for children aged 4 to 17 years with active polyarticular-course juvenile idiopathic arthritis whose condition has not responded adequately to, or who have proved intolerant of, methotrexate.

NICE technology appraisals on [abatacept](#) and [adalimumab](#) for the treatment of juvenile idiopathic arthritis were discontinued in 2010 and 2011 respectively. The abatacept appraisal was removed from the work programme because the marketing authorisation suggests limited use of this drug for a small population of those with juvenile idiopathic arthritis. The appraisal on adalimumab was discontinued because the cost and benefit profile of adalimumab in comparison with etanercept, and its existing usage on the NHS, meant a technology appraisal would not provide value to the NHS.

In November 2013, NICE announced that a [review](#) of NICE technology appraisal guidance on [etanercept for the treatment of juvenile idiopathic arthritis](#) will be scheduled into the work programme. This review will be carried out using the multiple technology appraisal process and will also include adalimumab, tocilizumab, and if timing allows, golimumab and abatacept. The inclusion of these extra biological agents will be subject to formal referral by the Department of Health.

## Introduction

Juvenile idiopathic arthritis is a term that covers a heterogeneous group of syndromes in which the onset of inflammatory arthritis occurs before the age of 16 years and lasts for more than 6 weeks. The cause of juvenile idiopathic arthritis is poorly understood, but may relate to genetic and environmental factors. Systemic juvenile idiopathic arthritis is a multi-organ disease characterised by arthritis symptoms (persistent joint swelling, pain and limitation of movement), intermittent fever, transient rash, and liver and spleen enlargement.

Systemic juvenile idiopathic arthritis can lead to growth retardation, joint contractures, eye problems, destructive joint disease requiring joint replacements, permanent disability, amyloidosis and sudden hyperactivity of the immune system, known as macrophage-activation syndrome, which can be fatal if not recognised early and treated aggressively.

Juvenile idiopathic arthritis is a relatively rare disease, with an estimated incidence in the UK of 0.1 per 1000 children per year, equivalent to 1000 children diagnosed per year. The prevalence is in the order of 1 per 1000 children; about 10,000 children in the UK are affected at any one time.

Approximately 10% of children diagnosed with juvenile idiopathic arthritis have systemic juvenile idiopathic arthritis.

Treatment aims to control pain, fever and inflammation, and to reduce joint damage, disability and loss of function, thereby improving quality of life. The standard treatment for systemic juvenile idiopathic arthritis includes combinations of non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, corticosteroids and methotrexate. Oral corticosteroids such as prednisolone are used initially before progressing to non-biological disease-modifying antirheumatic drugs (DMARDs) such as methotrexate.

Biological DMARDs are generally only used when standard treatment with NSAIDs, corticosteroids and methotrexate has not worked.

Tocilizumab and canakinumab are currently the only biological DMARDs licensed in the UK specifically for the treatment of active systemic juvenile idiopathic arthritis in children and young people. Tocilizumab is licensed for the treatment of active systemic juvenile idiopathic arthritis in patients aged 2 years and older, whose condition has responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. It is recommended by NICE for children and young people aged 2 years and older whose disease has responded inadequately to NSAIDs, systemic corticosteroids and methotrexate if the manufacturer makes tocilizumab available with the discount agreed as part of the patient access scheme. Tocilizumab is not recommended for children and young people aged 2 years and older whose disease continues to respond to methotrexate or has not been treated with methotrexate. Tocilizumab can be given as monotherapy (in case of intolerance to methotrexate or where treatment with methotrexate is inappropriate) or in combination with methotrexate (see RoActemra 20mg/ml Concentrate for Solution for Infusion summary of product characteristics).

Tocilizumab is also licensed for use in combination with methotrexate for the treatment of polyarticular juvenile idiopathic arthritis (rheumatoid factor positive or negative and extended oligoarthritis) in patients aged 2 years and older, whose condition has responded inadequately to previous therapy with methotrexate. Tocilizumab can be given as monotherapy in case of intolerance to methotrexate or where continued treatment with methotrexate is inappropriate (see RoActemra 20mg/ml Concentrate for Solution for Infusion summary of product characteristics).

Etanercept is not licensed specifically for the treatment of active systemic juvenile idiopathic arthritis, but is licensed for the treatment of juvenile idiopathic arthritis, which includes:

- polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and young people from the age of 2 years whose condition has responded inadequately to, or who have proved intolerant of, methotrexate
- psoriatic arthritis in young people from the age of 12 years whose condition has responded inadequately to, or who have proved intolerant of, methotrexate, and
- enthesitis-related arthritis in young people from the age of 12 years whose condition has responded inadequately to, or who have proved intolerant of, conventional therapy (see [Etanercept for injection](#) summaries of product characteristics).

Etanercept is [recommended by NICE](#) for children and young people aged 4 to 17 years with active polyarticular-course juvenile idiopathic arthritis whose condition has not responded adequately to, or who have proved intolerant of, methotrexate.

Abatacept and adalimumab are also not licensed specifically for the treatment of active systemic juvenile idiopathic arthritis. Abatacept in combination with methotrexate is licensed for the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis in paediatric patients aged 6 years and older whose condition has responded inadequately to other DMARDs including at least one tumour necrosis factor (TNF) inhibitor (see [ORENCIA 250 mg powder for concentrate for solution for infusion](#) summary of product characteristics). Adalimumab in combination with methotrexate is licensed for the treatment of active polyarticular juvenile idiopathic arthritis in children and young people from the age of 2 years whose condition has responded inadequately to 1 or more DMARDs. Adalimumab can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate (see [Humira Pre-filled Pen, Pre-filled Syringe and Vial](#) summary of product characteristics).

Other biological DMARDs sometimes used for juvenile idiopathic arthritis, such as anakinra ([Kineret 100 mg solution for injection in a pre-filled syringe](#) summary of product characteristics) and infliximab ([Remicade 100mg powder for concentrate for solution for infusion](#) summary of product characteristics), are not licensed for juvenile idiopathic arthritis.

Suggested treatment pathways for systemic juvenile idiopathic arthritis are published in [Paediatric Rheumatology \(Oxford University Press 2012\)](#). There are also American College of Rheumatology treatment guidelines for systemic juvenile idiopathic arthritis ([DeWitt 2012](#) and [Ringold 2013](#)).

## Product overview

### *Drug action*

Systemic juvenile idiopathic arthritis is a severe auto-inflammatory disease. Although it is somewhat clinically and immunologically heterogeneous, a key pathway involves interleukin-1 beta. Canakinumab is a human monoclonal antibody that binds with high affinity to human interleukin-1 beta, blocking its effects and preventing the production of downstream inflammatory mediators. See the [Ilaris 150mg powder for solution for injection](#) summary of product characteristics.

### *New licensed therapeutic indication*

In October 2009, [canakinumab](#) (Ilaris) was licensed for treating cryopyrin-associated periodic syndromes. In February 2013, the marketing authorisation was extended to include the symptomatic treatment of frequent gouty arthritis attacks (at least 3 attacks in the previous 12 months) in adults in whom non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine are contraindicated, not tolerated, or do not provide an adequate response, and in whom repeated courses of corticosteroids are not appropriate.

In August 2013, the marketing authorisation was further extended to include the treatment of active systemic juvenile idiopathic arthritis in patients aged 2 years and older whose condition has responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. Canakinumab can be given as monotherapy or in combination with methotrexate in systemic juvenile idiopathic arthritis.

### *Course and cost*

According to the [summary of product characteristics](#), canakinumab should be initiated and supervised by physicians experienced in diagnosing and treating systemic juvenile idiopathic arthritis.

The recommended dose of canakinumab for children and young people with systemic juvenile idiopathic arthritis and body weight of at least 7.5 kg is 4 mg/kg (up to a maximum of 300 mg) administered every 4 weeks by subcutaneous injection. Continued treatment without clinical improvement should be reconsidered by the treating physician.

The cost of 1 vial of canakinumab 150 mg powder for solution for injection is £9,927.80 excluding VAT ([MIMS](#), February 2014). The annual cost of canakinumab for a child weighing 20 kg (assuming no wastage) is £68,833 excluding VAT.

## Evidence review

This evidence summary is based on 2 phase III [randomised controlled trials](#) (trial 1 and trial 2), the results of which were published in 1 paper ([Ruperto et al. 2012a](#)). The rationale for trial 1 was to provide evidence that canakinumab is effective at controlling fever within a few days of administration. The rationale for trial 2 was to investigate the oral corticosteroid-tapering potential of canakinumab and how well the drug works for preventing disease flare during up to 2 years of treatment.

There is also a published phase II dose-ranging study ([Ruperto et al. 2012b](#)) and 1 uncontrolled extension study that is ongoing ([ClinicalTrials.gov Identifier: NCT00891046](#)).

### Trial 1: [Ruperto et al. \(2012a\)](#)

- Design: multicentre, 29-day, single-dose, randomised, double-[blind](#), placebo-controlled trial. Allocation was concealed.
- Population: 84 children and young people aged 2–19 years (median age 8 or 9 years, 60% female) with systemic juvenile idiopathic arthritis (median duration just over 2 years) including active systemic features and arthritis (intermittently spiking temperatures of more than 38°C, 2 or more active joints, and C-reactive protein level of over 30 mg per litre). Background therapy with oral corticosteroids (prednisone equivalent up to 1.0 mg per kilogram per day) and stable doses of NSAIDs and methotrexate were allowed. At baseline, about 70% of children or young people were receiving oral corticosteroids and about 63% were receiving methotrexate. Concomitant treatment with another biological agent or disease-modifying drug was excluded. However, over half of the children or young people had received biological agents previously (most often anakinra). Other exclusions were diagnosis of the macrophage activation syndrome in the 6 months before enrolment, active tuberculosis, and live-virus vaccination in the 3 months before enrolment. Baseline characteristics were generally well balanced across the treatment groups.
- Intervention and comparison: children and young people were randomised to receive a single subcutaneous dose of canakinumab 4 mg per kilogram or placebo.

- **Outcomes:** the primary outcome was the proportion of children or young people with an 'adapted juvenile idiopathic arthritis (JIA) American College of Rheumatology (ACR) 30 response' at day 15. This was defined as an improvement of 30% or more in at least 3 of the 6 core criteria for juvenile idiopathic arthritis, worsening of more than 30% in no more than 1 of the criteria, and resolution of fever.
  - Resolution of fever was defined as the documented absence of fever due to systemic juvenile idiopathic arthritis (body temperature of 38°C or less) in the week preceding the assessment according to a paper diary.
  - The 6 juvenile idiopathic arthritis core-set variables (with higher values indicating higher disease activity) were the number of joints with active arthritis (0 to 73 joints), the number of joints with limited range of motion (0 to 69 joints), the physician's global assessment of disease activity (on a 100 mm visual-analogue scale, with higher scores indicating more disease activity), the parent's global assessment of the patient's overall wellbeing (on a 100 mm visual-analogue scale, with higher scores indicating worse overall wellbeing), an assessment of physical function with the use of the cross-culturally adapted and validated version of the disability index of the childhood health assessment questionnaire (CHAQ-DI; on a scale of 0 to 3, with higher scores indicating greater disability), and a C-reactive protein level standardised to 0 to 10 mg per litre. An independent joint examiner was required at each centre.
- Participants with persistent fever (temperature over 38°C after day 3) were made aware of the study assignment at the physician's discretion and, if they were receiving placebo, were permitted to enrol in trial 2. Participants whose condition had a response to canakinumab at day 15, according to the 'adapted JIA ACR 30 response', were immediately enrolled in trial 2 on day 29. Trial 1 was stopped early on the recommendation of the independent data and safety monitoring committee after the planned interim analysis showed the primary end point had been reached ( $p=0.00697$ ). Results are reported for the intention-to-treat population.

#### **Trial 2:** [Ruperto et al. \(2012a\)](#)

- **Design:** multicentre 2-part study. Part 1 was a single-arm study in which participants received open-label treatment. Part 2 was a randomised, double-blind, placebo-controlled, event-driven withdrawal design study. Allocation was concealed.
- **Population:** part 1 included 177 children and young people aged 2–19 years (median age 8 years, 55% female) with systemic juvenile idiopathic arthritis (median duration just over 2 years) including active systemic features and arthritis (intermittently spiking temperatures of at least 38°C, 2 or more active joints, and C-reactive protein level of over 30 mg per litre).

Part 2 included 100 children and young people (with similar characteristics to those in part 1). Background therapy with oral corticosteroids (prednisone equivalent up to 1.0 mg per kilogram per day) and stable doses of NSAIDs and methotrexate were allowed. At baseline of trial 2, 72% of children or young people were receiving oral corticosteroids and 53% were receiving methotrexate. Concomitant treatment with another biological agent or disease-modifying drug was excluded. However, about two thirds of children or young people had received biological agents previously (most often anakinra). Other exclusions were diagnosis of the macrophage activation syndrome in the 6 months before enrolment, active tuberculosis, and live-virus vaccination in the 3 months before enrolment. Baseline characteristics were generally well balanced across the treatment groups.

- **Intervention and comparison:** in part 1, children and young people received a subcutaneous dose of canakinumab 4 mg per kilogram every 4 weeks for 12 to 32 weeks. Standardised tapering of oral corticosteroids was permitted from week 9 to 28, if at least an 'adapted JIA ACR 50 improvement' was achieved. This was defined as an absence of fever and an improvement of at least 50% in at least 3 of the 6 core criteria for juvenile idiopathic arthritis, with a worsening of more than 30% in no more than 1 of the criteria. In part 2, children and young people who were not receiving oral corticosteroids or who had tapered oral corticosteroids and achieved 'adapted JIA ACR 30 responses' were randomised to continue canakinumab 4 mg per kilogram every 4 weeks or switch to placebo.
- **Outcomes:** in part 1, the primary outcome was to determine whether at least 25% of the children and young people who were being treated with oral corticosteroids could have their dose tapered. In part 2, the primary outcome was time to flare of systemic juvenile idiopathic arthritis. Flare was defined as the recurrence of fever lasting for 2 or more consecutive days; a worsening of 30% or more in 3 or more of the 6 variables of the juvenile idiopathic arthritis core set, with no more than 1 variable improving by 30% or more (minimum contingencies included worsening in at least 2 joints with active or limited disease, at least a 20 mm worsening on the visual-analogue scale in the physician's or parent's global assessment of disease activity, and a C-reactive protein level of 30 mg per litre); or discontinuation of treatment, except in the case of discontinuation because of inactive disease at 24 weeks or more.
- **Other outcomes** included adapted 'JIA ACR 50', 'JIA ACR 70', 'JIA ACR 90', and 'JIA ACR 100' responses. These were defined as absence of fever plus improvements of 50% or more, 70% or more, 90% or more, and 100% respectively, in at least 3 of the 6 response variables and a worsening of more than 30% in no more than 1 of the 6 variables, and inactive disease. Safety assessments included the collection of data on adverse events and serious adverse events.

- To achieve 90% power, 37 events (flares) were needed. Results are reported for the intention-to-treat population.

Table 1 Summary of trial 1 and trial 2 (Ruperto et al. 2012a)

	Canakinumab 4 mg/kg	Placebo	Analysis
Efficacy	Trial 1, n=43 Trial 2 (part 1), n=177 Trial 2 (part 2), n=50	Trial 1, n=41 Trial 2 (part 1), N/A Trial 2 (part 2), n=50	
Primary outcome trial 1: number of participants with 'adapted JIA ACR 30 response' at day 15	36/43 (84%)	4/41 (10%)	OR 62.29 (95% CI 12.68 to 306.07); p<0.0001
Primary outcome trial 2 (part 1): oral corticosteroid tapering in at least 25% of participants being treated with oral corticosteroids	128/177 (72%) prescribed oral corticosteroids at study entry	-	57/128 (45%; 90% CI 37 to 52; p<0.001) able to undergo tapering from mean dose of 0.34 mg/kg to 0.05 mg/kg 42/128 (33%) discontinued oral corticosteroids completely

Primary outcome trial 2 (part 2): time to flare of systemic JIA	Median time to flare not observable because <50% of participants had flare Number of participants with no flare: 39/50 (74% <sup>a</sup> )	Median time to flare 236 days (95% CI 141 to 449) Number of participants with no flare: 24/50 (25% <sup>a</sup> )	HR 0.36 (95% CI 0.17 to 0.75); p=0.003 by log-rank test
Selected secondary outcomes:			
Number of participants with inactive disease at end of trial 1 (day 29)	13/43 (30%)	0/41 (0%)	No analysis available
Number of participants with inactive disease at end of trial 2	31/50 (62%)	17/50 (34%)	OR 3.4 (95% CI 1.5 to 8.0); p=0.002 <sup>b</sup>
<b>Safety</b>	Trial 1, n=43 Trial 2 (part 1), n=177 Trial 2 (part 2), n=50	Trial 1, n=41 Trial 2 (part 1), N/A Trial 2 (part 2), n=50	
Participants reporting serious adverse events	5% (2/43) in trial 1 8% (15/177) in trial 2, part 1 12% (6/50) in trial 2, part 2	5% (2/41) in trial 1 N/A for trial 2, part 1 12% (6/50) in trial 2, part 2	No statistical analysis reported

Participants reporting any adverse event	56% (24/43) in trial 1 78% (138/177) in trial 2, part 1 80% (40/50) in trial 2, part 2	39% (16/41) in trial 1 N/A for trial 2, part 1 70% (35/50) in trial 2, part 2	No statistical analysis reported
Participants reporting infections	30% (13/43) in trial 1 55% (97/177) in trial 2, part 1 54% (27/50) in trial 2, part 2	12% (5/41) in trial 1 N/A for trial 2, part 1 38% (19/50) in trial 2, part 2	No statistical analysis reported
Participants with adverse events leading to withdrawal	0% (0/43) in trial 1 3% (5/177) in trial 2, part 1 0% (0/50) in trial 2, part 2	0% (0/41) in trial 1 N/A for trial 2, part 1 12% (6/50) in trial 2, part 2	No statistical analysis reported
<p>Abbreviations: ACR, American College of Rheumatology; CI, <u>confidence interval</u>; HR, <u>hazard ratio</u>; JIA, juvenile idiopathic arthritis; OR, <u>odds ratio</u>, p, <u>p value</u>.</p> <p><sup>a</sup> Kaplan–Meier estimates.</p> <p><sup>b</sup> From <u>European public assessment report for canakinumab (EMA/H/C/001109/II/0026)</u>.</p>			

## Clinical effectiveness

In the single-dose study (trial 1; [Ruperto et al. 2012a](#)), at day 15, more children and young people in the canakinumab group had an 'adapted JIA ACR 30 response' (the primary end point) than in the placebo group (36 of 43 [84%] compared with 4 of 41 [10%];  $p < 0.0001$ ). This was defined as an improvement of 30% or more in at least 3 of the 6 core criteria for juvenile idiopathic arthritis,

worsening of more than 30% in no more than 1 of the criteria, and resolution of fever. These responses were sustained at day 29 with an 'adapted JIA ACR 30 response' in 81% of the canakinumab group and 10% of the placebo group ( $p < 0.001$ ). At day 29, adapted 'JIA ACR 50', 'JIA ACR 70', 'JIA ACR 90', and 'JIA ACR 100' responses with canakinumab were achieved in 79%, 67%, 47% and 33% of participants respectively. At the end of the trial, 13 participants (30%) who received canakinumab had inactive disease compared with none who received placebo. The [European public assessment report for canakinumab](#) suggests these data demonstrate a clinically relevant, statistically significant superiority of canakinumab compared with placebo. Results were consistent across subgroups, and oral corticosteroid use at baseline did not affect response to canakinumab.

In part 1 of trial 2 ([Ruperto et al. 2012a](#)), 177 children and young people received open-label canakinumab every 4 weeks for up to 32 weeks. The primary objective of this part of the study was to determine whether at least 25% of the children and young people who were being treated with oral corticosteroids could have their dose tapered. Oral corticosteroids were prescribed for 128 of the 177 participants at study entry, and 57 of these 128 (45%; 90% confidence interval [CI] 37 to 52;  $p < 0.001$ ) were able to successfully taper their corticosteroid dose from a mean dose of 0.34 mg per kilogram per day to 0.05 mg per kilogram per day. Of the 128 participants, 42 (33%) discontinued oral corticosteroids completely. The [European public assessment report for canakinumab](#) suggests these results are clinically important as frequent long-term use of oral corticosteroids is accompanied by severe and major side effects, especially in children.

In part 2 of trial 2 ([Ruperto et al. 2012a](#)), 100 children and young people who were not receiving oral corticosteroids or had tapered their oral corticosteroids and had achieved 'adapted JIA ACR 30 responses' were randomised to continue canakinumab every 4 weeks or switch to placebo until 37 flares occurred. It should be kept in mind that participants in the placebo group had received canakinumab in part 1 of the study. The primary objective of this part of the study was to demonstrate that time to flare was higher with canakinumab than with placebo. There was a statistically significant relative risk reduction in time to flare of 64% (hazard ratio [HR] 0.36; 95% CI 0.17 to 0.75;  $p = 0.003$ ). There were 11 flare events in the canakinumab group and 26 in the placebo group. The median time to flare was 236 days (95% CI 141 to 449) in the placebo group. The median time to flare was not observable in the canakinumab group because less than 50% of the participants had a flare. The [European public assessment report for canakinumab](#) suggests that, in the first 4 months, the probability to flare was similar in the canakinumab and placebo groups. Beyond 4 months, the rate of flare remained constant with placebo whereas only a few flares were seen with canakinumab.

In part 2 of trial 2 (Ruperto et al. 2012a), there was also a statistically significant relative risk reduction of 51% for worsening in ACR level with canakinumab compared with placebo (HR 0.49; 95% CI 0.27 to 0.90; p=0.0131). The median time to worsening in ACR level was 141 days in the placebo group. This could not be observed in the canakinumab group because less than 50% of participants experienced a worsening in ACR level. The probability of the ACR level not worsening was the same for canakinumab and placebo in the first 2 months, but improved from 2 months on in favour of canakinumab. At the end of the study, more children and young people had inactive disease with canakinumab than with placebo (31/50 [62%] with canakinumab compared with 17/50 [34%] with placebo, odds ratio [OR] 3.4; 95% CI 1.5 to 8.0; p=0.002). See the [European public assessment report for canakinumab](#) for details.

An uncontrolled extension study to trial 1 and trial 2 is ongoing ([ClinicalTrials.gov Identifier: NCT00891046](#)). The [European public assessment report for canakinumab](#) states that the data from this study are complex owing to different treatment regimens and durations. However, the efficacy data available for canakinumab 4 mg/kg every 4 weeks (to a median of 49 weeks of follow-up) support the results gained from the 2 pivotal trials. Of the 147 children and young people receiving canakinumab who were assessed at the time of the interim analysis, 76 (52.1%) had inactive disease. Sixty-nine children and young people were taking oral corticosteroids when they entered the extension study. Of these, 20 (29.0%) were corticosteroid-free and 13 (18.8%) were able to successfully reduce their corticosteroid dose at the time of the interim analysis; 27 (39.1%) did not attempt tapering and in 9 (13.0%) corticosteroid tapering failed.

Both trial 1 and trial 2 had secondary end points related to functional ability and quality of life. In trial 1, a comparison between the treatment groups showed that the least squares mean change from baseline over time in the childhood health assessment questionnaire (CHAQ: an assessment of physical function on a scale of 0 to 3, with higher scores indicating greater disability) was statistically significantly greater in the canakinumab group compared with the placebo group (p=0.0002). The estimated median difference was -0.69; this is greater than the CHAQ minimal clinically important difference of -0.19. In trial 2, from baseline to the end of part 1 of the trial, the median change in the CHAQ was -0.9. See the [European public assessment report for canakinumab](#) for details.

## Safety

The [European public assessment report for canakinumab](#) concluded that systemic juvenile idiopathic arthritis is a serious condition responsible for high childhood mortality and severe morbidity and disability. Taking into consideration that therapeutic options are limited and potentially very toxic, the safety profile for canakinumab treatment in children and young people

with this condition is acceptable. Full safety concerns are outlined in the [summary of product characteristics](#) (SPC).

The SPC states that more than 2300 people have been treated with canakinumab at a range of doses, including children, healthy volunteers and people in blinded and open-label clinical trials with cryopyrin-associated periodic syndromes, systemic juvenile idiopathic arthritis, gouty arthritis or other interleukin-1 beta-mediated diseases. This includes a total of 201 people aged 2 to 20 years with systemic juvenile idiopathic arthritis in clinical trials.

Particular risks identified with canakinumab for the treatment of systemic juvenile idiopathic arthritis include serious infections, neutropenia, leukopenia and thrombocytopenia. Despite the efficacy of canakinumab, macrophage activation syndrome, a life-threatening disorder, can still occur and has been seen in clinical trials of canakinumab for systemic juvenile idiopathic arthritis (in both the placebo and canakinumab groups).

The SPC states that canakinumab is associated with an increased incidence of serious infections, and that patients should be monitored carefully for signs and symptoms of infections during and after treatment. Canakinumab should not be initiated or continued in patients during an active infection requiring medical intervention. Caution should be exercised when giving canakinumab to patients with infections, a history of recurring infections, or underlying conditions that may predispose them to infections.

The SPC also states that neutropenia and leukopenia have been observed with medicinal products that inhibit interleukin-1, including canakinumab. Treatment with canakinumab should not be initiated in patients with neutropenia or leukopenia, and white blood cell counts are recommended before starting treatment and again after 1 to 2 months, or periodically during treatment.

The SPC states that if macrophage activation syndrome occurs, or is suspected, evaluation and treatment should be started as early as possible. Physicians should be attentive to symptoms of infection or worsening of systemic juvenile idiopathic arthritis because these are known triggers for the disorder. Based on clinical trial experience, canakinumab does not appear to increase the incidence of macrophage activation syndrome in children or young people with systemic juvenile idiopathic arthritis, but no definitive conclusion can be made.

In the pooled systemic juvenile idiopathic arthritis population reported in the [European public assessment report for canakinumab](#), 85% of children and young people who received canakinumab experienced at least 1 adverse event. The most frequently affected system organ classes were infections and infestations (71%), gastrointestinal disorders (53%), musculoskeletal and connective

tissue disorders (42%) and respiratory, thoracic and mediastinal disorders (38%). Severe adverse events were seen in 17% of this population.

In the single-dose study, trial 1 ([Ruperto et al. 2012a](#)), no children or young people discontinued the study because of an adverse event. Two serious adverse events were reported in each group. In the canakinumab group, there was 1 episode each of macrophage activation syndrome and varicella; in the placebo group, there was 1 episode each of macrophage activation syndrome and gastroenteritis.

In the open-label canakinumab phase of trial 2 (part 1, [Ruperto et al. 2012a](#)), 15 participants (8%) had a serious adverse event and 5 withdrew because of an adverse event. Seven participants had serious non-opportunistic infections (2 associated with macrophage activation syndrome). In part 2 of this study, 6 participants in the placebo group had a serious adverse event, 3 of which (macrophage activation syndrome, pneumonia, and flare of systemic juvenile idiopathic arthritis) led to withdrawal. Serious adverse events occurred in 6 participants in the canakinumab group (arm pain and lymphadenopathy; otitis media and leg fracture; leukopenia, thrombocytopenia and aminotransferase elevations; aminotransferase elevations; respiratory tract infection; and splenic cyst) but none of these led to discontinuation of the study drug.

For all treatment groups, the most common adverse events were infections. Neutropenia and thrombocytopenia were seen in both trials. In trial 1, thrombocytopenia developed in 2 (5%) participants in the canakinumab group and 1 (3%) in the placebo group. Neutropenia developed in 2 (5%) participants in the canakinumab group and none in the placebo group. In the open-label phase of trial 2 (part 1), 11 (6%) participants taking canakinumab had thrombocytopenia and 10 (6%) had neutropenia. In part 2 of this study, 3 (6%) participants in the canakinumab group and 1 (2%) in the placebo group had thrombocytopenia; and 6 (12%) in the canakinumab group and 1 (2%) in the placebo group had neutropenia.

There were 7 reported cases of macrophage activation syndrome across the 2 trials (2 with placebo and 5 with canakinumab). Two participants died in trial 2: a 16-year-old girl who had received canakinumab followed by placebo, and had progressive clinical worsening and urosepsis; and a 13-year-old boy, who was receiving canakinumab, had previously been treated with anakinra and tocilizumab, and had macrophage activation syndrome and severe pulmonary hypertension.

## *Evidence strengths and limitations*

The [European public assessment report for canakinumab](#) concluded that the objectives and end points of trial 1 and trial 2 ([Ruperto et al. 2012a](#)) were appropriate. However, the number of protocol deviations were high (at over 50%) in both studies.

The authors highlight other limitations, including that children and young people without fever were excluded from participation, so the efficacy of canakinumab in these people is unknown. In addition, information on the efficacy, and in particular safety, of canakinumab in children and young people with systemic juvenile idiopathic arthritis is limited because of the short duration of exposure to placebo in both trials and the use of a withdrawal design. Trial 1 was a 29-day, placebo-controlled, single-dose study. Trial 2 was a 2-part study in which children and young people received open-label canakinumab in part 1 for a median of 113 days (4 injections of canakinumab), and double-blind canakinumab or placebo in part 2 until 37 flare events were reached.

The ongoing, unpublished, open-label extension study provides data on canakinumab 4 mg/kg every 4 weeks to a median of 49 weeks of follow-up in 147 children and young people. However, further longer-term safety and efficacy data in more children and young people with systemic juvenile idiopathic arthritis are needed to ascertain potential rare and long-term adverse effects.

Both trials either compared canakinumab with placebo, or were single-arm, open-label in design. There are currently no trials comparing canakinumab with other active treatment in systemic juvenile idiopathic arthritis, although, in both trials, background therapy with oral corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) and methotrexate (but not another biological agent or disease-modifying drug) were allowed.

Participants in both trials were enrolled from 63 centres in numerous countries. Therefore, some centres are likely to have enrolled very few children and young people. It is possible that this may have affected how consistently trial outcomes were assessed.

## **Context**

### *Treatment alternatives*

Canakinumab is licensed for the treatment of active systemic juvenile idiopathic arthritis in patients aged 2 years and older whose condition has responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids. Canakinumab can be given as monotherapy or in combination with methotrexate (see the [Ilaris 150 mg powder](#)

[for solution for injection](#) summary of product characteristics). Tocilizumab is the only other biological disease-modifying antirheumatic drug (DMARD) licensed in the UK specifically for the treatment of active systemic juvenile idiopathic arthritis. Tocilizumab is also licensed for the treatment of juvenile idiopathic polyarthritis (see the [RoActemra 20 mg/ml Concentrate for Solution for Infusion](#) summary of product characteristics). See [Introduction](#) for details.

The other biological DMARDs licensed for the treatment of juvenile idiopathic arthritis, but not specifically active systemic juvenile idiopathic arthritis, are etanercept ([Etanercept summaries of product characteristics](#)), abatacept ([ORENCIA 250 mg powder for concentrate for solution for infusion](#) summary of product characteristics) and adalimumab ([Humira Pre-filled Pen, Pre-filled Syringe and Vial](#) summary of product characteristics). See [Introduction](#) and summaries of product characteristics for details.

Other biological DMARDs sometimes used for juvenile idiopathic arthritis, such as anakinra ([Kineret 100 mg solution for injection in a pre-filled syringe](#) summary of product characteristics) and infliximab ([Remicade 100mg powder for concentrate for solution for infusion](#) summary of product characteristics), are not licensed for juvenile idiopathic arthritis.

For children and young people with systemic juvenile idiopathic arthritis that does not respond to any other treatment, a bone marrow transplant and stem cell procedures may be considered.

### Costs of treatment alternatives

	Estimated dose for systemic juvenile idiopathic arthritis <sup>a</sup>	Estimated annual cost excluding VAT <sup>b</sup> (no wastage)	Estimated annual cost excluding VAT <sup>b</sup> (wastage)
Canakinumab	4 mg/kg (up to a maximum of 300 mg) every 4 weeks by subcutaneous injection in patients weighing at least 7.5 kg	£68,833	£129,061
Tocilizumab	8 mg/kg every 2 weeks in patients weighing at least 30 kg or 12 mg/kg every 2 weeks in patients weighing less than 30 kg by intravenous infusion	£7,987	£9,318

Etanercept	0.4 mg/kg (up to a maximum of 25 mg per dose) given twice a week by subcutaneous injection with an interval of 3–4 days between doses	£2,974	£3,718
Abatacept	10 mg/kg by intravenous infusion in patients weighing less than 75 kg. After initial administration, given at 2 weeks, then 4 weeks then every 4 weeks	£3,629	£4,536
Adalimumab	24 mg/m <sup>2</sup> body surface area up to a maximum single dose of 20 mg (for patients aged 2 to <4 years) and up to a maximum single dose of 40 mg (for patients aged 4 to 12 years) by subcutaneous injection every 2 weeks	£4,944	£9,156
Anakinra	2 mg/kg daily by subcutaneous injection (usual maximum dose 100 mg daily)	£2,546	£9,548
Infliximab <sup>c</sup>	5–6 mg/kg every 4–8 weeks by intravenous infusion	£6,546	£10,910

<sup>a</sup> Not all of these biological disease-modifying antirheumatic drugs (DMARDs) are licensed for systemic juvenile idiopathic arthritis. The conditions and the age of children that they are licensed for varies (see summaries of product characteristics, [treatment alternatives](#) and [introduction](#) for details). Estimated doses have been used to produce costs. Discussions with clinicians indicate that in practice, doses and treatment frequency may vary. The doses shown do not imply therapeutic equivalence.

<sup>b</sup> Annual costs are based on prescribing for a 5-year-old child weighing 20 kg and with a body surface area of 0.9 m<sup>2</sup>. Costs are taken from [MIMS](#) February 2014. Costs do not take account of any patient access scheme discount or locally negotiated procurement discounts. Costs are given excluding VAT. Depending on whether these drugs are given in hospital or delivered to home will affect whether they are VAT exempt or not (drugs given intravenously, and canakinumab, are likely to be administered in hospital and VAT will apply).

<sup>c</sup> Used 6 mg/kg every 4 weeks to calculate costs.

## Estimated impact for the NHS

### *Likely place in therapy*

The 2 trials showed canakinumab 4 mg/kg was effective in children and young people with systemic juvenile idiopathic arthritis. More children and young people responded to treatment with canakinumab than with placebo; canakinumab reduced the risk of disease flare compared with

placebo; and in an uncontrolled study (no placebo group), treatment with canakinumab allowed tapering of doses of oral corticosteroids. The [European public assessment report for canakinumab](#) notes that this last finding is particularly clinically important as frequent long-term use of oral corticosteroids is accompanied by serious side effects especially in children.

Canakinumab treatment does, however, have risks and these are outlined in full in the [summary of product characteristics](#). These include serious infections, neutropenia, leukopenia and thrombocytopenia. The [European public assessment report for canakinumab](#) notes that, overall, more serious adverse events were seen in trials of canakinumab for systemic juvenile idiopathic arthritis than in trials of canakinumab for cryopyrin-associated periodic syndromes. There is also a particular concern about macrophage activation syndrome in children and young people with systemic juvenile idiopathic arthritis that is treated with canakinumab.

Canakinumab is licensed for the treatment of active systemic juvenile idiopathic arthritis in children and young people whose condition has responded inadequately to previous therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and oral corticosteroids. It can be given as monotherapy or in combination with methotrexate, and should be initiated and supervised by physicians experienced in diagnosing and treating this condition.

Specialists have advised that it is important to ensure that standard treatments for systemic juvenile idiopathic arthritis (NSAIDs, oral corticosteroids and methotrexate) have been optimised before canakinumab is considered. Canakinumab may be an option, as tocilizumab is (see NICE technology appraisal guidance on [tocilizumab for the treatment of systemic juvenile idiopathic arthritis](#)), for children and young people aged 2 years and older whose disease has responded inadequately to NSAIDs, systemic corticosteroids and methotrexate. NICE does not recommend tocilizumab for children and young people aged 2 years and older whose disease continues to respond to methotrexate or has not been treated with methotrexate. In systemic juvenile idiopathic arthritis, tocilizumab is given as an intravenous infusion every 2 weeks, whereas canakinumab is given by subcutaneous injection every 4 weeks. This may be a practical advantage; however, specialists have advised that canakinumab is likely to be given in a hospital setting.

The annual cost of canakinumab for a child weighing 20 kg (assuming no wastage) is £68,833 excluding VAT. This is considerably more expensive than tocilizumab, which for a child weighing 20 kg (assuming no wastage) is £7,987 (MIMS, February 2014).

The canakinumab [summary of product characteristics](#) (SPC) states that continued treatment with canakinumab in patients without clinical improvement should be reconsidered by the treating physician. The [European public assessment report for canakinumab](#) notes that approximately 20%

of children and young people receiving canakinumab did not reach the 'adapted JIA ACR 30 response', and it is currently uncertain how long treatment should be continued if no rapid clinical response is seen. It is also currently unknown if people who achieve inactive or stable, less active disease might be maintained on a lower dose or less-frequent dosing schedule long-term, which could possibly offer benefits from a safety perspective. These questions will be addressed in a new phase IV study.

The canakinumab [SPC](#) states that, although limited, evidence from clinical trials suggests that systemic juvenile idiopathic arthritis that does not respond to tocilizumab or anakinra (off-label use) may respond to canakinumab. However, this is based on very small patient numbers.

### *Estimated usage*

The manufacturer was unable to provide estimated usage data for canakinumab. However, the costing statement associated with the NICE technology appraisal guidance on [tocilizumab for the treatment of systemic juvenile idiopathic arthritis](#) estimated that there was an eligible population of 372 children and young people in England with systemic juvenile idiopathic arthritis that had not responded to methotrexate. It was estimated that a population of 150,000 (including approximately 25,600 children and young people aged 2 to 18 years) was likely on average to have only 1 patient with systemic juvenile idiopathic arthritis.

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## About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, but this summary is not NICE guidance.

For information about the process used to develop this evidence summary, see Evidence summaries: new medicines – integrated process statement.

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