



**CLINICAL PRIORITIES ADVISORY GROUP**  
**18 07 2021**

<b>Agenda Item No</b>	2.1
<b>National Programme</b>	Blood and Infection
<b>Clinical Reference Group</b>	Immunology and Allergy
<b>URN</b>	2002

<b>Title</b>
<b>Canakinumab for patients with systemic-onset juvenile idiopathic arthritis (SJIA) or adult-onset Still's disease (AOSD) refractory to anakinra and tocilizumab</b>

<b>Actions Requested</b>	1. Support the adoption of the policy proposition
	2. Recommend its relative Prioritisation

<b>Proposition</b>
<p>For routine commissioning</p> <p>This is a clinical commissioning policy proposition for the use of canakinumab as 4<sup>th</sup> line treatment for adults and children 2 years and over with Still's disease.</p> <p>Still's disease is the umbrella term used for two conditions: <i>systemic-onset juvenile idiopathic arthritis (SJIA)</i> in children and <i>adult-onset Still's disease (AOSD)</i> in adults.</p> <p>Still's disease is a rare inflammatory condition that can manifest at any age, usually with symptoms of fever, joint pain, rash, weight loss and muscle aches. Patients with a diagnosis of Still's disease are usually treated with non-steroidal anti-inflammatory drugs (such as ibuprofen) and corticosteroids.</p> <p>If these treatments do not help control symptoms, they can be given disease-modifying anti-rheumatic drugs (such as methotrexate). Often, even this does not help control symptoms and patients are started on newer drugs such as anakinra or tocilizumab. For a very small number of patients, their symptoms may not be controlled by any of these medications, or they may be intolerant to these medications. Currently there are no further treatment options for these patients.</p>

This policy proposition recommends the use of canakinumab for adults and children 2 years and over with Still's disease where their symptoms are not controlled by any of the currently available treatments, which can be life-changing for these severely affected patients.

**Clinical Panel recommendation**

The Clinical Panel recommended that the policy proposition progress as a routine commissioning policy.

**The committee is asked to receive the following assurance:**

1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head of Acute Programmes confirms the proposition is supported by an: Impact Assessment; Engagement Report; Equality and Health Inequalities Impact Assessment; Clinical Policy Proposition. The relevant National Programme of Care has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

**The following documents are included (others available on request):**

1.	Clinical Policy Proposition
2.	Engagement Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment

In the Population what is the clinical effectiveness and safety of the Intervention compared with Comparator?

Outcome	Evidence statement
<b>Clinical effectiveness</b>	
<b>Critical outcomes</b>	
<p><b>Outcome 1</b></p> <p><b>Quality of Life</b></p> <p><b>Certainty of evidence:</b> Not applicable</p>	<p>Quality of life is important to patients because of the impact on the patient's function, activities of daily living and self-perceived well-being. Improvement in quality of life is a marker of successful treatment.</p> <p><u>Patients with SJIA</u> No evidence was identified for this outcome.</p> <p><u>Patients with AOSD</u> No evidence was identified for this outcome.</p>
<p><b>Outcome 2</b></p> <p><b>Reduction and resolution of symptoms (as measured by the juvenile arthritis disease activity score (JADAS), disease activity score (DAS28) or similar)</b></p> <p><b>Certainty of evidence:</b> Very Low</p>	<p>Improvement in symptoms is important to patients because this could help determine treatment choice (such as reduction of corticosteroids) and because of the impact on the patient's function and activities of daily living. Resolution of symptoms also indicates clinical remission.</p> <p><b>Patients with SJIA</b></p> <p>Three case series (Barut et al 2019, Horneff et al 2017 and Nishimura et al 2020) provided non-comparative evidence relating to resolution and reduction of symptoms as measured by the JADAS-10 score<sup>1</sup>, American College of Rheumatology (ACR)<sup>2</sup> criteria, ACR paediatric 30/50/70 criteria<sup>3</sup> or study's own criteria in a subgroup of patients treated with canakinumab following tocilizumab in all or the majority of cases.</p> <p>Remission (defined as JADAS-10 score <math>\leq 1</math>):</p> <ul style="list-style-type: none"> <li>• 1 prospective case series (Horneff et al 2017) of 245 patients from a national registry of SJIA patients on biologics reported results for 7 patients treated with canakinumab following tocilizumab providing non-comparative evidence that remission (defined as JADAS-10 score <math>\leq 1</math>) was achieved in 55% of these in scope patients at last documented response (estimated from graph; median/mean timepoint not reported). (<b>VERY LOW</b>)</li> </ul> <p>Remission (defined by American College of Rheumatology (ACR) criteria):</p> <ul style="list-style-type: none"> <li>• 1 prospective case series (Horneff et al 2017) of 245 patients from a national registry of SJIA patients on biologics reported results for 7 patients treated with</li> </ul>

canakinumab following tocilizumab providing non-comparative evidence that remission (defined by American College of Rheumatology (ACR) criteria) was achieved in 43% of these in scope patients at last documented response (estimated from graph; median/mean timepoint not reported). **(VERY LOW)**

Achieving ACR paediatric 30, 50 and 70 criteria:

- 1 prospective case series (Nishimura et al 2020) of 19 SJIA patients treated with canakinumab reported results for a subgroup of 15 patients previously treated with tocilizumab providing non-comparative evidence that ACR paediatric 30, 50 and 70 criteria was achieved in all patients at 8 weeks. **(VERY LOW)**

Remission off medication (study's criteria):

- 1 single centre retrospective case series (Barut et al 2019) of 168 SJIA patients reported results for 27 patients treated with canakinumab providing non-comparative evidence that remission<sup>4</sup> off medication (no usage of any anti-rheumatic drugs during the last 12 months) was achieved in 3 (11.5%) patients treated with canakinumab with follow-up for a minimum of 12 months (timepoint not reported). While it is likely that canakinumab was given as 4th line treatment following tocilizumab or anakinra, only up to 67% of patients can have been previously treated with tocilizumab. **(VERY LOW)**

Minimal disease activity on medication (not defined):

- 1 single centre retrospective case series (Barut et al 2019) of 168 SJIA patients reported results for 27 patients treated with canakinumab providing non-comparative evidence that minimal disease activity on medication was achieved in 23 (85%) patients treated with canakinumab with follow-up of a minimum of 12 months (timepoint not reported). While it is likely that canakinumab was given as 4th line treatment following tocilizumab or anakinra, only up to 67% of patients can have been previously treated with tocilizumab. **(VERY LOW)**

**These studies provided very low certainty evidence that compared to baseline, canakinumab reduces and resolves symptoms in patients with SJIA refractory to or intolerant of tocilizumab.**

#### **Patients with AOSD**

One retrospective case series (Colafrancesco et al 2017) (n=140) provided non-comparative evidence on the reduction and resolution of symptoms as measured by a modified version of the Pouchot's disease activity score 5

at 3, 6 and 12 months in four AOSD patients (mean age 34.2 (+/- 15.4) years; three systemic disease and one chronic articular profile). Patients were treated with canakinumab (two patients on monotherapy and two in combination with conventional disease-modifying antirheumatic drugs (cDMARDs)) after failure of therapy based on non-steroidal anti-inflammatory drugs (NSAIDs), immunosuppressive drugs and anakinra with or without prior tocilizumab. Two patients also received other biologic agents (infliximab, etanercept and/or adalimumab) prior to anakinra and therefore are not strictly in scope. One patient (prior treatment not reported) discontinued canakinumab at 9 months due to loss of efficacy and was excluded from the 12 month follow-up results. Mean Pouchot's scores were estimated from a bar chart for 6 and 12 month follow-up results.

At 3 months:

- 1 case series (Colafrancesco et al 2017) (n=4) provided non-comparative evidence that mean Pouchot's score improved significantly ( $p < 0.0001$ ) from 4.25 (Standard deviation (SD) 2.6; range 2 to 8) to 1.25 (SD 1.8; range 1 to 4) in patients with AOSD treated with canakinumab after failed anakinra (with or without prior tocilizumab) therapy. **(VERY LOW)**

At 6 months:

- 1 case series (Colafrancesco et al 2017) (n=4) provided non-comparative evidence that Pouchot's score improved statistically significantly ( $p < 0.0001$ ) from 4.25 (SD 2.6; range 2 to 8) to 1.5 (estimated from bar chart) in patients with AOSD treated with canakinumab after failed anakinra (with or without prior tocilizumab) therapy. **(VERY LOW)**

At 12 months:

- 1 case series (Colafrancesco et al 2017) (n=3) provided non-comparative evidence that Pouchot's score improved statistically significantly ( $p < 0.0001$ ) from 4.25 (SD 2.6; range 2 to 8) to 1.0 (estimated from bar chart) in patients with AOSD treated with canakinumab after failed anakinra (with or without prior tocilizumab) therapy. **(VERY LOW)**

**This study provided very low certainty evidence that compared to baseline, canakinumab improves symptoms as measured by a modified version of the Pouchot's disease activity score up to 12 months in patients with AOSD refractory to or intolerant of anakinra and tocilizumab.**

<p><b>Outcome 3</b></p> <p><b>Reduction in corticosteroid use</b></p> <p><b>Certainty of evidence:</b> <b>Very Low</b></p>	<p>Assessment of corticosteroid use is important to patients because long-term steroid use can be harmful and cause side effects unwanted by patients and may affect treatment choice.</p> <p><b>Patients with SJIA</b></p> <p>One prospective case series (Nishimura et al 2020) provided non-comparative evidence relating to reduction in corticosteroid use in a subgroup of patients treated with canakinumab following tocilizumab.</p> <p>Successful oral corticosteroid tapering:</p> <ul style="list-style-type: none"> <li>• 1 prospective case series (Nishimura et al 2020) of 19 SJIA patients treated with canakinumab reported results for a subgroup of 15 patients previously treated with tocilizumab providing non-comparative evidence that successful oral corticosteroid tapering<sup>6</sup> was achieved at 28 weeks in 11 (73.3%) of these in scope patients, of which 10 (66.7%) were tapered and 1 (6.7%) was corticosteroid-free. <b>(VERY LOW)</b></li> </ul> <p><b>This study provided very low certainty evidence that compared to baseline, canakinumab reduces corticosteroid use up to 28 weeks in patients with SJIA refractory to or intolerant of tocilizumab.</b></p> <p><b>Patients with AOSD</b></p> <p>One retrospective case series (Colafrancesco et al 2017) (n=140) provided non-comparative evidence on concomitant corticosteroid use and mean dosage at 3, 6 and 12 months in four AOSD patients (mean age 34.2 (+/- 15.4) years; three systemic disease and one chronic articular profile). Patients were treated with canakinumab (2 patients on monotherapy and 2 in combination with cDMARDs) after failure of therapy based on NSAIDs, immunosuppressive drugs and anakinra with or without prior tocilizumab. Two patients also received other biologic agents (infliximab, etanercept and/or adalimumab) prior to anakinra and therefore are not strictly in scope. One patient (prior treatment not reported) discontinued canakinumab at 9 months due to loss of efficacy and was excluded from the 12 month follow-up results.</p> <p>At 3 months:</p> <ul style="list-style-type: none"> <li>• 1 case series (Colafrancesco et al 2017) (n=4) provided non-comparative evidence that concomitant corticosteroid use did not change with no discontinuation of use reported in patients with AOSD treated with canakinumab</li> </ul>
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	<p>after failed anakinra (with or without prior tocilizumab) therapy. <b>(VERY LOW)</b></p> <ul style="list-style-type: none"> <li>• 1 case series (Colafrancesco et al 2017) (n=4) provided non-comparative evidence that mean prednisone dosage (8.2 mg; SD 7.8) was statistically significantly lower (<math>p &lt; 0.0001</math>) compared to baseline (143.7 mg; SD 238.2). <b>(VERY LOW)</b></li> </ul> <p>At 6 months:</p> <ul style="list-style-type: none"> <li>• 1 case series (Colafrancesco et al 2017) (n=4) provided non-comparative evidence that concomitant corticosteroid use did not change with no discontinuation of use in patients with AOSD treated with canakinumab after failed anakinra (with or without prior tocilizumab) therapy. <b>(VERY LOW)</b></li> <li>• 1 case series (Colafrancesco et al 2017) (n=4) provided non-comparative evidence that mean prednisone dosage (16.2 mg; SD 13) was lower compared to baseline (143.7 mg; SD 238.2). Statistical significance not reported. <b>(VERY LOW)</b></li> </ul> <p>At 12 months:</p> <ul style="list-style-type: none"> <li>• 1 case series (Colafrancesco et al 2017) (n=3) provided non-comparative evidence that concomitant corticosteroid use did not change with no discontinuation of use in patients with AOSD treated with canakinumab after failed anakinra (with or without prior tocilizumab) therapy. <b>(VERY LOW)</b></li> <li>• 1 case series (Colafrancesco et al 2017) (n=3) provided non-comparative evidence that mean prednisone dosage (10 mg; SD 7.1) was statistically significantly lower (<math>p &lt; 0.0001</math>) compared to baseline (143.7 mg; SD 238.2). <b>(VERY LOW)</b></li> </ul> <p><b>This study provided very low certainty evidence that compared to baseline, canakinumab reduces prednisone corticosteroid dosage up to 12 months in patients with AOSD refractory to or intolerant of anakinra and tocilizumab.</b></p>
<b>Important outcomes</b>	
<p><b>Outcome 4</b></p> <p><b>Control of biochemical markers of inflammation (C-reactive protein (CRP), serum amyloid A (SAA) and erythrocyte</b></p>	<p>Assessment of inflammatory biomarkers is important to patients because these blood tests are a direct, quantifiable measure of disease activity and treatment response. Return to normal levels can indicate biochemical remission.</p> <p><b>Patients with SJIA</b></p> <p><b>No evidence was identified for this outcome.</b></p>

<p><b>sedimentation rate (ESR))</b></p> <p><b>Certainty of evidence:</b>  Patients with SJIA  Not applicable  Patients with AOSD  Very low</p>	<p><b>Patients with AOSD</b></p> <p>One retrospective case series (Colafrancesco et al 2017) (n=140) provided non-comparative evidence on the control of CRP and ESR at 3, 6 and 12 months in four AOSD patients (mean age 34.2 (+/- 15.4) years; three systemic disease and one chronic articular profile). Patients were treated with canakinumab (two patients on monotherapy and two in combination with cDMARDs) after failure of therapy based on NSAIDs, immunosuppressive drugs and anakinra with or without prior tocilizumab. Two patients also received other biologic agents (infliximab, etanercept and/or adalimumab) prior to anakinra and therefore are not strictly in scope. One patient (prior treatment not reported) discontinued canakinumab at 9 months due to loss of efficacy and was excluded from the 12 month follow-up results.</p> <p>Up to 12 months:</p> <ul style="list-style-type: none"> <li>• 1 case series (Colafrancesco et al 2017) (n=4, up to 9 months; n=3, 9 to 12 months) provided non-comparative evidence that “CRP was higher at baseline and after 3 months in all of the patients, it was decreased in two patients at the 6 months time point, and in another at the 12 months time point” in patients with AOSD treated with canakinumab after failed anakinra (with or without prior tocilizumab) therapy. No further details were reported. <b>(VERY LOW)</b></li> <li>• 1 case series (Colafrancesco et al 2017) (n=4, up to 9 months; n=3, 9 to 12 months) provided non-comparative evidence that “ESR was elevated at baseline and at the end of the third month in 3 of the 4 patients; it was reduced in one patient after 6 months, and it was reduced in another after 12 months” in patients with AOSD treated with canakinumab after failed anakinra (with or without prior tocilizumab) therapy. No further details were reported. <b>(VERY LOW)</b></li> </ul> <p><b>This study provided very low certainty evidence that compared to baseline, canakinumab reduces biomarkers of inflammation (CRP and ESR) up to 12 months in patients with AOSD refractory to or intolerant of anakinra and tocilizumab.</b></p>
<p><b>Outcome 5</b></p> <p><b>Changes in systemic features of disease (fever, rash, weight</b></p>	<p>Assessment of systemic disease is important to patients because this could help determine treatment choice and because of the impact on the patient's self-perceived well-being.</p>



<p><b>change and hepatosplenomegaly)</b></p> <p><b>Certainty of evidence:</b> Very Low</p>	<p><b>Patients with SJIA</b></p> <p>One prospective case series (Horneff et al 2017) provided non-comparative evidence relating to changes in systemic features of disease in a subgroup of patients treated with canakinumab following tocilizumab.</p> <ul style="list-style-type: none"> <li>• 1 prospective case series (Horneff et al 2017) of 245 patients from a national registry of SJIA patients on biologics reported results for 7 patients treated with canakinumab following tocilizumab providing non-comparative evidence that 85% of patients had no fever at last documented response (estimated from graph; median/mean timepoint not reported). (VERY LOW)</li> </ul> <p><b>This study provided very low certainty evidence that compared to baseline, canakinumab improves systemic features of disease in patients with SJIA refractory to or intolerant of tocilizumab.</b></p> <p><b>Patients with AOSD</b></p> <p>One retrospective case series (Colafrancesco et al 2017) (n=140) provided non-comparative evidence on the changes in fever, rash and hepatosplenomegaly or increased liver enzymes at 3, 6 and 12 months in four AOSD patients (mean age 34.2 (+/- 15.4) years; three systemic disease and one chronic articular profile). Patients were treated with canakinumab (two patients on monotherapy and two in combination with cDMARDs) after failure of therapy based on NSAIDs, immunosuppressive drugs and anakinra with or without prior tocilizumab. Two patients also received other biologic agents (infliximab, etanercept and/or adalimumab) prior to anakinra and therefore are not strictly in scope. One patient (prior treatment not reported) discontinued canakinumab at 9 months due to loss of efficacy and was excluded from the 12 month follow-up results.</p> <p>At 3 months:</p> <ul style="list-style-type: none"> <li>• 1 case series (Colafrancesco et al 2017) (n=4) provided non-comparative evidence that the number of patients with fever reduced compared to baseline (4 patients (100%) vs 1 (25%)) in patients with AOSD treated with canakinumab after failed anakinra (with or without prior tocilizumab) therapy. Statistical significance not reported. <b>(VERY LOW)</b></li> <li>• 1 case series (Colafrancesco et al 2017) (n=4) provided non-comparative evidence that the number of patients with rash reduced compared to baseline (2 patients (50%))</li> </ul>
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	<p>vs 0 (0%)) in patients with AOSD treated with canakinumab after failed anakinra (with or without prior tocilizumab) therapy. Statistical significance not reported. <b>(VERY LOW)</b></p> <ul style="list-style-type: none"> <li>• 1 case series (Colafrancesco et al 2017) (n=4) provided non-comparative evidence that there was no change in the number of patients with hepatomegaly or increased liver enzymes compared to baseline (1 patient (25%) vs 1 (25%)) in patients with AOSD treated with canakinumab after failed anakinra (with or without prior tocilizumab) therapy. Statistical significance not reported. <b>(VERY LOW)</b></li> </ul> <p>At 6 months:</p> <ul style="list-style-type: none"> <li>• 1 case series (Colafrancesco et al 2017) (n=4) provided non-comparative evidence that the number of patients with fever reduced compared to baseline (4 patients (100%) vs 2 (50%)) in patients with AOSD treated with canakinumab after failed anakinra (with or without prior tocilizumab) therapy. Statistical significance not reported. <b>(VERY LOW)</b></li> <li>• 1 case series (Colafrancesco et al 2017) (n=4) provided non-comparative evidence that the number of patients with rash reduced compared to baseline (2 patients (50%) vs 0 (0%)) in patients with AOSD treated with canakinumab after failed anakinra (with or without prior tocilizumab) therapy. Statistical significance not reported. <b>(VERY LOW)</b></li> <li>• 1 case series (Colafrancesco et al 2017) (n=4) provided non-comparative evidence that there was no change in the number of patients with hepatomegaly or increased liver enzymes compared to baseline (1 patient (25%) vs 1 (25%)) in patients with AOSD treated with canakinumab after failed anakinra (with or without prior tocilizumab) therapy. Statistical significance not reported. <b>(VERY LOW)</b></li> </ul> <p>At 12 months:</p> <ul style="list-style-type: none"> <li>• 1 case series (Colafrancesco et al 2017) (n=3) provided non-comparative evidence that the number of patients with fever reduced compared to baseline (4 patients (100%) vs 0 (0%)) in patients with AOSD treated with canakinumab after failed anakinra (with or without prior tocilizumab) therapy. Statistical significance not reported. <b>(VERY LOW)</b></li> <li>• 1 case series (Colafrancesco et al 2017) (n=3) provided non-comparative evidence that the number of patients with rash reduced compared to baseline (2 patients (50%) vs 0 (0%)) in patients with AOSD treated</li> </ul>
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	<p>with canakinumab after failed anakinra (with or without prior tocilizumab) therapy. Statistical significance not reported. <b>(VERY LOW)</b></p> <ul style="list-style-type: none"> <li>• 1 case series (Colafrancesco et al 2017) (n=3) provided non-comparative evidence that there was no change in the number of patients with hepatomegaly or increased liver enzymes compared to baseline (1 patient (25%) vs 1 (33%)) in patients with AOSD treated with canakinumab after failed anakinra (with or without prior tocilizumab) therapy. Statistical significance not reported. <b>(VERY LOW)</b></li> </ul> <p><b>This study provided very low certainty evidence that compared to baseline, canakinumab reduces fever and rash and has no effect on hepatosplenomegaly up to 12 months in patients with AOSD refractory to or intolerant of anakinra and tocilizumab.</b></p>
<p><b>Safety</b></p>	
<p><b>Outcome 1</b></p> <p><b>Adverse effects</b></p> <p><b>Certainty of evidence:</b> Very low</p>	<p>Safety outcomes are relevant to patients because adverse events can affect survival, quality of life, tolerability and overall responses.</p> <p><b><u>Patients with SJIA:</u></b></p> <p>Three case series (Barut et al 2019, Horneff et al 2017 and Nishimura et al 2020) provided non-comparative evidence relating to adverse effects in a subgroup of patients treated with canakinumab following tocilizumab.</p> <p><b><u>Severe adverse effects:</u></b></p> <ul style="list-style-type: none"> <li>• 1 single centre retrospective case series (Barut et al 2019) of 168 SJIA patients reported results for a subgroup of 27 patients treated with canakinumab providing non-comparative evidence that “one patient treated with canakinumab had pneumonia”. While it is likely that canakinumab was given as 4th line treatment following tocilizumab or anakinra, only up to 67% can have been previously treated with tocilizumab. <b>(VERY LOW)</b></li> </ul> <p><b><u>Experience ≥1 adverse event(s) during the study:</u></b></p> <ul style="list-style-type: none"> <li>• 1 prospective case series (Nishimura et al 2020) of 19 SJIA patients treated with canakinumab reported results for a subgroup of 15 patients previously treated with tocilizumab providing non-comparative evidence that “all patients experienced ≥1 AE during the study”. <b>(VERY LOW)</b></li> </ul>

	<p><u>Discontinuation of medication due to intolerance:</u></p> <ul style="list-style-type: none"> <li>• 1 prospective case series (Horneff et al 2017) of 245 patients from a national registry of SJIA patients on biologics reported results for 7 patients treated with canakinumab following tocilizumab providing non-comparative evidence that “1 patient on canakinumab treatment who had MAS discontinued due to intolerance”.</li> </ul> <p><b>(VERY LOW)</b></p> <p>This study provided very low certainty evidence on the safety of canakinumab in patients with SJIA refractory to or intolerant of tocilizumab.</p> <p><b><u>Patients with AOSD</u></b></p> <p>One retrospective case series (Colafrancesco et al 2017) (n=140) provided non-comparative evidence on the number of registered adverse events at 3, 6 and 12 months in four AOSD patients (mean age 34.2 (+/- 15.4) years; three systemic disease and one chronic articular profile). Patients were treated with canakinumab (two patients on monotherapy and two in combination with cDMARDs) after failure of therapy based on NSAIDs, immunosuppressive drugs and anakinra with or without prior tocilizumab. Two patients also received other biologic agents (infliximab, etanercept and/or adalimumab) prior to anakinra and therefore are not strictly in scope. One patient (prior treatment not reported) discontinued canakinumab at 9 months due to loss of efficacy and was excluded from the 12 month follow-up results.</p> <p><u>Up to 12 months:</u></p> <ul style="list-style-type: none"> <li>• 1 case series (Colafrancesco et al 2017) (n=4, up to 9 months; n=3, 9 to 12 months) provided non-comparative evidence that there were no adverse events registered in patients with AOSD treated with canakinumab after failed anakinra (with or without prior tocilizumab) therapy.</li> </ul> <p><b>(VERY LOW)</b></p> <p>This study provided very low certainty evidence on the safety of canakinumab up to 12 months in patients with AOSD refractory to or intolerant of anakinra and tocilizumab.</p>
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**In the Population what is the cost effectiveness of the Intervention compared with Comparator?**

Outcome	Evidence statement
	No evidence was identified for cost effectiveness

From the evidence selected, are there any subgroups of patients that may benefit from the intervention more than the wider population of interest?

Outcome:	Evidence statement
<b>Certainty of evidence:</b> <b>Subgroups</b>	No evidence was identified regarding any subgroups of patients that would benefit more from treatment with canakinumab as 4th line treatment

<b>Patient Impact Summary</b>
<p data-bbox="204 611 1278 647"><b>The condition has the following impacts on the patient's everyday life:</b></p> <ul data-bbox="252 689 1382 1061" style="list-style-type: none"> <li data-bbox="252 689 1382 757">• <b>mobility:</b> patients can have severe problems in walking about or are unable to walk about</li> <li data-bbox="252 763 1382 831">• <b>ability to provide self-care:</b> patients can have severe problems in washing or dressing or are unable to wash or dress</li> <li data-bbox="252 837 1382 904">• <b>undertaking usual activities:</b> patients can have severe problems in doing their usual activities or are unable to do their daily activities</li> <li data-bbox="252 911 1382 978">• <b>experience of pain/discomfort:</b> patients can have severe pain or discomfort</li> <li data-bbox="252 985 1382 1052">• <b>experience of anxiety/depression:</b> patients can be severely anxious or depressed</li> </ul>
<p data-bbox="204 1137 810 1173"><b>Further details of impact upon patients:</b></p> <p data-bbox="204 1211 1362 1720">People with severe Still's disease which has not responded to other treatments usually have severe joint swelling, which can impact on their mobility and necessitate the use of mobility aids. If this joint swelling affects the arms or hands it can impact on their ability to write or use a mouse and keyboard, or other tasks, which can make school or work challenging. Frequent breaks may be required to help manage the pain. Similarly, personal care tasks can be restricted such as fastening buttons or zips, reaching into pockets, cooking or using utensils. Pain can be an ongoing problem, with many people experiencing mouth ulcers, which can also make it difficult to eat and drink. People also describe hot, itchy rashes. People also require frequent hospitalisations with symptoms of the disease or infections due to their increased risk of infection. Many people suffer with fatigue and breathlessness. All the symptoms of the disease, plus any medication side effects and the loss of independence can lead to patients feeling anxious or depressed.</p> <p data-bbox="204 1742 783 1778"><b>Further details of impact upon carers:</b></p> <p data-bbox="204 1785 1382 1957">Still's disease can affect children or adults and can lead to a high burden on the carer to help with many self-care tasks, which may be difficult or impossible for the person during a flare-up. Families and/or carers may have to help with tasks such as bathing, cleaning teeth, dressing and undressing, cooking and preparing meals, ironing, cleaning the house, getting out and about or help using mobility aids.</p>

People with Still's disease also describe difficulty losing their independence and can lash out at their family and carers adding strain to their relationships.

**Considerations from review by Rare Disease Advisory Group**

**Not Applicable**

**Pharmaceutical considerations**

The clinical commissioning policy proposition recommends that canakinumab is used as a as fourth-line treatment option for adults and children 2 years and over with a diagnosis of Still's disease where the patient is refractory to or did not tolerate therapy with NSAIDs, corticosteroids, DMARDs, tocilizumab and anakinra. The prescribing clinician should be aware of the special warnings and precautions for use of canakinumab as detailed in the [Summary of Product Characteristics](#).

Children should have been treated with methotrexate and adults should have been treated with at least 2 DMARDs.

When treating patients under 18 years this MDT should include a paediatric consultant specialising in rheumatology

**Considerations from review by National Programme of Care**

The proposal received the full support of the Blood and Infection Programme of Care on 19 April 2022.