ID1463 ERG STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Anakinra for treating Still's disease [ID1463]

Confidential until published

This report was commissioned by the NIHR Systematic Reviews Programme as project number 128239

Completed 18th December 2019

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Anakinra for treating Still's disease [ID1463]

Produced by: Liverpool Reviews & Implementation Group (LR*i*G)

Authors: Janette Greenhalgh, Senior Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

Tosin Lambe, Research Associate (Health Economics), LR*i*G, University of Liverpool

James Mahon, Director, Coldingham Analytical Services, Berwickshire

Marty Chaplin, Research Associate (Medical Statistician), LR*i*G, University of Liverpool

Angela Boland, Director, LR*i*G, University of Liverpool

Sophie Beale, Research Associate (Decision Analysis), LR*i*G, University of Liverpool

Yenal Dundar, Research Fellow (Information Specialist), LR*i*G, University of Liverpool

Joanne McEntee, Senior Medicines Information Pharmacist, North West Medicines Information Centre, Liverpool

Tom Kennedy, Consultant in Acute Medicine and Rheumatology, Royal Liverpool and Broadgreen University Hospitals NHS Foundation Trust

Correspondence to: Janette Greenhalgh, Senior Research Fellow, Liverpool Reviews and Implementation Group, University of Liverpool, Whelan Building, The Quadrangle, Brownlow Hill, Liverpool L69 3GB

Date completed: 18 December 2019

Source of funding: This report was commissioned by the NIHR Systematic Reviews Programme as project number 128239

Acknowledgements: The authors would like to thank Dr Ethan Sen, Consultant Paediatric Rheumatologist, Newcastle upon Tyne Hospitals NHS Foundation Trust, who provided clinical advice to the ERG and provided feedback on a final draft version of the report. The authors would also like to thank Aragon Octavio, Paediatric Rheumatology pharmacist, Alder Hey Children's NHS Foundation Trust who provided the ERG with pharmaceutical advice.

Rider on responsibility for report: The views expressed in this report are those of the authors and not necessarily those of the NIHR Systematic Reviews Programme. Any errors are the responsibility of the authors.

Declared competing interests of the authors: Professor Kennedy and Aragon Octavio have no competing interests to declare. In the last 3 years, Dr Sen has received hospitality from SOBI Ltd.

This report should be referenced as follows: Greenhalgh J, Lambe T, Mahon J, Richardson M, Boland A, Beale S, Dundar Y, McEntee J, Kennedy T. Anakinra for treating Still's disease [ID1463]: A Single Technology Appraisal. LR*i*G, University of Liverpool, 2019

Contributions of authors:

Janette Greenhalgh	Project lead, critical appraisal of the clinical evidence and supervision of the production of the final report
Tosin Lambe	Critical appraisal of the economic evidence
James Mahon	Critical appraisal of the economic model
Marty Chaplin	Critical appraisal of the statistical evidence
Sophie Beale	Critical appraisal of the clinical and economic evidence, editorial input
Angela Boland	Critical appraisal of the clinical and economic evidence, editorial input
Yenal Dundar	Critical appraisal of the adverse event data and cross checking of the company search strategies
Joanne McEntee	Critical appraisal of the company submission
Tom Kennedy	Clinical advice and critical appraisal of the clinical sections of the company submission

Table of contents

List of tables

List of figures

LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
ACR Pedi 30/90	American College of Rheumatology Paediatric Response Criteria
AE	adverse events
AOSD	adult-onset Still's disease
bDMARD	biologic disease-modifying anti-rheumatic drug
BMT	bone marrow transplant
BNF	British National Formulary
BNFc	British National Formulary for children
CHAQ	Childhood Health Assessment Questionnaire
CI	confidence interval
CMA	cost minimisation analysis
CS	company submission
csDMARDs	conventional synthetic disease-modifying anti-rheumatic drugs
DMARDs	disease-modifying anti-rheumatic drugs
EMA	European Medicines Agency
eMIT	electronic Marketing Information Tool
ERG	Evidence Review Group
EPAR	European Public Assessment Report
EQ-5D	EuroQol-5 Dimensions
HAQ	Health Assessment Questionnaire
HRQoL	health-related quality of life
ICU	intensive care unit
IL	interleukin
ISR	injection site reaction
ITT	intention-to-treat
IV	intravenous
JIA	juvenile idiopathic arthritis
JRA	juvenile rheumatoid arthritis
LY	life year
MAS	macrophage activation syndrome
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NMB	net monetary benefit
NSAIDs	nonsteroidal anti-inflammatory drugs
PAS	Patient Access Scheme
PSA	probabilistic sensitivity analysis
QALY	quality adjusted life year
RCT	randomised controlled trial
RF	rheumatoid factor
SAE	serious adverse events
SC	subcutaneous
SF-36	Short Form (36) Health Survey
SJIA	systemic juvenile idiopathic arthritis
SJRA	systemic juvenile rheumatoid arthritis

SOBI	Swedish Orphan Biovitrum
SmPC	Summary of Product Characteristics
TNF-α	tumour necrosis factor alpha
VAS	visual analogue scale
vs	versus

1 SUMMARY

1.1 Scope of the submission

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal process. Clinical and economic evidence has been submitted to NICE by Swedish Orphan Biovitrum (SOBI) Ltd in support of the use of anakinra (Kineret®) as a monotherapy and in combination with other anti-inflammatory drugs and disease modifying anti-rheumatic drugs (DMARDs) for the treatment of Stills disease (systemic juvenile idiopathic arthritis [SJIA] and adult-onset Still's disease [AOSD]).

1.2 Critique of the decision problem in the company submission

1.2.1 Population

The population discussed in the company submission (CS) matches the population described in the final scope issued by NICE, i.e., patients with Still's disease (including SJIA and AOSD). Clinical evidence is only available for the separate populations. The company states that SJIA and AOSD are generally treated as separate diseases, but that '…there is growing acceptance that SJIA and AOSD are the same disease (i.e., Still's disease) with onset at different ages'. Clinical advice to the ERG agrees with the company's statement.

1.2.2 Intervention

The intervention specified in the final scope issued by NICE and discussed in the CS is anakinra. Anakinra is licensed in Europe for use in adults, adolescents, children and infants aged 8 months and older with a body weight of 10kg or above for the treatment of Still's disease, including SJIA and AOSD, with active systemic features of moderate to high disease activity, or in patients with continued disease activity after treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids. It can be used as a monotherapy or in combination with other anti-inflammatory drugs and DMARDs. It is available in pre-filled syringes and administered via subcutaneous injection with dose varying depending on body weight (1-2 mg/kg/day for patients weighing less than 50kg, and 100mg/day for patients weighing 50kg or more).

1.2.3 Comparators

The comparators listed in the final scope issued by NICE differ depending on whether disease has been previously treated and the nature of that previous treatment.

In the three randomised controlled trials (RCTs) (Quartier; Ilowite; Nordstrom) presented in the CS, the patients had all received previous treatment with NSAIDs, systemic corticosteroids and conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs). There is, therefore, no comparative evidence to support the use of anakinra to treat patients (with SJIA or AOSD) who have not received any previous treatment, or patients who have been previously treated with NSAIDs and systemic corticosteroids.

For patients previously treated with NSAIDs, systemic corticosteroids and DMARDs, the relevant comparator is biological DMARDs (bDMARDs). However, patients enrolled in the three RCTs all received concomitant medications as well as a bDMARD (tocilizumab), which, combined with protocol design limitations, makes the relative effectiveness of anakinra unclear. Further information at this point in the disease treatment pathway is available for patients with SJIA from a UK registry study (anakinra versus tocilizumab) and from a network meta-analysis (NMA) that included anakinra, tocilizumab and canakinumab. There is no comparative evidence for the clinical effectiveness of anakinra versus canakinumab in patients with AOSD.

1.2.4 Outcomes

The company has provided, from the three RCTs and the UK registry study, outcome data relating to disease activity, glucocorticoid tapering, adverse events (AEs) and health-related quality of life (HRQoL). However, the ERG does not consider that the available RCT evidence is relevant to the decision problem set out in the final scope issued by NICE. Further, all four studies included small numbers of patients and, in all studies, the follow-up periods were short, which render the results unreliable.

1.2.5 Subgroups

The subgroups listed in the final scope issued by NICE are (i) patients with SJIA or AOSD, (ii) patients with macrophage activation syndrome (MAS), and (iii) level of disease activity. Within the CS, separate evidence is provided for patients with SJIA and for those with AOSD. None of the available studies specifically include patients with MAS and the ERG agrees with the company that, given the small numbers of patients in the RCTs, it is not possible to carry out any analyses based on levels of disease activity.

1.2.6 Other considerations

The company has (appropriately) not put forward a case for anakinra to be considered under NICE's End of Life treatment criteria. Anakinra is not available to the NHS at a discounted price, however, there is a Patient Access Scheme (PAS) agreement in place for tocilizumab. The discounted price of tocilizumab is not known to the company.

1.3 Summary of the clinical evidence submitted by the company

RCT evidence

The company has presented data from three small RCTs: two in patients with SJIA (Quartier and Ilowite) and one in patients with AOSD (Nordstrom).

Patients recruited to the Quartier trial had previously been treated with glucocorticoids, DMARDs or bDMARDs. They were randomised to treatment with anakinra (n=12) or placebo (n=12) for 1 month. Stable doses of NSAIDs and corticosteroids were administered throughout the trial.

The Ilowite trial include a subgroup of patients (n=15) with a diagnosis of SJIA. Prior to randomisation, all patients had been treated with methotrexate; treatment with NSAIDS, corticosteroids and methotrexate was also permitted throughout the trial. During the initial 12-week open-label phase all patients received anakinra. The 11 responders in the SJIA subgroup were then randomised to receive anakinra or placebo and participated in the second, 16-week blinded, phase. The blinded phase (n=10 patients with a diagnosis of SJIA) was followed by a 12-month open-label extension phase during which all patients received anakinra.

The patients recruited to the Nordstrom trial had a diagnosis of AOSD which was refractory to corticosteroids and csDMARDs. Patients were randomised to treatment with anakinra (n=12) or a csDMARD (n=10) and were permitted to receive NSAIDs and corticosteroids, if required, throughout the trial. The duration of the trial was 24 weeks. A 28-week open-label extension (with switching or add-on treatment with the comparator drug) was possible if improvement did not occur within the initial 24-week period.

Non-RCT evidence

The company has presented clinical effectiveness from a UK registry study, which included 22 patients treated with anakinra and 54 treated with tocilizumab, and from NMA that compared anakinra, tocilizumab and canakinumab. The company has also provided (CS appendices) results from 10 uncontrolled studies (reported in 11 papers) in patients with SJIA and 11 uncontrolled studies in patients with AOSD.

The ERG considers that the company has provided all the available (RCT and non-RCT) evidence that is relevant to the current appraisal. The company considers, and clinical advice to the ERG supports the company view, that future RCTs of anakinra are unlikely to be carried out.

1.4 Summary of the ERG's critique of clinical effectiveness evidence submitted

Direct evidence

RCT evidence. The ERG does not consider that the clinical effectiveness evidence from any of the three RCTs discussed in the CS is reliable as it is derived from small numbers of patients who were followed up for short periods of time. Additionally, the trial protocols do not match the comparator treatments, and treatment lines, specified in the final scope issued by NICE.

Non-RCT evidence. The ERG agrees with the company that the clinical effectiveness derived from the UK registry study is unreliable. First, because of the study design (i.e., patients were not randomised to treatments) and second, because of important differences in the baseline characteristics of the patients who were treated with anakinra, compared with patients who were treated with tocilizumab.

Indirect evidence

The ERG agrees with the company that the results of the NMA comparing anakinra, tocilizumab and canakinumab in patients with SJIA are not useful to this appraisal. Aside from issues associated with small numbers of patients and short periods of follow-up, the main NMA outcome is the number of patients who respond to treatment using the modified American College of Rheumatology Paediatric 30 response criteria (ACR Pedi 30 criteria), which the company considers would not be considered as 'remission' in clinical practice. Clinical advice to the ERG is that ACR Pedi 90 would be a more stringent outcome measure.

1.5 Summary of cost effectiveness evidence submitted by the company

The company developed a de novo Markov cohort model in Microsoft Excel to compare the cost effectiveness of three strategies for treating Still's disease. These strategies were per-label use of anakinra, no anakinra and post-csDMARD use of anakinra. The population considered in the company base case analysis comprised 62.5% of patients with SJIA and 37.5% of patients with ASOD. Subgroup analyses were carried out to generate cost effectiveness results separately for the two populations.

The model comprised 13 mutually exclusive health states: five active disease health states based on treatment (NSAIDs±systemic corticosteroids, csDMARD #1 and #2, bDMARD #1 and #2), six remission health states, an unresolved state and death. The model time horizon was set at 30 years, the cycle length was 1 week, and the perspective was that of the UK NHS. Outcomes were measured in quality adjusted life years (QALYs) and both costs and QALYs were discounted at an annual rate of 3.5%, as recommended by NICE.

The treatment effectiveness (i.e., remission rates, treatment discontinuation rates and relapse rates) of NSAIDs±systemic corticosteroids, csDMARDs and bDMARDs were based on information reported in published studies, a previous NICE technology appraisal (TA238) and clinical assumptions made by the company. Constant treatment effectiveness rates were used throughout the whole model time horizon. Patients were modelled as having either monocyclic or chronic disease. Patients with monocyclic disease, who initially had active disease, could not experience a relapse after entering remission, whilst those with chronic disease could experience relapse following remission after initial and subsequent active disease episodes.

Data reported in TA238 were used to represent the HRQoL in the model. Except for the unresolved health state, resource use and costs for the model health states were based on clinical advice to the company. To estimate drug costs, the company applied an 'assumed PAS discount' to the list price of tocilizumab. All other drugs are only available to the NHS at list prices.

The company's deterministic base case cost effectiveness results showed that per-label anakinra was cheaper than no anakinra or post-csDMARDS (by -£56,790 and -£23,026 respectively) and more effective (by +0.666 and +0.313 respectively). Results from the company's probabilistic sensitivity analysis are consistent with the company's base case (deterministic) analysis results. The company carried out a wide range of deterministic sensitivity analyses. The most influential parameters were the probability of maintaining or achieving remission and the probability of discontinuing treatment with a biologic.

1.6 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG considers the most important issue is the lack of relevant and robust clinical evidence to support an economic model. The second main area of concern is the model structure; structural flaws lead to clinically implausible situations. See Section 1.8.2 for details of these two issues.

In addition to the structural issues, the company has also made a number of parameter assumptions and modelling choices that the ERG considers are inaccurate or implausible. However, given the model structural flaws these are of minor importance (see Section 1.8.2 for details).

1.7 End of Life

A treatment may be considered as a NICE End of Life treatment if the following criteria are satisfied:

(i) the treatment provides an extension to life of more than an average of 3 months compared to current NHS treatment

(ii) treatment is indicated for patients with a short life expectancy, normally a mean life expectancy of less than 24 months.

The company has not made a case for anakinra to be considered as an End of Life treatment and the ERG considers that this is appropriate.

1.8 ERG commentary on the robustness of evidence submitted by the company

1.8.1 Strengths

Clinical evidence

- The company provided a detailed submission that included all available evidence for the clinical effectiveness of anakinra
- The ERG's requests for additional information were addressed to a good standard
- The safety profile of anakinra in other diseases is well known and there is over 15 years of post-marketing experience in a number of licensed indications, including rheumatoid arthritis

Cost effectiveness evidence

- The company has produced a model that is easy to understand, and it is evident that significant efforts have been made to use the limited clinical effectiveness evidence that is available
- Company model parameter values matched those documented in the CS

1.8.2 Weaknesses and areas of uncertainty

Clinical evidence

- The company has provided all of the available evidence for the clinical effectiveness of anakinra for patients with SJIA and AOSD. However, the RCT evidence is limited to two RCTs in patients with SJIA and one RCT in patients with AOSD. The ERG considers that the data from the three RCTs are unreliable due to very small patient numbers and short durations of follow-up
- The treatment protocols in the RCTs do not match the comparator treatments and treatment lines specified in the final scope issued by NICE
- Other evidence for the use of anakinra is derived from studies of patients with SJIA, i.e., from a UK registry study and a NMA. The company and the ERG consider that, for methodological reasons, results from the UK registry study and the NMA are of little value to this appraisal of anakinra

- The company considers, and the ERG agrees, that it is unlikely that any future trials of anakinra will be conducted due to the small numbers of patients with SJIA and AOSD and the availability of other biologic treatments.

Cost effectiveness evidence

- The structure of the company model does not sufficiently reflect the complexity of the natural history of Still's disease. However, there is insufficient relevant robust clinical evidence with which to populate a model that would reflect the NICE decision problem
- The structure of the model allows clinically implausible situations to arise:
    - a patient can remain on an ineffective treatment for the whole model time horizon
    - a patient may remain in the following loop, which could happen 26 times a year, for the whole model time horizon: start a treatment, achieve remission, experience relapse and return to the same treatment before entering remission again
    - half of patients receiving a bDMARD will remain on that treatment during remission and, when they relapse, will return to treatment with the same bDMARD that they were prescribed before remission
    - over time, the population in each health state becomes more heterogeneous (due to patients experiencing different numbers of remissions and the lengths of periods in remission also varying). The ERG, therefore, considers that it is not appropriate to use invariant disease state transition probabilities for the whole model time horizon
- The company has made a number of parameter assumptions and modelling choices that the ERG considers are inaccurate or implausible:
    - underestimation of the effectiveness of prior treatments in the post-csDMARD strategy
    - differential effectiveness of bDMARDs by treatment line was an assumption and should not have been modelled in the base case
    - canakinumab should have been a treatment option in the third-line setting and for patients with unresolved disease
    - model time horizon was not sufficiently long to allow all costs and benefits to be captured

1.9 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG considers that a discrete event simulation model would be needed to model the complexities of the Still's disease pathway. However, constructing such a model is beyond the remit of the ERG. Further, robust data to populate such a model are not available.

Whilst it would have been possible for the ERG to generate alternative cost effectiveness results using ERG preferred parameter assumptions and modelling choices, the model's structural flaws mean that such results would be uninformative and potentially misleading. In the absence of a robust economic model, the ERG has undertaken cost minimisation analyses (CMAs). Clinical advice to the ERG and the results of a published NMA suggest that treatment with anakinra, tocilizumab and canakinumab can be assumed to be equally effective and are associated with the same serious adverse event profiles and discontinuation rates in the third-line setting.

For patients weighing 25kg, using list prices, weekly treatment with anakinra costs £106.67 less than treatment with tocilizumab (80% receiving IV tocilizumab) and £2,298.34 less than canakinumab. For patients weighing 50kg, using list prices, weekly treatment with anakinra costs £129.50 less per week than treatment with tocilizumab (80% receiving IV tocilizumab) and £4,780.29 less than treatment with canakinumab. For patients with AOSD, using list prices, weekly treatment with anakinra is £45.54 cheaper than treatment with tocilizumab and £4,780.29 cheaper than treatment with canakinumab. No conclusions can be drawn on the cost effectiveness of anakinra in the first-line setting (versus NSAIDs and/or steroids) or in the second-line setting (versus csDMARDs).

Results from the CMAs generated using the confidential discounted price for tocilizumab are available in a confidential appendix.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

The company's description of the underlying health problem is presented in Section B.1.3 of the company submission (CS). The Evidence Review Group (ERG) considers that the company's description is a reasonable summary of the underlying health problem. Key points made by the company are presented in Box 1.

Still's disease is a rare inflammatory disease that can present in children as systemic juvenile idiopathic arthritis (SJIA) and in adults as adult-onset Still's disease (AOSD).[1] SJIA is a rare subtype of juvenile idiopathic arthritis (JIA) and is clinically different from other forms of JIA.[2] Patients presenting with symptoms of Still's disease in their late teens might be diagnosed with SJIA or AOSD. The company states (CS, p13) that SJIA and AOSD are generally treated as separate diseases, but that '…there is growing acceptance that SJIA and AOSD are the same disease (i.e., Still's disease) with onset at different ages'.

Box 1 Key points from the company's description of the underlying health problem

Description of disease

- SJIA and AOSD are characterised by arthritic symptoms (such as joint pain and inflammation, commonly in the knees, wrists and ankles), spiking fever (defined as ≥39C and usually peaking in the late afternoon/early evening), transient pink/salmon coloured rash (usually during the fever episodes and affecting the chest, thighs, arms, legs and face), muscle pain, and liver and spleen enlargement. In some cases, there can be inflammation of the membrane surrounding the heart (pericarditis) or the heart muscle (myocarditis) and the membrane lining the chest cavity can also become inflamed causing fluid to accumulate around the lungs (pleural effusion).[3]
- In both SJIA and AOSD, fever is the most common symptom at initial presentation. While febrile, other symptoms such as rash or arthritis can worsen and cause significant disturbance to regular daily activities.[3,4]
- Onset of SJIA typically occurs between 3 and 5 years of age.[5]
- AOSD is diagnosed when the disease begins in patients over the age of 16 years.[4] AOSD has a bimodal age distribution, the first peak between the ages of 15 to 25 years and the second between the ages of 36 to 46 years.[6] However, about three-quarters of patients report the onset of disease between 16 and 35 years of age.[6]
- Patients with SJIA are treated by paediatric rheumatologists/immunologists and patients with AOSD are treated by adult rheumatologists/immunologists.
- In AOSD, two different phenotypes have been described, systemic and arthritis predominant. In the systemic form, the disease presents with acute onset characterised by fever, weight loss and other systemic manifestations.[4,7,8] The disease may be monocyclic or chronic (polycyclic or persistent).[8,9] The arthritis predominant form of AOSD is characterised by indolent onset mainly affecting the joints.[4,7,8]
- The pathogenesis of SJIA and AOSD is still not completely understood but is believed to be of an autoinflammatory nature. Laboratory and clinical observations suggest an inappropriate activation of the innate immune system, with hypersecretion of the proinflammatory cytokines IL-1 and IL-6 in both SJIA and AOSD.

Epidemiology

- AOSD and SJIA are rare diseases.
- Published data indicate that the incidence of SJIA in Europe ranges between 0.4 and 0.9 per 100,000 children per year.[10-17] The estimated incidence of SJIA in the UK is 0.1 per 10,000 children per year (equivalent to 100 children diagnosed per year),[17] and prevalence in the UK is estimated

at 1 per 10,000 children (equivalent to 1,000 children affected by SJIA at any one time). Clinical experts to the company consider that the proportion of males to females with SJIA is 1:1.[18] However, the experts also noted that there is some evidence which points to there being more female than male patients.[18]
- The estimated incidence of AOSD is 0.14 to 0.40 cases per 100,000 people and prevalence is 1 to 34 cases per million people.[19,20] In England, estimated incidence is 55 to 110 cases of AOSD per year, and prevalence is estimated to be 400 to 800 patients.[21] Published literature suggests that more females than males are affected by AOSD, with women representing up to 70% of patients.[9,22-24] However, clinical advice to the company is that the split could more closely resemble 1:1.[18]

AOSD=adult-onset Still's disease; IL=interleukin; SJIA=systemic juvenile idiopathic arthritis
Source: adapted from CS, Section B1.3

The company describes the burden of disease in Section B.1.3.1.5 of the CS. Key points made by the company are presented in Box 2. The ERG considers the company's description represents a reasonable summary of the burden of disease.

Box 2 Key points from the company's description of the burden of disease

Disease-specific issues
- Patients typically live with impaired function due to joint swelling, pain and stiffness (e.g., problems dressing and grooming, arising, eating, walking, hygiene, reach, grip and activities),[25-30] and increased fatigue which impedes personal and social functioning.[31,32]
- The disease course is generally progressive and leads to significant pain, joint destruction and functional decline.[3] Patients are likely to need to make frequent visits to their GP, hospital, and therapists to manage the disease.[18]
- Patients may also experience different complications affecting their clinical picture, management and prognosis; for example, macrophage activation syndrome.[33]

Treatment-related issues
- Available treatments for SJIA and AOSD aim to improve patient well-being while minimising side effects. First-line treatments for the control of inflammation are usually NSAIDs and intra-articular glucocorticoid injections.[34] However, high doses of corticosteroids, particularly over a prolonged period of time, are associated with changes in appearance including a "moon-face", weight gain, centripetal redistribution of fat, muscle wasting, acne, bruising, thinning of the skin, and stretch marks.[35] High doses can also precipitate or exacerbate existing diabetes mellitus and cause hypertension. Prolonged use may impair the physiological process of bone mass accrual and the attainment of peak bone mass leading to an increased risk of osteoporosis and causing the suppression of growth that is crucial for paediatric age.[35] Long-term use of high-dose corticosteroids can also lead to steroid dependency in both children and adults.[20]
- Second-line treatments usually include csDMARDs, such as methotrexate or ciclosporin. These are often needed to achieve adequate control of the disease and reduce the dose of corticosteroids. However, the efficacy of these drugs in the control of disease activity is variable, and in some cases, they are associated with side-effects (e.g., csDMARDs may also be toxic to the liver or bone marrow and cause rashes and stomach disturbances).[36]

Well-being issues
- A study by Shenoi[37] in patients with SJIA (n=61), reported mean Child Health Questionnaire Parent-Form 50 physical, and psychosocial summary scores to be substantially lower for SJIA patients than for the normative population (physical 40.0 [SD18.2} versus 53.0 [SD]8.8 and psychosocial 46.6 [SD11.3] versus 51.2 [SD9.1]). The study[37] also found that over a period of 2 months, patients with SJIA missed 2.9 school days due to SJIA (10% yearly loss). The company considers that it is reasonable to assume that HRQoL is substantially lower in patients with AOSD compared with the general population, and may be poorer than that of the SJIA population given the increased severity of the AOSD population.[33]
- Given the severity of AOSD it is reasonable to assume that the impact of AOSD on HRQoL may be similar to that of rheumatoid arthritis, or worse depending on the severity of symptoms. In adults with rheumatoid arthritis, limitations in physical function as well as increased pain and fatigue have been shown to affect patients' attendance at paid work, work performance within and outside the

home, and participation in family, social, and leisure activities.[38] Additional paid or unpaid support, as well as increased flexibility and job modifications from employers, are often required so that patients can meet their role obligations.[38] Disease-related reductions in productivity are not just due to the physical limitations posed by rheumatoid arthritis; mental/emotional limitations also play a key role in reducing HRQoL and productivity.[38]

Families and carers

- SJIA and AOSD can also impose a substantial health burden on caregivers and families. A caregiver role can affect work productivity on several levels, including quitting the workforce, missed work time (absenteeism) and decreased productivity while at work.[39,40]

Economic burden

- No data on economic burden were identified in the SJIA or AOSD populations. However, UK data[41,42] from patients with JIA (mean age 21.4 years) were indicative of an economic burden on society due to the substantial costs associated with healthcare resource utilisation. The study estimated direct health care costs comprising 46% of total costs, direct non-health care costs amounting to 26.4%, and productivity losses comprising 27.6%. The largest expenditures on average were accounted for by early retirement (27.0%), followed by informal care (24.1%), medications (21.1%), outpatient and primary care visits (13.2%) and diagnostic tests (7.9%). Costs for JIA patients in need of caregiver assistance were 43% higher than those for patients not in need of assistance.[41,42]

AOSD=adult-onset Still's disease; csDMARD=conventional synthetic disease-modifying anti-rheumatic drug; HRQoL=health-related quality of life; JIA=juvenile idiopathic arthritis; NSAID=non-steroidal anti-inflammatory drug; SJIA=systemic juvenile idiopathic arthritis; SD=standard deviation
Source: CS Section B1.3

2.1.1 Macrophage activation syndrome

The company (CS, p26) describes macrophage activation syndrome (MAS) as the most frequent life-threatening complication of Still's disease in both paediatric and adult patients. The ERG notes that MAS (also known as haemophagocytic lymphohistiocytosis [HLH] or haemophagocytic syndrome secondary to autoimmune disease) is a rare immune disorder characterised by the body reacting inappropriately to a trigger, usually an infection.[43] Specialist white blood cells (T cells and macrophages) are over-activated causing severe inflammation and damage to tissues including the liver, spleen and bone marrow.[43] MAS can precipitate multiple organ failure (CS, p26). It is difficult to diagnose MAS as symptoms are similar to severe infections and other conditions.[43] The company states (CS, p26) that approximately 10% of patients with SJIA and AOSD will develop MAS and that between 30% and 40% of patients with AOSD and SJIA have subclinical MAS. It is stated in the CS (p27) that MAS is the most significant cause of mortality in patients with SJIA. The company's clinical experts suggested that the most reliable estimate of mortality in patients with AOSD who develop MAS is 12.9%.[44] However, the ERG notes that this estimate is from a study that includes some patients with underlying diseases other than AOSD and that the mortality rate for the subgroup of patients with underlying AOSD in this study who developed MAS was 9.7%. In SJIA and AOSD, common causes of MAS are infection, drugs and disease flare.[45,46] Treatments for MAS include steroids, ciclosporin, anakinra and intravenous immunoglobulin (CS, p27).

2.1.2 Diagnosis

The company states (CS, p21) that diagnosing SJIA and AOSD is problematic. First, because clinical presentations of the disease vary between patients and second, because there are no disease-specific tests or laboratory parameters. Diagnosis is based on clinical evaluation, patient history and the exclusion of other diseases (for example, other autoimmune diseases). The company states (CS, p22) that misdiagnosis and length of time before diagnosis are significant sources of stress and suffering for patients.

The company presents the diagnostic criteria for SJIA and for AOSD in Table 3 and Table 4 respectively of the CS (reproduced in Appendix 1 of this ERG report). Clinical advice to the ERG is that these criteria are used in the NHS as a guide to the diagnosis of SJIA and AOSD.

2.1.3 Disease course

The company describes (CS, p23) three disease courses associated with SJIA and AOSD (see Table 1) and states that polycyclic and persistent disease are considered 'chronic' disease. The ERG highlights that the disease course of an individual patient can only be identified retrospectively. The ERG also notes that, for approximately 50% of patients with SJIA, the disease is resolved before adulthood.[1]

Table 1 Company description of disease course

Disease course	Estimated proportion of SJIA population	Estimated proportion of AOSD population
Monocyclic disease	11% to 40%	33%
Polycyclic disease	2.3% to 34%	33%
Persistent disease	51% to 66%	33%

Source: CS, p23

2.1.4 Company's overview of current service provision

The company's overview of current service provision is presented in Section B.1.3 of the CS. The ERG considers that the company's overview presents an accurate summary of current service provision and key points made by the company are provided in Box 2. For clarity, the ERG highlights that two different types of disease-modifying anti-rheumatic drugs (DMARDs) are used to treat SJIA and AOSD, namely conventional synthetic DMARDs (csDMARDs) and biologic DMARDs (bDMARDs). Table 2 provides a summary of the licensed indications and dosing schedules for the bDMARDs relevant to this appraisal (anakinra, tocilizumab and canakinumab).

Clinical advice to the ERG is that canakinumab is not routinely used in the NHS to treat patients with SJIA or AOSD.

Table 2 Summary of licensed indication and dosing for anakinra, tocilizumab and canakinumab

bDMARD	Licensed indication	Administration and dosing	ERG comment
Anakinra (Kineret)	Adults, adolescents, children and infants aged 8+ months with a body weight of 10kg+ for the treatment of Still's disease, (inc. SJIA and AOSD), with active systemic features of moderate to high disease activity, or in patients with continued disease activity after treatment with NSAIDs or glucocorticoids. Anakinra can be given as monotherapy or with other anti-inflammatory drugs and DMARDs.	**Pre-filled syringe.** The recommended dose for patients weighing ≥50kg is 100mg/day by SC injection. Patients weighing <50kg should be dosed by body weight with a starting dose of 1 to 2mg/kg/day. Response to treatment should be evaluated after 1 month: in case of persistent systemic manifestations dose may be adjusted in children or continued treatment should be reconsidered by the treating physician.	Anakinra is currently being appraised by NICE. Anakinra is recommended for use by NHS England[47] in patients with SJIA who have failed treatment with MTX or patients with SJIA who have severe or steroid resistant MAS. Anakinra is recommended for use by NHS England[21] in patients with AOSD who fail to respond to, or are intolerant of, standard immunosuppressive therapy, including at least two of the following agents: MTX, ciclosporin, azathioprine, leflunomide, cyclophosphamide and mycophenolate or where standard therapies are contraindicated.
Tocilizumab (RoActemra)	Active SJIA in patients 1+ year, who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids. Tocilizumab can be given as monotherapy (in case of intolerance to MTX or where treatment with MTX is inappropriate) or with MTX.	**Pre-filled syringe.** The recommended posology in patients 1+ year is 162mg once every week in patients weighing ≥30kg+ or 162mg once every 2 weeks in patients weighing <30kg. Patients must have a minimum body weight of 10kg when receiving SC tocilizumab. **IV administration.** The recommended posology in patients 2+ years is 8mg/kg once every 2 weeks in patients weighing ≥30kg or 12mg/kg once every 2 weeks in patients weighing <30kg. The dose should be calculated based on the patient's body weight at each administration. A change in dose should only be based on a consistent change in the patient's body weight over time. The safety and efficacy of IV tocilizumab in children <2 years has not been established.	Tocilizumab is recommended by NICE (TA238[48]) for the treatment of SJIA in children and young people aged 2+ years whose disease has responded inadequately to NSAIDs, systemic corticosteroids and MTX if the manufacturer makes tocilizumab available with the discount agreed as part of the PAS. Tocilizumab is not licensed for the treatment of AOSD, but is recommended for use by NHS England[21] in patients with AOSD who fail to respond to, or are intolerant of, standard immunosuppressive therapy, including at least two of the following: methotrexate, ciclosporin, azathioprine, leflunomide, cyclophosphamide and mycophenolate or where standard therapies are contraindicated.
Canakinumab (Ilaris)	Active Still's disease (inc. AOSD and SJIA) in patients aged 2+ years who have responded inadequately to previous therapy NSAIDs and systemic corticosteroids. Canakinumab can be given as monotherapy or with MTX.	The recommended dose of canakinumab for patients with Still's disease (AOSD and SJIA) with body weight ≥7.5kg is 4mg/kg (up to a maximum of 300mg) administered every 4 weeks via SC injection. Continued treatment with canakinumab in patients without clinical improvement should be reconsidered by the treating physician. The safety and efficacy of canakinumab in SJIA patients under 2 years of age have not been established.	NICE was unable to make a recommendation about the use of canakinumab in the NHS as the company responsible for the technology did not provide an evidence submission to NICE (TA302[49]). Canakinumab is not recommended by NHS England for the treatment of SJIA or AOSD.

AOSD=adult-onset Still's disease; bDMARD=biologic DMARD; DMARD=disease-modifying anti-rheumatic drug; ERG=Evidence Review Group; inc=including; IV=intravenous; MAS=macrophage activation syndrome; MTX=methotrexate; NSAID=non-steroidal anti-inflammatory drug; PAS=Patient Access Scheme; SC=subcutaneous; SJIA=systemic juvenile idiopathic arthritis
Source: Table developed by the ERG

Box 2 Key points from the company's overview of current service provision

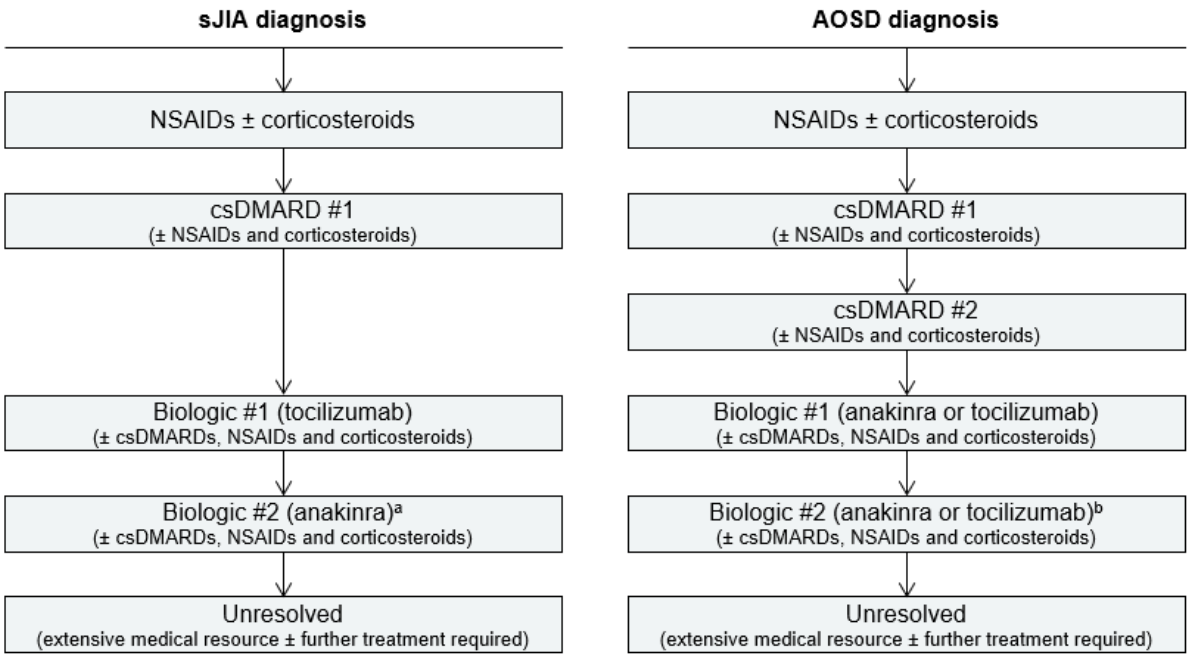
Treatment aims
The aim of treatment is to achieve remission of symptoms by controlling pain, fever and inflammation and to minimise joint damage.

Treatment options
- In the UK, the current clinical pathway for the pharmacological treatment of SJIA and AOSD includes sequential NSAIDs, corticosteroids (intra-articular, intravenous or oral) and csDMARDs, specifically methotrexate.[21,47,48]
- Patients are typically first treated with NSAIDs and corticosteroids; steroids are also useful in the diagnostic work-up. After failing to achieve remission with NSAIDs and corticosteroids, patients progress to csDMARDs such as methotrexate.
- csDMARDs are considered when patients are non-responsive to NSAIDs or present with predictive factors for steroid-dependence, or at the first signs of steroid-dependence.[21,47] In accordance with NHS commissioning policy[21] for AOSD, following methotrexate, AOSD patients are required to be treated with a second csDMARD (likely ciclosporin) before biologic treatment may be considered. Patients with SJIA, however, typically only receive treatment with one csDMARD (e.g., methotrexate) prior to the use of bDMARDs.[47]
- Patients with AOSD may receive anakinra or tocilizumab first, based on clinician preference. Patients with SJIA currently receive tocilizumab first, based on current NICE guidance (TA238[48]). Traditionally, the choice between tocilizumab and anakinra was informed by arthritis involvement; however, baseline arthritis rates are relatively low in practice and some patients may present with symptoms associated with MAS. The NHS policy for SJIA states that where MAS is severe or steroid resistant, treatment with anakinra may be life-saving and should not be delayed.[47] Canakinumab is not recommended for the routine treatment of Still's disease in the NHS in England, but may be used if refractory to other recommended treatments.[49]

AOSD=adult-onset Still's disease; bDMARD=biologic disease-modifying anti-rheumatic drug; csDMARD=conventional synthetic disease-modifying anti-rheumatic drug; MAS=macrophage activation syndrome; NSAID=non-steroidal anti-inflammatory drug; SJIA=systemic juvenile idiopathic arthritis
Source: adapted from CS, Section B1.3

The current treatment pathway described in the CS for patients with SJIA and AOSD is presented in Figure 1. The company correctly states (CS, p29 and Figure 1) that the NHS England Commissioning Policy[21] is that anakinra will only be commissioned for patients with AOSD who have failed to respond to (or are intolerant to) at least two csDMARDs. Clinical advice to the ERG is that, in the NHS, most patients with AOSD are treated with a bDMARD after failing to respond to one csDMARD (usually methotrexate). However, clinical advice provided to the company was that the NHS England Commissioning Policy reflects current practice for adult patients with AOSD who will receive two DMARDS before biologics.

The ERG notes (Table 2) that tocilizumab is not licensed in Europe for the treatment of AOSD and, therefore, has not been appraised by NICE as a treatment for this condition. However, tocilizumab is recommended for use by NHS England[21] for disease that is refractory to non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and two csDMARDs.



AOSD=adult-onset Still's disease; csDMARDs=conventional synthetic disease-modifying anti-rheumatic drugs; MAS=macrophage activation syndrome; NSAIDs=non-steroidal anti-inflammatory drugs; SJIA=systemic juvenile idiopathic arthritis
[a] Anakinra is recommended for SJIA that does not respond to tocilizumab and for patients with MAS-associated symptoms
[b] Anakinra or tocilizumab in refractory polyarticular or systemic AOSD
Source: CS, Figure 1 (NICE TA238;[48] NHS England[21])

Figure 1 Company depiction of the current clinical pathway for patients with SJIA and AOSD

2.1.5 Proposed positioning of anakinra in the treatment pathway

The company's proposed positioning of anakinra is as a treatment following failure to achieve remission after treatment with NSAIDs and corticosteroids (CS, p30). The company states that the benefits of using anakinra earlier in the treatment pathway are two-fold: i) so that patients can achieve disease remission earlier and ii) to potentially reduce the number of patients who fail to achieve disease remission with all possible recommended treatment options (unresolved disease).

2.1.6 Innovation

The company has set out the case for anakinra as an innovative treatment (Box 3).

Box 3 Key points from the company's case for anakinra as an innovative treatment

- Biologic treatments that specifically inhibit IL-1 have improved the clinical outcomes for many patients with Still´s disease and have confirmed the pathogenic role of this cytokine in the disease process. Clinical studies focusing on the effect of IL-1 inhibition with anakinra support the conclusion that anakinra is an effective treatment to reduce clinical signs and symptoms of SJIA and AOSD, including normalisation of laboratory parameters, and allowing a clinically meaningful tapering of glucocorticoids in many patients.
- Anakinra is the only biologic therapy available for the treatment of Still's disease in children aged 8 months to 2 years old.
- In all age groups there is a medical need for IL-1 inhibitor treatment, particularly early during the disease course.[50] In addition, it has been suggested that the use of IL-1 blockade early in the treatment pathway (post NSAIDs and/or corticosteroids), may take advantage of a "window of opportunity" in which disease pathophysiology can be altered to prevent the occurrence of chronic arthritis.[51-53] Early treatment with an IL-1 inhibitor may also reduce the risk of later development of arthritis.[54] and enables withdrawal or tapering of glucocorticoids, therefore avoiding the risk of dependency and the associated risks of infections, osteoporosis, hypertension, growth disturbances and diabetes particularly in paediatric patients.[50]

AOSD=adult-onset Still's disease; IL-1=interleukin-1; NSAID=non-steroidal anti-inflammatory drug; SJIA=systemic juvenile idiopathic arthritis
Source: CS, p104

2.1.7 Number of patients eligible for treatment with anakinra

In Document A of the CS (Table 10), the company estimates that, in England, between 190 and 235 patients with Still's disease would be eligible for treatment with anakinra annually. The company's estimate of 235 patients includes 179 patients with SJIA and 56 patients with AOSD. Clinical advice to the ERG is that the range estimated by the company is reasonable.

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

A summary of the ERG's comparison of the decision problem outlined in the final scope[1] issued by NICE and that addressed within the CS is presented in Table 3. Each parameter is discussed in more detail in the text following the table (Section 3.1 to Section 3.8).

The company has presented evidence from two randomised controlled trials (RCTs) conducted in patients with SJIA (Quartier[55] and Ilowite[56]) and one RCT conducted in patients with AOSD (Nordstrom[57]). The company has also provided evidence, from a UK registry study[2] and a network meta-analysis[58] (NMA), of the effectiveness of anakinra as a treatment for patients with SJIA. Evidence is also presented from several uncontrolled studies carried out in patients with SJIA[50,52-54,59-65] and AOSD[20,63,66-74] (see Appendix 2 of this ERG report for a list of these studies).

Table 3 Comparison between final scope issued by NICE and company decision problem

Final scope issued by NICE **Parameter and specification**	**ERG summary of a comparison between the decision problem stated in the final scope issued by NICE and addressed in the company submission**
Population People with Still's disease (including SJIA and AOSD)	Two populations are discussed separately in the CS: patients with active SJIA and patients with active AOSD
Intervention Anakinra as monotherapy or in combination with other anti-inflammatory drugs and DMARDs	The evidence presented in the CS is for the use of anakinra in combination with anti-inflammatory drugs and/or DMARDs
Comparator **For previously untreated disease** • NSAIDS and systemic corticosteroids	**For previously untreated disease** There is no randomised evidence to support the use of anakinra in patients with previously untreated disease All patients included in the three RCTs[55-57] discussed in the CS had received previous treatment(s)
For disease previously treated with NSAIDS or systemic corticosteroids • DMARDs	**For disease previously treated with NSAIDS or systemic corticosteroids** There is no randomised evidence to support the use of anakinra to treat patients with disease previously treated only with NSAIDs or systemic corticosteroids All patients included in the three RCTs[55-57] discussed in the CS had received previous treatment(s) with NSAIDs, systemic corticosteroids and with DMARDs
For disease previously treated with DMARDs • Tocilizumab (only for SJIA that has responded inadequately to methotrexate) • Canakinumab	**For disease previously treated with DMARDs** <u>Tocilizumab (only for SJIA that has responded inadequately to methotrexate)</u> For the comparison of anakinra versus tocilizumab in patients with SJIA that has responded inadequately to methotrexate, the company has cited evidence from a UK registry study[2] that compares anakinra with tocilizumab The company has also presented evidence from a network meta-analysis[58] of anakinra, canakinumab and tocilizumab in patients with SJIA

	Canakinumab The company has presented evidence from a network meta-analysis[58] of anakinra, canakinumab and tocilizumab in patients with SJIA No evidence is presented for the comparison of anakinra with tocilizumab or canakinumab in patients with AOSD
Outcomes • disease activity (including disease flares and remission) • fever • physical function • blood markers (including markers for inflammation) • glucocorticoid tapering • rash • mortality • AEs • HRQoL	The company has presented data, from three RCTs,[55-57] for most of the listed outcomes. However, the ERG queries the usefulness of these results as: i) the data were derived from patients who were pre-treated with NSAIDs, corticosteroids and DMARDs prior to entering the trial(s). The patient populations in the trials are, therefore, not relevant to any of the populations specified in the scope ii) no reliable conclusions can be drawn from the data due to small patient populations and the limited length of trial follow-up
Economic analysis The cost effectiveness of treatments should be expressed in terms of ICER per QALY gained The time horizon should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs should be considered from an NHS and Personal Social Services perspective. The availability of any PAS for the intervention or comparator technologies will be taken into account	Results are presented as ICERs per QALY gained The model time horizon is 30 years. The ERG considers that 30 years is not sufficiently long to reflect all differences in costs or outcomes between the technologies being compared Costs have been calculated from an NHS perspective In the company base case, the company uses an 'assumed PAS' for tocilizumab. None of the other drugs included in the company cost effectiveness analyses are available to the NHS at discounted prices
Other considerations Where the evidence allows, the following subgroups will be considered: • People with SJIA or AOSD • People with MAS • Level of disease activity Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator	There are no clinical trials that have recruited a combined population of patients with SJIA and patients with AOSD. Hence, the company has presented the clinical effectiveness evidence separately for patients with SJIA and for patients with AOSD. The company has presented cost effectiveness evidence for patients with SJIA and AOSD separately, and in combination No evidence is presented for patients with MAS. The company states (CS, Table 1) that there are no trials with MAS as an inclusion criterion and that MAS is generally treated as an AE rather than as a patient subgroup The company has not presented outcomes for patients based on levels of disease activity. The ERG considers that subgroup analyses based on level of disease activity is not possible given the very small numbers of patients recruited to the trials and because disease activity can only be retrospectively assigned

AE=adverse event; AOSD=adult-onset Still's disease; CS=company submission; DMARD=disease modifying anti-rheumatic drug; HRQoL=health-related quality of life; ICER=incremental cost effectiveness ratio; MAS=macrophage activation syndrome; NSAIDs=non-steroidal anti-inflammatory drugs; PAS=Patient Access Scheme; QALY=quality adjusted life year; RCT=randomised controlled trial; SJIA=systemic juvenile idiopathic arthritis
Source: CS, adapted from Table 1

3.1 Population

Two populations are discussed in the CS, patients with SJIA and patients with AOSD. All of the available trials were conducted in patients with either SJIA (Quartier[55] and Ilowite[56]) or AOSD (Nordstrom[57]). The Quartier[55] trial recruited 24 patients with SJIA and outcomes were reported at 1 month. The Ilowite[56] trial recruited 82 patients with JIA, including a subgroup of 15 patients with a diagnosis of SJIA and reported outcomes at 4 months. The Nordstrom[57] trial recruited 22 patients with AOSD and outcomes were reported at 6 months. The ERG considers the results of the RCTs are unreliable as they are based on small numbers of patients who were followed-up for short durations.

3.2 Intervention

The intervention specified in the final scope[1] issued by NICE and discussed in the CS, is anakinra. Anakinra is a recombinant antagonist of the interleukin-1 (IL-1) receptor and inhibits the binding of pro-inflammatory cytokines IL-1α and IL-1ß. See Table 2 of this ERG report for details of the European Medicines Agency (EMA)[75] marketing authorisation for anakinra. Anakinra is also licensed in Europe for the treatment of rheumatoid arthritis in adults and for the treatment of cryopyrin-associated periodic syndromes in adults, adolescents, children and infants aged 8 months and older.[75]

3.3 Comparators

The comparators listed in the final scope[1] issued by NICE depend on whether disease has been previously treated and the nature of that previous treatment. The company states (CS, p108) that the populations recruited to the three RCTs[55-57] were patients who had not responded to prior treatment including glucocorticoids, methotrexate, or other csDMARDs. In Document A of the CS (p18) the company highlights that they did not identify any evidence for the use of anakinra in patients with AOSD who had not been treated with systemic corticosteroids, csDMARDs, or other bDMARDs and that only four[50,52-54,62] uncontrolled studies (reported in five papers) provide information about the use of anakinra to treat patients with SJIA who have not been previously treated with corticosteroids, csDMARDs or other bDMARDS.

Previously untreated disease

NSAIDs and systemic corticosteroids are the comparators listed in the final scope[1] issued by NICE for previously untreated disease. However, the patients in all three RCTs[55-57] had previously been treated with NSAIDs, systemic corticosteroids and DMARDs; therefore, there

is no RCT evidence to support using anakinra to treat patients with previously untreated disease.

Disease previously treated with NSAIDs or systemic corticosteroids

DMARDs are the comparators listed in the final scope[1] issued by NICE for disease previously treated with NSAIDs or systemic corticosteroids. All patients in the three RCTs[55-57] had received previous treatment with NSAIDs, systemic corticosteroids and DMARDs; therefore, there is no RCT evidence of the comparative effectiveness of anakinra in this patient population.

Disease previously treated with DMARDs

Two comparators are listed in the final scope[1] issued by NICE for treating disease previously treated with DMARDS: tocilizumab and canakinumab (both bDMARDs).

Tocilizumab

Tocilizumab is recommended by NICE (TA238[48]) for the treatment of SJIA in children and young people aged 2+ years whose disease has responded inadequately to NSAIDs, systemic corticosteroids and methotrexate. None of the three RCTs[55-57] discussed in the CS include tocilizumab as a comparator. However, the company has presented relevant evidence from a published UK registry study.[2] The company decided not to use the results from the UK registry study[2] to inform their economic model as they considered that the patient baseline characteristics were too different between treatment arms. Clinical advice to the ERG is that the differences in patient baseline characteristics between the treatment arms are important and would likely result in biased estimates of treatment effect. See Section 4.2.2 of this ERG report for a discussion of this UK registry study.[2]

The company has also presented results from a published NMA[58] that compares the clinical effectiveness of anakinra, tocilizumab and canakinumab in patients with SJIA. The NMA[58] results are not used in the company model but are presented in the CS as supporting information. The company considers (CS, Appendix A, p20) that: i) the outcome reported in the NMA (modified [American College of Rheumatology Paediatric 30 response criteria] ACR Pedi 30[76]) is not a useful measure of remission and ii) the results from the NMA[58] should be treated with caution due to methodological differences between the included trials. Clinical advice to the ERG is that ACR Pedi 30[76] is considered a low threshold and that a more stringent outcome measure (ACR Pedi 90[76]) is used in current studies of JIA. The ERG notes that only one of the five RCTs[55,77-79] synthesised in the NMA[58] included anakinra as a trial treatment (Quartier[55]). Furthermore, only 12 patients in the Quartier[55] trial were treated with anakinra. See Section 4.2.3 of this report for further discussion of the NMA.[58]

The ERG notes that tocilizumab is not licensed in Europe for the treatment of AOSD and has, therefore, not been appraised by NICE as a treatment for AOSD. However, NHS England[21] recommends tocilizumab for the treatment of AOSD that is refractory to NSAIDs, corticosteroids and two DMARDs.

No evidence is presented in the CS for the use of anakinra compared with tocilizumab in patients with AOSD.

Canakinumab

None of the three RCTs[55-57] include canakinumab as a comparator. However, the company has presented results from a published NMA[58] that compares the clinical effectiveness of anakinra, tocilizumab and canakinumab in a patient population with SJIA. The company has not used the results from the NMA[58] in their economic model but the results are presented as supporting information. The relevance of the NMA[58] to this appraisal is discussed earlier in this section of the ERG report (see 'tocilizumab') and further details are provided in Section 4.2.3 of this report.

No evidence is presented in the CS for the use of anakinra compared with canakinumab in patients with AOSD.

3.4 Evidence

The ERG is aware that the company has provided all the available evidence (RCT and non-RCT) relevant to the use of anakinra and clinical advice to the ERG is that future RCTs of anakinra are unlikely to be carried out. The company reports (CS, p104) that a phase III RCT (anaStills[80]) comparing anakinra with placebo in patients with SJIA and AOSD was terminated in June 2019 due to recruitment problems (the enrolment target of 81 patients was no longer considered feasible within a reasonable time). The company explains (CS, p107) that conducting new RCTs in patients with SJIA and AOSD is challenging; first, because of the small patient populations and second, because biologic drug treatments (anakinra, canakinumab and tocilizumab) are available, meaning that patients with SJIA or AOSD are unlikely to choose to participate in a clinical trial that compares a biologic treatment with placebo or a DMARD.

3.5 Outcomes

As discussed in Section 3.3, the ERG considers that the available RCT evidence[55-57] is not relevant to the decision problem set out in the final scope[1] issued by NICE. The ERG also considers that the small numbers of patients recruited to the trials and the short durations of patient follow-up render the trial results unreliable. The ERG considers that the results of the UK registry study[2] are unreliable due to the non-randomised design and important differences in baseline characteristics of the included patients. For information, details of the outcomes addressed in the CS are provided in Table 4.

Table 4 Outcomes addressed in the CS

Outcome in scope	Quartier (2011)[55] SJIA	Ilowite (2009)[56] SJIA	Kearsley-Fleet (2019)[2] UK registry study SJIA	Nordstrom (2012)[57] AOSD
	Anakinra vs placebo	Anakinra vs placebo	Anakinra vs tocilizumab	Anakinra vs csDMARD
Disease activity (including disease flares and remission) Physical function Blood markers Fever	• Response rate according to modified ACR Pedi 30 • Proportion of patients with inactive disease at Month 6	• Proportion of patients with disease flares in the blinded phase • Changes in SJIA core components	• Proportion of patients achieving MDA • Proportion of patients achieving clinically inactive disease • Proportion of patients achieving ACR Pedi 90 response • Change in active joint count, limited joint count, PGA, PGE, CHAQ, ESR and JADAS-71	• Remission according to specific study criteria, including body temperature, CRP, serum ferritin, normal SJC or TJC • Response rate
Glucocorticoid tapering	Yes	No	No	Yes
Rash	No	No	No	No
Mortality	No	No	No	No
AEs	Yes	Yes	Yes	Yes
HRQoL	No	No	No	SF-36

ACR Pedi 30=American College of Rheumatology Paediatric 30% improvement; ACR Pedi 90=American College of Rheumatology Paediatric 90% improvement; AE=adverse event; AOSD=adult-onset Still's disease; CHAQ=Childhood Health Assessment Questionnaire; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; HRQol=health-related quality of life; JADAS-71=71-joint juvenile arthritis disease activity score; MDA=minimal disease activity; PGA=physician global assessment; PGE=patient (or parent) global evaluation of wellbeing; SJC=swollen joint count; SJIA=systemic juvenile idiopathic arthritis; SF-36=short-form 36; TJC=tender joint count
Source: CS, Section B.2.2

3.6 Economic analysis

As specified in the final scope[1] issued by NICE, the cost effectiveness of treatments was expressed in terms of incremental cost per quality adjusted life year (QALY) gained. Outcomes were assessed over a 30-year time horizon (considered by the company to be long enough to reflect all important differences in costs or outcomes between the technologies being compared). The costs included in the company model are those relevant to the NHS. When

generating cost effectiveness estimates, the company used list prices for all drugs, except for tocilizumab which is the only included drug that is available to the NHS at a discounted price (via a Patient Access Scheme [PAS]). However, details of this PAS are not known to the company, so the company used an 'assumed PAS discount' when carrying out their base case analysis.

3.7 Subgroups

Within the final scope[1] issued by NICE it is stipulated that, if the evidence allows, three subgroups of patients should be considered, namely patients with SJIA or AOSD, patients with MAS, and level of disease activity.

All the relevant clinical trials include patients with SJIA **or** patients with AOSD and, therefore, in terms of clinical effectiveness, the two populations are considered separately in the CS. However, the company has provided economic results separately and for a combined population. The company states (CS, Table 1) that there are no studies that specifically include patients with MAS. The company has not discussed subgroup analyses based on levels of disease activity. The ERG considers that given the small numbers of patients in the three RCTs[55-57] it would not be possible to carry out any analyses based on levels of disease activity.

3.8 Other considerations

The ERG considers that the company has (appropriately) not put forward a case for anakinra to be considered under NICE's End of Life treatment criteria. Anakinra is not available to the NHS at a discounted price; however, there is a PAS agreement in place for tocilizumab.

Clinical advice to the ERG is that patients under 16 years with onset of disease would be diagnosed with SJIA and they would retain this diagnosis even when older than 16 years and into adulthood although, at some point between age 16 and 18 years, their care will transition from Paediatric to Adult Rheumatology. However, there is increasing recognition that SJIA and AOSD are biologically the same disease with onset at different ages.

4 CLINICAL EFFECTIVENESS

4.1 Systematic review methods

Full details of the process and methods used by the company to identify and select the clinical evidence relevant to the technology being appraised are presented in the CS (Appendix D). The ERG considered whether the review was conducted in accordance with the key criteria listed in Table 5. Overall, the ERG considers the methods used by the company to conduct the systematic review of clinical effectiveness evidence were appropriate.

Table 5 ERG appraisal of systematic review methods

Review process	ERG response
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes
Were appropriate sources searched?	The company did not search the Cochrane library for potential studies of SJIA
Was the timespan of the searches appropriate?	Yes
Were appropriate search terms used?	Yes
Were the eligibility criteria appropriate to the decision problem?	Yes
Was study selection applied by two or more reviewers independently?	Not explicitly stated
Were data extracted by two or more reviewers independently?	Not explicitly stated
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes
Was the quality assessment conducted by two or more reviewers independently?	Not explicitly stated
Were appropriate methods used for data synthesis?	Not applicable

SJIA=systemic juvenile idiopathic arthritis
Source: LRiG checklist

4.1.1 Search strategy

In Appendix D of the CS, the company lists the databases searched for articles relevant to treatment with anakinra in patients with SJIA and AOSD. To identify articles relevant to SJIA, the company searched MEDLINE, Embase, BIOSIS Previews, PASCAL, and SciSearch. To identify articles relevant to AOSD, the company searched MEDLINE, Embase and the Cochrane Library. The ERG notes that the company did not search the Cochrane Library for articles relevant to SJIA; however, ERG searches which included a search of the Cochrane Library did not reveal any additional publications.

4.1.2 Study selection

It is not stated in the CS whether the study selection process was carried out by two independent reviewers. The ERG notes that the company has excluded one uncontrolled study by Saccomanno[81] on the grounds that it was unobtainable. In addition, the study publication year is cited in the CS as 2016, however, the actual publication year is 2019. The

ERG notes that the Saccomanno[81] study is an uncontrolled retrospective study of 62 patients with SJIA who were treated with anakinra in Italy between 2004 and 2017. As there is no comparator arm in the Saccomanno study,[81] the ERG considers that the study adds little to the clinical effectiveness evidence presented in the CS.

4.1.3 Literature search

The company reports details of two RCTs[55,56] conducted in patients with SJIA. Details relating to the Quartier[55] trial that are presented in the CS have been taken from the published paper.[55] Details of the Ilowite[56] trial that are presented in the CS have been taken from the published paper[56] and from data held on file by the company.[82]

The company reports details of one RCT[57] conducted in patients with AOSD. Details relating to the Nordstrom[57] trial that are presented in the CS have been taken from the published paper[57] and from data held on file by the company.[82]

The company has also provided evidence from the following sources:

- a published UK registry study[2] of the clinical effectiveness of anakinra and tocilizumab conducted in patients with SJIA
- a published NMA[58] assessing the effectiveness of biologic treatments (anakinra, tocilizumab and canakinumab) in patients with SJIA
- 10 uncontrolled studies (reported in 11 papers) of anakinra in SJIA (see Appendix 9.2 of this ERG report)
- 11 uncontrolled studies[20,63,66-74] of anakinra in AOSD (see Appendix 9.2 of this ERG report)
- a meta-analysis[75] of anakinra in patients with SJIA (CS, Appendix D)
- a meta-analysis[75,83] of anakinra in patients with AOSD (CS, Appendix D)

Details relating to the UK registry study,[2] the NMA[58] and the uncontrolled studies[20,50,52-54,59-74] (listed in Appendix 9.2 of this ERG report) that were presented in the CS have been taken from published papers, unless otherwise stated.

The methodology and results of the meta-analyses[75,83] of the clinical effectiveness of anakinra for the treatment of i) SJIA and ii) AOSD are provided in Appendix D of the CS.

4.1.4 Quality assessment methods

The ERG considers that the company's quality assessment strategy is appropriate (see Table 6 for details). However, it is not reported in the CS whether the quality assessment exercises were completed by one reviewer or, independently, by two reviewers. The quality of the two meta-analyses[75,83] and the NMA[58] was not assessed by the company.

Table 6 The company's quality assessment strategy

Trial/Study type	Quality assessment method	Location in the CS
RCT	The criteria specified by the Centre for Reviews and Dissemination at the University of York[84]	Table 25 and Table 27
UK registry study	The Cochrane ROBINS-I tool[85]	Table 26
Uncontrolled studies	Modified ROBINS-1 tool[85]	Appendix D

RCT=randomised controlled trial; ROBINS-I=Risk Of Bias In Non-Randomized Studies of Interventions

4.1.5 Data synthesis

The company identified two RCTs[55,56] that reported clinical effectiveness outcomes for anakinra in patients with SJIA and one RCT[57] that reported clinical effectiveness outcomes for anakinra in patients with AOSD. The company has not conducted any data synthesis of the clinical effectiveness evidence of anakinra for this single technology appraisal. However, the company has presented the results of a published NMA[58] that compares the clinical efficacy of anakinra with tocilizumab, canakinumab, and rilonacept in patients with SJIA (CS, Section B.2.10.1). The comparison with rilonacept is not relevant to the appraisal of anakinra.

The company also provides details of a meta-analysis[75] of studies of anakinra in patients with SJIA and a meta-analysis[75,83] of studies of anakinra in patients with AOSD. The details of the meta-analyses[75,83] are presented in Appendix D of the CS. The company states that the meta-analyses[75,83] were conducted in support of the marketing authorisation application to the EMA and were not updated for this appraisal.

All information presented in this chapter of the ERG report is taken directly from the CS, unless otherwise stated.

4.2 Studies of anakinra

4.2.1 RCT evidence

Table 7 presents an overview of the three RCTs[55-57] discussed in the CS.

Table 7 Overview of the RCTs discussed in the CS

	Quartier (2011)[55]	Ilowite (2009)[56]	Nordstrom (2012)[57]
Patient population	SJIA	JRA	AOSD
Number of patients	24 (12 anakinra and 12 placebo)	SJIA subgroup=15 Overall JRA trial population=86	22 (12 anakinra and 10 DMARD)
Setting	France	USA, Canada, Australia, New Zealand, and Costa Rica	Finland, Norway, and Sweden
Design	Two-part trial: RCT (1 month) Open-label treatment (11 months)	Three-part trial: Open-label run in (12 weeks) RCT phase (16 weeks) Open-label extension (12 months)	Two-part trial: Open-label RCT (24 weeks) Open-label extension (28 weeks)
Primary outcome	The efficacy of treatment with anakinra vs placebo (measured by modified ACR pedi 30) at 1 month	Safety Primary efficacy endpoint was proportion of patients with disease flare at 16 weeks	Remission at 8, 12 and 24 weeks defined as: afebrile, absence of NSAIDs, CRP and ferritin within reference limits, normal swollen and tender joint counts
Inclusion criteria (key)	• Age 2 years to 20 years • SJIA • >6 months' disease duration • Active systemic disease • Intravenous or intra-articular steroids, immunosuppressive drugs and DMARDs stopped at least 1 month prior to study	• Age 2 years to 17 years • JRA • Minimum weight 10kg • ≥5 swollen joints due to active arthritis • 3 joints with limitation of motion • Stable dose of MTX for 6 weeks before study entry • No biologic therapy within 4 weeks of trial	• Age ≥18 years • AOSD according to Yamaguchi classification • Corticosteroid and possibly a DMARD for ≥2 months • Refractory to corticosteroids and DMARD (defined as active disease in spite of ≥10mg prednisolone daily +/- a DMARD) • Doses of NSAID and oral corticosteroid stable for ≥2 weeks before randomisation • If using a DMARD, doses stable for ≥4 weeks before randomisation
Exclusion criteria (key)	• Previous treatment with an IL-1 inhibitor • Immunosuppressive treatment contraindicated	• Receiving treatment with a DMARD other than MTX • Receiving intra-articular or systemic corticosteroid injections within 4wks of study entry • Trial specific laboratory parameters not met	• Use of corticosteroids below prednisolone equivalent of 10 mg/day • Specified laboratory parameters not met • Use of anti-TNF agents ≤ 4 weeks (etanercept) or ≤ 8 weeks (infliximab or adalimumab)
Intervention and	Anakinra (2mg/kg/day to 100mg//day, SC) +NSAIDs+corticosteroids (if needed)	Open-label run-in: Anakinra (1mg/kg/day to100mg/day, SC)	Anakinra (100mg/day, SC) + Prednisolone ≥10 mg/day (if needed)

Comparator	Placebo +NSAIDs+corticosteroids (if needed)	+MTX +NSAIDs+corticosteroids (if needed) Randomised phase: Anakinra (1mg/kg/day to100mg/day) + MTX +NSAIDs+corticosteroids (if needed) Placebo + MTX +NSAIDs+corticosteroids (if needed) Open-label extension: anakinra (1mg/kg/day to 100mg/kg/day)	+ NSAIDs (if needed) DMARD MTX (10mg to 25mg weekly, oral, SC or IM) Azathioprine (1mg/kg/day to 3mg/kg/day, oral) Leflunomide (20mg/day, oral) Ciclosporin (2.5mg/kg/day to 5mg/kg/day, oral) Sulfasalazine (1,000mg to 2000mg per day, oral) + Prednisolone ≥10mg/day + NSAIDs (if needed)
Concomitant treatment	NSAIDs and corticosteroids at a stable dosage for 1 month prior to and 1 month after Part 1 No immunosuppressant or DMARDs	MTX dose was kept stable during the open-label and blinded phases of the trial If administered, doses for NSAIDs and oral corticosteroids had to be kept stable for 4 weeks before the first dose of anakinra and during the course of the trial	Doses of NSAID and oral corticosteroid had to have been stable for at least 2 weeks, and doses of csDMARD had to be stable for at least 4 weeks, prior to randomisation Patients were allowed two intra-articular corticosteroid injections in 24 weeks
Outcomes used in the economic model (For the table of values see Appendix 9.3)	• Probability of injection site reaction for treatment with anakinra • Baseline age of people with SJIA	• None	• Remission rate for treatment with csDMARD • Remission rate for treatment with anakinra and tocilizumab (post-csDMARD) • Probability of injection site reaction for treatment with anakinra • Baseline age of people with AOSD • Discontinuation rate with csDMARD
ERG comments	• Small patient population (n=24) • The randomised period of the trial was short (1 month) • ACR Pedi 30 is a poor indicator of response to treatment	• SJIA patient subgroup was small (n=15) • The trial did not include SJIA as a stratification factor • The overall trial population (n=86) was not large enough to meet the sample size needed to assess treatment efficacy • Randomised period was short (16wks)	• Small patient population (n=22) • The numbers of patients recruited to the trial did not fulfil the required sample size (n=30 in each group) to assess treatment efficacy

ACRpedi 30 score=American College of Rheumatology Pediatric 30 score; AE=adverse event; AOSD=adult-onset Still's disease; CRP=c-reactive protein; csDMARD=conventional synthetic disease-modifying anti-rheumatic drug; DMARD=disease-modifying anti-rheumatic drug; IL-1=interleukin 1; IM=intramuscular; JRA=juvenile rheumatoid arthritis; MTX=methotrexate; NSAID=non-steroidal anti-inflammatory drug; RCT=randomised controlled trial; SC=subcutaneous; SJIA=systemic juvenile idiopathic arthritis; TNF=tumour necrosis factor. Source: CS, Section B2.2

Quality assessment

The company assessed the quality of the three RCTs[55-57] using the criteria specified by the Centre for Reviews and Dissemination at the University of York.[84] Overall, the ERG agrees with the company's assessments of each of the quality criteria (Table 8).

The ERG agrees that the primary outcomes of the Quartier[55] and Nordstrom[57] trials were assessed using data from all randomised patients and were therefore intention-to-treat (ITT) analyses. The ERG agrees with the company that the SJIA population of the Ilowite[56] trial was a subgroup of the overall trial population.

The ERG agrees with the company's observation (CS, p73 and p92) that the small numbers of patients recruited to each of the trials means that any differences in baseline characteristics between trial arms can have a disproportionate effect on the trial results. The ERG notes that in the Nordstrom[57] trial, the authors highlight that patients randomised to receive anakinra had higher serum ferritin levels and received higher prednisolone doses compared with patients treated with DMARDs.

The ERG notes that Ilowite[56] and Nordstrom[57] both report that the trials were insufficiently powered for reliable statistical conclusions to be drawn. In addition, the SJIA population in the Ilowite[56] trial was small (n=15) and SJIA was not specified as a stratification factor.

Table 8 Results of the company's quality assessment exercise (RCTs)

Trial	Quartier (2011)[55]	Ilowite (2008)[56]	Nordstrom (2012)[57]	ERG comment
Was randomisation carried out appropriately?	Yes	NR	Yes	Agree
Was the concealment of treatment allocation adequate?	Yes	NR	Unclear	Agree
Were the groups similar at the outset of the study in terms of prognostic factors?	Unclear	Unclear	Unclear	Generally agree However, the Nordstrom trial authors report that serum ferritin levels and doses of prednisolone were greater in the anakinra vs DMARD arm of the trial
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Unclear	No	Agree
Were there any unexpected imbalances in drop-outs between groups?	No	No	No	Agree
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No	Agree
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes, however, methods to account for missing data not discussed	No, the SJIA population were a subgroup of the total JIA population	Unclear	The primary outcomes of the Quartier[55] and Nordstrom[57] trials were assessed using data from all randomised patients and were therefore intention-to-treat (ITT) analyses. SJIA patients in the Ilowite trial were a subgroup of the whole trial population

DMARD=disease-modifying anti-rheumatic drug; ITT=intention-to-treat; JIA=juvenile idiopathic arthritis; SJIA=systemic juvenile idiopathic arthritis
Source: CS Table 25 and Table 27

4.2.2 Non-randomised evidence

UK registry study

The published UK registry study[2] compares the outcomes of patients with SJIA included in the UK Biologics for Children with Rheumatic Diseases study who were treated with anakinra (n=22) or tocilizumab (n=54) between 2010 and 2016. The company has not used the results reported in the UK registry study[2] to inform the economic model. The company states (CS, Table 55) that the study was not randomised and that there are differences in patient baseline characteristics that may result in biased estimates of treatment effect. Clinical advice to the ERG is that the between-arm differences in the disease characteristics of patients at baseline are important.

The baseline characteristics of patients included in the UK registry study[2] are shown in Table 9. The company highlights that a greater proportion of patients treated with anakinra had a history of MAS (37% versus 8%) and states that MAS is directly linked to poor disease control. The company also reports that a greater proportion of patients treated with anakinra were biologic naïve (86% versus 63%). The ERG notes the substantial differences in measures of C-reactive protein and erythrocyte sedimentation rate between the anakinra and tocilizumab arms. The ERG considers that the number of patients (n=22) included in the anakinra arm is small. The study authors concluded that the treatment outcomes of anakinra and tocilizumab appeared to be similar, although robust comparisons could not be made due to low patient numbers.

Table 9 Baseline characteristics of patients in the Kearsley-Fleet UK registry study

Characteristics	Anakinra N=22	Tocilizumab N=54
Female n (%)	15 (68)	28 (52)
First biologic n (%)	19 (86)	34 (63)
Previous biologic n	3	20
1 previous n (%)	2 (67)	12 (60)
2 previous n (%)	1 (33)	6 (30)
3 previous n (%)	-	2 (10)
Age years, median (IQR)	6 (2 to 13)	7 (4 to 11)
Disease duration, years (median IQR)	1 (0 to 1) [n=21]	2 (1 to 3)
Systemic features present n (%)	11 (79) [n=14]	24 (53) [n=45]
MAS history n (%)	7 (37) [n=19]	4 (8) [n=49]
Prior MTX exposure n (%)	19 (86)	53 (98)
Concomitant MTX n (%)	19 (86)	44 (81)
Prior steroid exposure n (%)	22 (100)	53 (98)
Concomitant steroids n (%)	13 (59)	36 (67)
Disease activity median (IQR)		
Active joint count 71 joints	5 (1 to 11) [n=17]	4 (1 to 8) [n=48]
Limited joint count 71 joints	3 (0 to 11) [n=18]	3 (1 to 7) [n=48]
CHAQ range 0 to 3	1.1 (0.5 to 2.0) [n=13]	0.9 (0.4 to 1.8) [n=34]
PGA 0-10 cm VAS	2 (2 to 6) [n=15]	4 (2 to 6) [n=34]
PGE 0-10 cm VAS	4 (1 to 6) [n=16]	4 (2 to 7) [n=34]
Pain VAS 0-10 cm VAS	4 (1 to 6) [n=14]	4 (1 to 6) [n=32]
ESR (mm/h)	55 (27 to 86) [n=17]	26 (10 to 58) [n=49]
CRP (mm/h)	64 (19 to 95) [n=18]	18 (4 to 63) [n=53]
JADAS-71	20 (11 to 26) [n=22]	19 (6 to 30) [n=11]

CHAQ=childhood health assessment questionnaire; CRP= C-reactive protein; ESR=erythrocyte sedimentation rate; IQR= interquartile range; JADAS-71=71-joint juvenile arthritis disease activity score; MAS=macrophage activation syndrome; mm/h=millimetres per hour; MTX=methotrexate; PGA=physician global assessment of disease; PGE=patient (or parent) global evaluation of wellbeing; VAS=visual analogue scale
Source: CS Table 17

Uncontrolled studies

The uncontrolled studies[20,50,52-54,59-74] of anakinra discussed in the CS are listed in Appendix 2 of this ERG report. The total number of patients included in the uncontrolled studies of anakinra in patients with SJIA is 250 (range: 7[61] to 46[54] patients). Five studies[52,53,60,63,65] are prospective and five[50,54,59,62,64] are retrospective. Patients were followed up over various intervals with mean/median follow-up ranging from 6.6 months[60] to 5.8 years.[52] The company states (CS, p106) that four studies[50,52-54,62] (reported in five papers) assessed anakinra as a first-line treatment. Results from the Pardeo[50] study of patients with SJIA are used in the company model to populate the following parameters: proportion of patients with inactive disease after 6 months and the proportions of patients likely to receive anakinra or tocilizumab after csDMARDs.

The total number of patients included in the uncontrolled studies of anakinra in AOSD is 250 (range: 6[20] to 140[73] patients). Three[63,67,68] of the uncontrolled AOSD studies are prospective and eight[20,66,69-74] are retrospective. Patients in the studies were followed up over various intervals with median/mean follow-up ranging from 6 months[67,68] to 7 years.[69] All of the uncontrolled studies were in patients with AOSD refractory to treatment with NSAIDs, systemic corticosteroids, csDMARDs or bDMARDs other than anakinra. None of the results from the uncontrolled studies in AOSD are used to inform the company model.

No evidence for anakinra versus any of the comparators outlined in the scope is available from these uncontrolled studies.

4.2.3 Meta-analyses and network meta-analyses

The company states (CS, p96) that a meta-analysis[75] of trials of anakinra in patients with SJIA and a meta-analysis[75,83] of trials of anakinra in patients with AOSD were submitted to the EMA in 2016 in support of the marketing authorisation application for anakinra. The ERG notes that the meta-analysis[75] for SJIA includes data from the Quartier[55] and Ilowite[56] trials, as well as data from uncontrolled studies. The meta-analysis[75,83] for AOSD includes data from the Nordstrom[57] trial, as well as data from uncontrolled studies. The ERG highlights that the meta-analyses[75,83] do not compare treatment with anakinra with any of the comparators listed in the final scope[1] issued by NICE for SJIA or AOSD and that none of the results are used to inform the company model.

The company also identified a published NMA[58] that was conducted to compare the efficacy of four biological treatments for the treatment of SJIA. The four treatments are anakinra, canakinumab, tocilizumab and rilonacept; rilonacept is not relevant to the appraisal of anakinra. Evidence from five randomised, placebo-controlled trials (one trial of anakinra,[55]

canakinumab[77] and tocilizumab[86] and two trials of rilonacept[78,79]) were synthesised in pairwise meta-analyses and NMAs. The primary efficacy outcome was defined as a 30% improvement according to the modified ACR Pedi 30,[76] and the primary safety outcome was serious adverse event (SAE). Results from the NMA[58] are reported in Table 10.

Table 10 Published NMA results: anakinra vs canakinumab and vs tocilizumab in SJIA

Comparison (anakinra vs)	Events/patients (%)			Relative, OR (95% CI)	Quality of evidence
	Anakinra	Canakinumab	Tocilizumab		
Modified ACR Pedi 30					
Canakinumab	11/12 (92)	35/43 (81)	-	0.55 (0.04 to 6.83)	Low
Tocilizumab	11/12 (92)	-	57/75 (76)	0.69 (0.06 to 8.18)	Low
Serious adverse events					
Canakinumab	0/12 (0)	2/43 (5)	-	Not estimable	Very low
Tocilizumab	0/12 (0)	-	3/75 (4)	Not estimable	Very low

ACR Pedi 30=American College of Rheumatology 30% improvement; CI=confidence interval; OR=odds ratio; vs=versus
Source: CS, Table 46 (corrected by the ERG)

The authors of the NMA[58] concluded that anakinra, canakinumab and tocilizumab appear to be of comparable efficacy and (to some extent) safety. The authors note the heterogeneity of the study designs, trial eligibility criteria and modified ACR Pedi 30[76] criteria across the five included trials.[55,77-79]

The results from the NMA[58] have not been used to inform the company model (CS, p97). The company does not consider that response to treatment measured by the modified ACR Pedi 30 is an appropriate measure of remission. Clinical advice to the ERG is that response according to the modified ACR Pedi 30[76] is a low threshold. In more recent clinical studies, the outcome measure used is response according to ACR Pedi 90.[76]

The company advises caution (CS Appendix A, p19) when interpreting the results from the NMA[58] due to differences between the patient populations recruited to the included trials.

The ERG notes that only one of the five RCTs[55,77-79] synthesised in the NMA[58] included anakinra as a treatment (Quartier[55]) and that only 12 patients in the Quartier trial[55] trial were treated with anakinra. Therefore, the ERG considers that results from the NMA[58] are of little value to this appraisal.

4.3 Adverse events

Adverse event data for patients with SJIA have been derived from the Quartier[55] and Ilowite[56] RCTs, the UK registry study[2] and from the uncontrolled studies[50,52-54,59-65] of anakinra (Section B.2.11 of the CS). Adverse event data for patients with AOSD have been derived from the Nordstrom[57] RCT and from the uncontrolled studies[20,63,66-74] of anakinra (listed in Appendix 7.2 of this ERG report).

Adverse events in patients with SJIA

Table 11 shows the AEs recorded during the Quartier[55] trial. The data are from i) the blinded, randomised phase (1 month) and ii) the open-label phase (11 months). The company reports (CS, p99) that during the 1-month double-blind phase of the trial there were 14 recorded AEs in the anakinra arm and 13 recorded AEs in the placebo arm. There were no SAEs in either arm. The company states (CS, p99) that the 89 AEs recorded during the open-label treatment period were mainly injection site reactions (ISRs) and infections.

Table 11 Summary of adverse events in the Quartier trial

	Randomised phase (Month 1)		Open-label phase (Month 1 to Month 12)
	Anakinra (n=12)	Placebo (n=12)	Anakinra (n=22)
Number of any AEs[a]	14	13	89
Number of SAEs	0	0	5[b]
Specific AEs (number of cases):			
Post-injection erythemas (patient-years)	3	1	6 (0.40)
Infections (patient-years)	2 (2)	2 (2)	44 (2.90)
ENT infections and laryngitis	1	1	20
Bronchitis events	0	0	8
Gastroenteritis	1	1	3
Skin infections	0	0	4
Other infections	0	0	9[c]
Vomiting	0	1	9
Other AE[d] (patient-year)	0 (0)	2 (2)	10 (0.66)

AE=adverse event; ENT=ear, nose and throat; SAE=serious adverse events
[a] Disease activity/flares was not systematically recorded as an AE
[b] Infections in 4 patients, vertebral collapse in one patient (these 5 patients continued the trial), skin and digestive symptoms leading to the diagnosis of Crohn's disease in one patient
[c] Varicella (n=3), vulvar candidiasis (n=2), isolated fever (n=2), atypical pneumonitis, urinary tract infection. Favourable outcome in all cases, no patient withdrawn from the trial
[d] Skin lesions (n=5), haematuria (n=2), back pain (n=2), dental fracture, asthenia, vertigo.
Source: CS, Table 48

The AE data from the Ilowite[56] trial are reported in the CS (Table 47). The company states (CS, p98) that no conclusions can be drawn about the AEs reported during the blinded phase of the trial as only three patients with SJIA were included in the placebo group.

The AE data from the UK registry study[2] are discussed in the CS (p100). The company reports that three patients treated with tocilizumab stopped treatment due to rash, neutropenia and active MAS. Four patients treated with anakinra stopped treatment due to stomach cramps and diarrhoea, ISR and difficulty with the daily injection (n=2).

Summary safety data from the uncontrolled studies[50,52-54,59-65] (listed in Appendix 7.2 of this ERG report) are presented in Table 49 of the CS.

Adverse events in patients with AOSD

The company reports (CS, p101) that during the randomised phase of the Nordstrom[57] trial, eight of the 12 patients treated with anakinra experienced an ISR. Three patients (one treated with anakinra) experienced an SAE (worsening of their AOSD).

Summary safety data from the uncontrolled studies[20,63,66-74] are presented in Table 50 of the CS.

The company considers (CS, p106) that anakinra has an established and acceptable safety profile and highlights that (i) anakinra has been approved for treatment for rheumatoid arthritis since 2002 and (ii) treatment with anakinra is associated with over 15 years of post-marketing experience in a number of licensed indications. The ERG notes from the SmPC[75] for anakinra that there is no evidence of any difference in the overall safety profile of anakinra in patients with Still's disease compared to patients with rheumatoid arthritis, except for the higher risk of MAS in patients with Still's disease.

4.4 Health-related quality of life

There are no HRQoL data reported in the CS for patients with SJIA.

Health-related quality of life data relevant to patients with AOSD were collected during the Nordstrom[57] trial using the Short Form (36) Health Survey (SF-36[87]). The company reports (CS, p91) that, compared with patients treated with csDMARDs, more patients treated with anakinra achieved improvements in physical health. No between group differences were found in comparisons of mental health. The ERG notes that the HRQoL data were derived from 24 patients (12 in each arm).

4.5 Conclusions of the clinical effectiveness section

The company has presented data from three small RCTs: two in patients with SJIA (Quartier[55] and Ilowite[56]) and one in patients with AOSD (Nordstrom[57]). The company has presented clinical effectiveness from a UK registry study[2] (anakinra versus tocilzumab) and from a NMA that compared anakinra, tocilizumab and canakinumab.[58] The ERG considers that the

company has provided all the available (RCT and non-RCT) evidence that is relevant to the current appraisal. However, the ERG considers that there is insufficient reliable clinical effectiveness evidence to inform decision making in this appraisal as:

- all studies[55-57] recruited small numbers of patients who were followed up for short periods of time
- the three RCT[55-57] trial protocols do not match the comparator treatments and treatment lines specified in the final scope issued by NICE
- the NMA[58] outcome measure is not relevant to NHS clinical practice
- patients included in the UK registry study[2] were not randomised to treatments (anakinra or tocilizumab) and there were important differences in baseline characteristics between the two study arms.

The company considers, and clinical advice to the ERG supports the company view, that future RCTs of anakinra are unlikely to be carried out.

5 COST EFFECTIVENESS

This section provides a structured critique of the economic evidence submitted by the company in support of the use of anakinra for the treatment of Still's disease (SJIA and AOSD). The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company has provided an electronic copy of their economic model, which was developed in Microsoft Excel.

5.1 Systematic review of cost effectiveness evidence

5.1.1 Objective of the company's systematic review

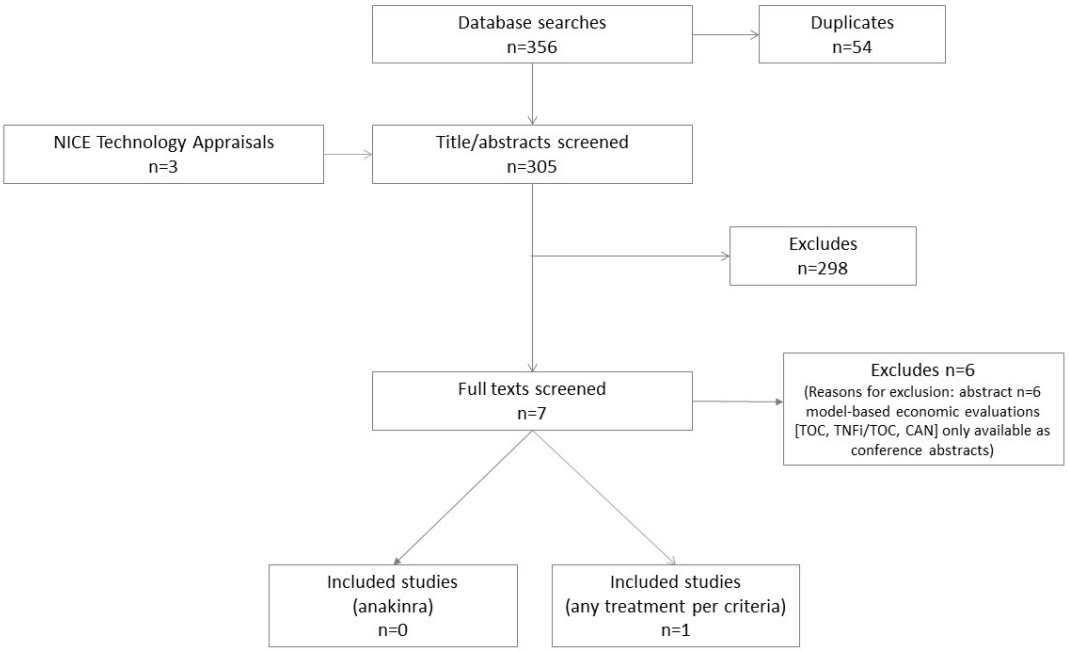
The objective of the literature search carried out by the company was to identify previously published cost effectiveness studies of anakinra for the treatment of Still's disease (defined as SJIA and/or AOSD).

5.1.1 Included and excluded studies

Inclusion and exclusion criteria were identical to those used in the clinical effectiveness review except that the intervention eligibility criterion was relaxed to include all interventions. In addition, non-randomised studies, full cost effectiveness studies and economic evaluations (if incremental cost effectiveness ratios could be calculated from published data) were included. Studies that measured costs but not health benefits were excluded, except for stand-alone cost analyses undertaken from the perspective of the UK NHS.

5.1.2 Findings from the company's cost effectiveness review

The company study selection process is summarised in the PRISMA diagram displayed in Figure 2.



Source: CS, Appendix G, Figure 1

Figure 2 Company study selection process

The only relevant study identified by the company's literature search was the NICE single technology appraisal TA238;[48] this appraisal considered the use of tocilizumab to treat SJIA. However, the company concluded that the relevance of this study was limited as:

- the model structure used to inform the submission did not align with the current NHS commissioning policy for SJIA (anti-tumour necrosis factor [TNF] drugs are not recommended for treating SJIA)[47]
- it was not relevant to patients with AOSD (NHS commissioning policy does not recommend use of anti-TNF drugs to treat AOSD)[21]
- it did not capture clinically important aspects of SJIA, including the development of MAS.

5.2 ERG critique of the company's literature review

The search strategy was comprehensive and included relevant databases: MEDLINE (Ovid) Embase (Ovid), EconLit (EbscoHost), Cochrane Database of Systematic Reviews, Economic Evaluations Database and Cochrane Central Register of Clinical Trials (via The Cochrane Library), NHS Economic Evaluation Database (NHS EED), Database of Abstracts of Reviews of Effects (DARE), and Health Technology Assessment database (via Centre for Reviews and Dissemination). The company also searched the NICE website.

The search strategies for the review of economic evaluations were developed by the company and run in 2019. The ERG notes that no language limits or data limits were applied, and that relevant index terms and free text words were used.

Overall, the searches reflect the population and the indication described in the final scope[1] issued by NICE. The ERG undertook its own scoping searches and is confident that relevant studies have not been missed by the company's searches.

A summary of the ERG's critique of the company's cost effectiveness systematic review methods (provided in Appendix G of the CS) is presented in Table 12.

Table 12 ERG appraisal of systematic review methods (cost effectiveness)

Review process	ERG response
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes
Were appropriate sources searched?	Yes
Was the timespan of the searches appropriate?	Yes
Were appropriate search terms used?	Yes
Were the eligibility criteria appropriate to the decision problem?	Yes
Was study selection applied by two or more reviewers independently?	One reviewer
Was data extracted by two or more reviewers independently?	One reviewer
Were appropriate criteria used to assess the quality of the primary studies?	Yes
Was the quality assessment conducted by two or more reviewers independently?	One reviewer
Were any relevant studies identified?	One

Source: LRiG checklist

5.3 ERG summary of the company's submitted economic evaluation

The company developed a de novo economic model to compare the cost effectiveness of per-label use of anakinra (per-label arm) versus no anakinra (no-anakinra arm) and versus post-csDMARD use of anakinra (post-csDMARD arm) for the treatment of Still's disease. The post-csDMARD arm in the company model is consistent with NHS England[21] recommendation on the use of anakinra (see Section 2.1.4).

5.3.1 Model structure

The company model structure (a Markov cohort model) is shown in Figure 3 and comprises 13 mutually exclusive health states. Patients enter the model in the NSAIDs±corticosteroids health state. At the end of each weekly cycle patients can remain in their current health state, achieve remission or progress to the next treatment-related health state (i.e., the active disease health states shown in Figure 3). Patients in remission experience a relapse and return to their previous treatment-related health state. Treatment-related health states vary by model arm and by Still's disease subpopulation (Figure 4). For example, the second csDMARD health state (csDMARD #2) allows entry by the AOSD subpopulation but not by the SJIA subpopulation. The second biologic health state (Biologic #2) allows entry by the patients in the anakinra arm but not by patients in the no-anakinra arm. Death is an absorbing health state from which transitions to other health states are not permitted.

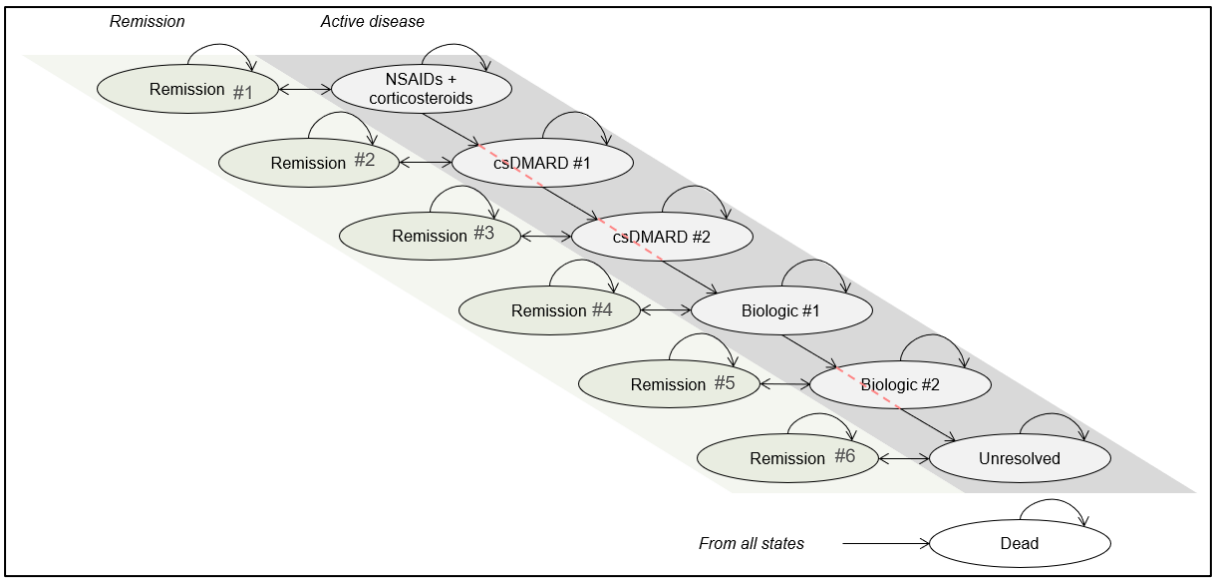


Figure 3 Structure of the company model

Red dashed lines- - - - - -=omitted health states in certain treatment arms and subpopulations
Source: adapted from CS, Section B.3.2.3, Figure 9

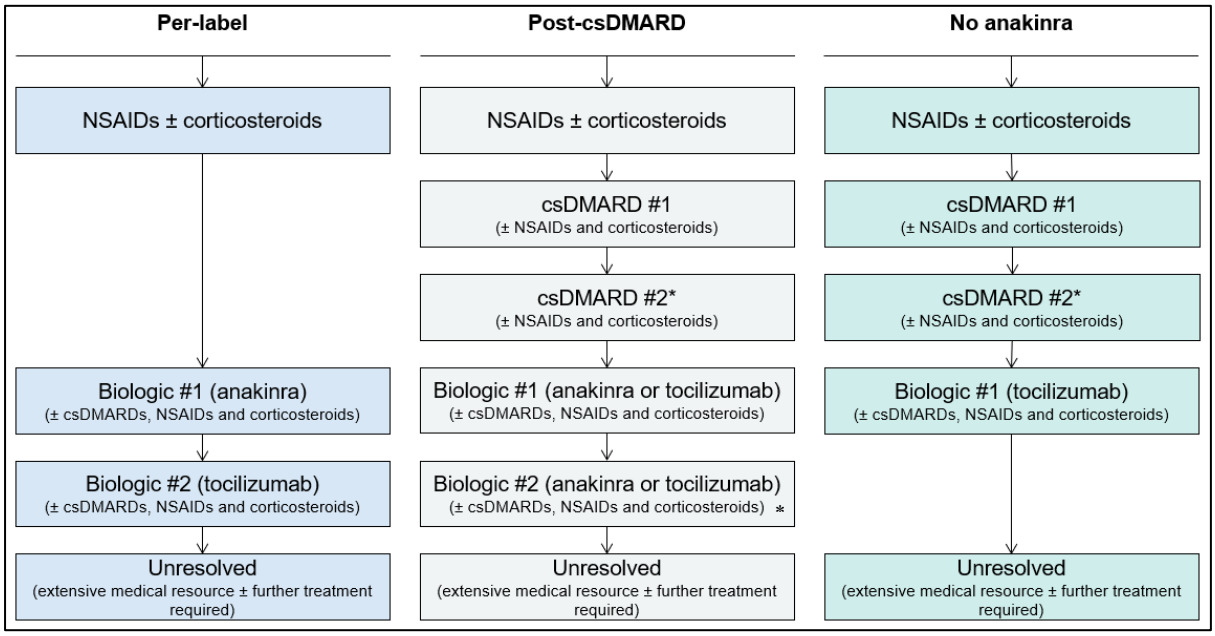


Figure 4 Company model permitted treatment-related health states

csDMARD=conventional synthetic disease-modifying anti-rheumatic drug; NSAID=non-steroidal anti-inflammatory drug
*=treatment-related health states not permitted in patients with SJIA
Source: CS, Section B.3.2.2, Figure 8

5.3.2 Population

The population reflected in the company model comprises children (SJIA subpopulation) and adults (AOSD subpopulation) with Still's disease. This population is consistent with the population in the final scope[1] issued by NICE. The company has produced cost effectiveness results for the SJIA and AOSD subpopulations and for the overall Still's disease population.

The company has modelled monocyclic and chronic disease separately. The company assumes that patients with the monocyclic disease pattern will experience an initial active disease episode (i.e., flare) followed by life-long remission, whilst patients with chronic disease will experience an initial active disease episode followed by a continuous loop of remission-to-relapse-to-remission.

Table 13 Modelled baseline patient characteristics

Parameter	Subpopulation	Value	Source or Justification
Age	SJIA	8.5 years	Nordström (2012),[57] Quartier (2011)[55]
	AOSD	39 years	
Female	SJIA and AOSD	70%	Efthmiou (2006),[24] Gerfaud-Valentin (2014),[9] Lebrun (2018),[23] Ruscitti (2016)[22]
Male		30%	
Monocyclic disease	SJIA and AOSD	25.5%	Grevich (2017)[88]
Chronic disease		74.5%	
SJIA:AOSD split	SJIA and AOSD	62.5%:37.5%	NICE final scope[1]

AOSD=adult-onset Still's disease; SJIA=systemic juvenile idiopathic arthritis
Source: CS, Section B.3.2.5, Table 52

5.3.3 Interventions and comparators

The per-label arm represents treatment with **anakinra** after a failure to achieve remission with treatment with NSAIDs±systemic corticosteroids. The no-anakinra arm represents treatment with **csDMARDs** after a failure to achieve remission with treatment with NSAIDs±systemic corticosteroids. The post-csDMARD arm represents treatment with a **bDMARD** (anakinra or tocilizumab) after a failure to achieve remission with treatment with csDMARD. A full description of the treatment pathways is shown in Figure 3.

5.3.4 Perspective, time horizon and discounting

The company states that costs are considered from the perspective of the NHS and Personal Social Services (PSS). The model cycle length is 1 week, and the time horizon is set at 30 years, which the company considers to be long enough to reflect all important differences across treatment arms. Relevant costs and outcomes have been discounted at 3.5% per annum.

5.3.5 Treatment effectiveness and extrapolation in the base case

The treatment effectiveness parameters in the model are remission rates, treatment discontinuation rates and relapse rates. The company assumes that all NSAIDs±systemic corticosteroid combinations are of equivalent effectiveness. The company also assumes that all treatments within a DMARD class (csDMARDs or bDMARDs) have the same treatment effectiveness.

Treatment effectiveness parameters used in the model are primarily based on clinical assumptions or are estimates reported in Nordstrom,[57] Horneff,[89] Sota,[90] Yamada,[91] Grom[92] or in a previous technology appraisal (TA238[48]).

The company uses different remission and treatment discontinuation rates for patients with monocyclic and chronic Still's disease. The company also links remission rates and treatment discontinuation rates by assuming that 95% of patients treated with NSAIDs±systemic corticosteroid or csDMARDs would either have achieved remission or discontinued treatment at 6 weeks; the company does not make this assumption for treatment with bDMARDs. Constant treatment effectiveness rates are used throughout the model time horizon. A summary of the treatment effectiveness rates used in the company model is provided in Table 14 and full details of the methods used by the company to estimate the rates can be found in the CS (Section B.3.3.1).

Table 14 Weekly remission probabilities, treatment discontinuation probabilities and relapse probabilities used in the company model

Parameter	Value	Model arm			Source/Justification
		Per-label	Post-csDMARD	No-anakinra	
Remission					
NSAIDs+C	12.56%;[MC] 0%[C]	✓*	✓*	✓*	Calibrated. MC: 5% on treatment after 6w, 30% in remission. C: 0% in remission
csDMARDs	0.93%;[MC] 0%[C]	×	✓*	✓*	MC: Nordström (2012)[57]: 20% remission after 24w. C: 0% in remission
Anakinra	4.41%	✓	×	×	Horneff (2018)[89]: 44.4% remission after 3mth
	2.85%	×	✓	×	Base-case: Nordström (2012)[57]: 50% remission after 24w
Tocilizumab	4.41%	✓	×	×	Same efficacy assumed for anakinra and tocilizumab
	2.85%	×	✓	✓	
Unresolved	0.02%	✓	✓	✓	Calculation based on assumption - remission only achieved through use of bone marrow transplant (all living patients) Grom (2016)[92]
Discontinuation					
NSAIDs+C	27.31%;[MC] 39.30%[C]	✓*	✓*	✓*	Calibrated. MC: assume 5% of patients would be on treatment after 6w and 30% in remission. C: 5% on treatment after 6w
csDMARDs	16.23%;[MC] 17.07%[C]	×	✓*	✓*	Calibrated. MC and C: assume 5% of patients would be on treatment after 16w
Anakinra	1.14%;[First] 2.03%[Second]	✓	✓	×	NICE TA238[48] company submission (12.6% over 12w) for first biologic used, hazard ratio of 1.818 applied to this probability for the second biologic used based on Sota (2019)[90]
Tocilizumab	1.14%;[First] 2.03%[Second]	✓	✓	✓	
Relapse					
All treatments	0.00%;[MC] 0.54% [C]	✓	✓	✓	Yamada (2018)[91]

C=chronic disease course; csDMARD=conventional synthetic disease-modifying anti-rheumatic drug; MC=monocyclic disease course; mth=month(s); NICE=National Institute for Health and Care Excellence; SA=sensitivity analysis; TA=technology appraisal; w=week(s)
*=only included if patients are assumed to start at this or an earlier stage within the pathway; [First]=discontinuation probability applied for first biologic used; [Second]=discontinuation probability applied for second biologic used
Source: adapted CS, Section B.3.3.1, Table 53

5.3.6 Health-related quality of life

HRQoL information for the remission health states (in remission) and the active disease health states (not in remission) are obtained from a previous NICE technology appraisal (TA238).[48] The company, during TA238,[48] had converted Childhood Health Assessment Questionnaire (CHAQ) scores to EQ-5D-3L scores using a mapping algorithm[93] that had initially be designed to map Health Assessment Questionnaire (HAQ) scores to EQ-5D-3L scores in adults (OPTION trial[94] and LITHE trial[95] participants; N=1800) with rheumatoid arthritis. The company in this appraisal has assumed that the mapping algorithm used in TA238[48] is valid for mapping CHAQ scores onto EQ-5D-3L scores in patients with Still's disease. The company, in the current appraisal, therefore, used the EQ-5D-3L score for the 'ACR90' health state and 'uncontrolled disease' from TA238[48] to represent the EQ-5D-3L score for the remission health states (remission #1 to remission #6) and active disease health states respectively (Table 15).

Age-adjusted utility decrements were applied to the model health state utility values using decrement factors obtained from Ara and Brazier (2011),[96] to account for the expected decline in utility over time. Utility loss associated with ISR (-0.01) and MAS (-0.468) are also modelled. The company has assumed that the durations of each episode of these events are 1 day and 14 days respectively.

Table 15 Utility values used in the company model

Health state	CHAQ (health state in TA238)	Utility value (95% confidence interval)	Source
In remission • Remission #1 to Remission #6	0.669 (ACR90)	0.715 (0.987 to 0.743)	TA238[48]
Not in remission • NSAID+C • csDMARD #1 • csDMARD #2 • Biologic #1 • Biologic #2 • Unresolved	1.744 (uncontrolled disease)	0.567 (0.537 to 0.598)	TA238[48]
Injection site reaction	Not applicable	-0.010 (-0.076 to 0.000)	Restelli (2017)[97]
Macrophage activation syndrome	Not applicable	-0.468 (0.421 to 0.516)	Beauchemin (2016)[98]

ACR=American College of Rheumatology; CHAQ=Childhood Health Assessment Questionnaire; csDMARD=conventional synthetic disease-modifying anti-rheumatic drug; NSAID=non-steroidal anti-inflammatory drug
Source: adapted CS, Section B.3.4.4, Table 56, Table 57 and Table 59

5.3.7 Adverse events

The company considered that the main AE associated with treatment with anakinra was ISR. The company notes that ISRs occur within the first week of treatment and that patients who do not experience an ISR within 4 weeks are unlikely to experience an ISR for the remainder of their treatment. ISRs also occur in patients treated with tocilizumab, but the company has made the conservative assumption that the probability of an ISR occurring in patients treated with tocilizumab is 0% as tocilizumab is administered less frequently than anakinra (Table 16).

Table 16 Injection site reaction rates using in the company model

Treatment	Group	Dosing frequency (per week)	Probability of reaction (per administration)	Source / Rationale
Anakinra	SJIA	7.00	0.42%	Quartier (2011)[55]
	AOSD	7.00	0.16%	Nordström (2012)[57]

AOSD=adult-onset Still's disease; SJIA=systemic juvenile idiopathic arthritis
Source: CS, Section B.3.3.4, Table 54

In addition to general population mortality risks, the company also attributes a disease-related excess mortality of 12.9% (Kumakura [2014][44]) to each MAS episode and 12.5% (Silva [2018][99]) to each bone marrow transplant (BMT) episode. The excess mortality rates are the same for patients with SJIA and AOSD across the three model arms.

5.3.8 Resources and costs

Drug costs

A PAS discount is available for tocilizumab. However, the PAS discount for tocilizumab is not known to the company. The company has used an 'assumed PAS discount' in their base case analysis. The dosing schedules and unit costs used in the company model for NSAIDs, systemic corticosteroids, csDMARDs and bDMARDs are provided in Section 3.5 of the CS and are summarised in Table 17 of this report. Vial sharing is not assumed in the base case analysis. For patients with SJIA, the company has assumed that the mean weight and body surface area (BSA) of the population during the period from 8.5 to 18 years are 25kg and 0.95m^2 respectively, after which the mean weight and BSA of patients with AOSD (weight=75kg and BSA=1.87m^2) have been assumed. A treatment administration cost of £154 per administration is applied to intravenous (IV) treatment. No treatment administration cost is applied to oral and subcutaneous (SC) treatments.

There are multiple drugs within each drug category. For instance, patients who are eligible to receive a systemic corticosteroid can either receive prednisolone or methylprednisolone. The company has assumed that the market share distribution determines the proportion of patients who would receive each drug within a particular drug category (see Table 18).

Table 17 Summary of drug doses and costs used in the company model

Drug category	Drug	Subpopulation	Dosing		Cost (pack size)	Source
			Dose/ admin	Frequency		
NSAIDs	Naproxen (500mg)	SJIA	3.1mg/kg	2 /d	£3.58 (56)	BNFc[100] and eMIT[101]
		AOSD	375.0mg	2/d		BNF[100] and eMIT[101]
	Ibuprofen (200mg)	SJIA	9.0mg/kg	5/d	£0.31 (48)	BNFc[100] and eMIT[101]
		AOSD	300.0mg	3/d		BNF[100] and eMIT[101]
Corticosteroids	Prednisolone (5mg)	SJIA	1.5mg/kg	1/d	£0.26 (28)	BNFc[100] and eMIT[101]
		AOSD	0.9mg/kg	1/d		AOSD policy NHS ref:170056P[21] and eMIT[101]
	Methyl-prednisolone (1,000mg)	SJIA	20.0mg/kg	0.75/d	£6.42 (1)	BNFc[100] and eMIT[101]
		AOSD	1000.0mg	1/d		Fujii (1997)[102] and eMIT[101]
csDMARDs	Azathioprine (50mg)	SJIA	2.0mg/kg	1/d	£1.59 (56)	Frosch (2008)[103] and eMIT[101]
		AOSD	2.0mg/kg	1/d		AOSD policy NHS ref:170056P[21] and eMIT[101]
	Ciclosporin (25mg)	SJIA	2.0mg/kg	2/d	£11.14 (30)	BNF,[100] AOSD policy NHS ref:170056P[21] and eMIT[101]
		AOSD	2.0mg/kg	2/d		
	Leflunomide (20mg)	SJIA	12.5mg	1/d	£3.57 (30)	Hayward (2009)[104] and eMIT[101]
		AOSD	15.0mg	1/d		AOSD policy NHS ref:170056P[21] and eMIT[101]
	Methotrexate (2.5mg)	SJIA	12.5mg/m²	1/w	£0.86 (24)	BNFc[100]
		AOSD	16.25mg	1/w		AOSD policy NHS ref: 170056P[21] and eMIT[101]
bDMARDs	Anakinra (100mg/0.67ml)	SJIA	1.5 mg/kg	1/d	£183.61 (7)	BNFc[100]
		AOSD	100.0mg	1/d		AOSD policy NHS ref:170056P[21] and BNF[100]
	Tocilizumab-IV (80mg/4ml)	SJIA	12.0mg/kg	0.50/w	£102.40 (1)	BNFc[100]
		AOSD	8.0mg/kg	0.25/w		BNF[100]
	Tocilizumab-SC (162mg/0.9ml)	SJIA	162.0mg	1/w	£913.12 (4)	BNFc[100]
		AOSD	162.0mg	0.50/w		BNF[100]
	Canakinumab (150mg/1ml)	SJIA	4.0mg/kg	0.25/w	£9,927.80 (1)	BNFc[100]
		AOSD	300.0mg	0.25/w		BNF[100]

Admin=administration; AOSD=adult-onset Still's disease; BNF=British National Formulary; BNFc=British National Formulary for children; d=day; freq=frequency; IV=intravenous; kg=kilogram; m²=metres squared; mg=milligram; ml=millilitre; NHS=National health service; ref=reference; SC=subcutaneous; subpop=subpopulation; SJIA=systemic juvenile idiopathic arthritis; w=week
Source: adapted from CS, Section B.3.5, Table 60 and Table 62

Table 18 Summary of market share assumptions used in the company model

Drug category	Drug	Market share assumptions
NSAIDs	Naproxen	• First-line: 50%
	Ibuprofen	• First-line: 50%
Corticosteroids	Prednisolone	• First-line: 50%
	Methylprednisolone	• First-line: 50%
csDMARDs	Azathioprine	• Not used
	Ciclosporin	• Second-line: 100% (AOSD only)
	Leflunomide	• Not used
	Methotrexate	• First-line: 100%
bDMARDs	Anakinra	• First-line: used in 50% of AOSD patients (regardless of positioning), 100% of SJIA patients if used before csDMARDs, and in 0% of SJIA patients if used after csDMARDs. In the no-anakinra arm, market share is 0% for all patients. • Second-line: used in 100% of patients after tocilizumab. In the no-anakinra arm, market share is 0% for all patients.
	Tocilizumab	• First-line: used in 50% of AOSD patients (regardless of positioning), 0% of SJIA patients if used before csDMARDs, and in 100% of SJIA patients if used after csDMARDs. • Second-line: used in 100% of patients after anakinra (not applicable for the no-anakinra arm).

AOSD=adult-onset Still's disease; bDMARDs=disease-modifying anti-rheumatic drugs; biologic csDMARDs=conventional synthetic disease-modifying anti-rheumatic drugs; NSAIDs=non-steroidal anti-inflammatory drugs; SJIA=systemic juvenile idiopathic arthritis
Source: CS, Section B.3.5.2, Table 61

Treatment progression in the model is generally from NSAIDs±systemic corticosteroid to csDMARDs to bDMARDs; patients in the per-label arm of the model do not receive csDMARDs. The company considered that some patients receiving csDMARDs or bDMARDs would continue to receive previous treatment in combination with their current treatment. Only the costs (not treatment benefits) of concomitant previous treatment were included in the model. As such, in the company base case analysis, an assumption was that patients receiving a csDMARD or bDMARD would continue to incur the costs of NSAIDs indefinitely, and that everyone receiving a csDMARD would also receive concomitant corticosteroids.

Resource use by health state

Patients in all health states were modelled to incur costs for routine health care. Except for the unresolved health state, the health care resource use of patients in the active disease health states who received NSAIDs±systemic corticosteroids, csDMARDs and bDMARDs are shown in Table 19. For the unresolved health state, the company assumed that the cost of this health state was 6.67 times higher than the cost of the NSAIDs+corticosteroids health state. The

company also assumed that 1% of patients in the unresolved health state would undergo BMT per year (0.0193% per model cycle) at a cost of £96,956 per transplant.

The company considered that patients in remission (i.e., Remission #1 to Remission #6 health states) required four rheumatology visits and four immunology visits per year. Additionally, 50% of patients who achieved remission whilst receiving a biologic agent (i.e., Remission #4 and Remission #5 health states) would incur the health care costs associated with the health state in which the remission had occurred. Full details of the health care resource use estimates used in the economic model are provided in the CS (Section B.3.5.5).

Table 19 Yearly resource use costs used in the company model for active disease health states

Resource	Unit cost		Resource use per year				
	SJIA	AOSD	NSAID+C	DM #1	DM #2	*Biologic #1 & #2	Rem
Full blood count	£2.51	£2.51	18.0	18.0	18.0	18.0	0.0
Liver function test	£1.11	£1.11	18.0	18.0	18.0	18.0	0.0
Erythrocyte sedimentation rate	£2.51	£2.51	18.0	18.0	18.0	18.0	0.0
C-reactive protein	£2.51	£2.51	18.0	18.0	18.0	18.0	0.0
Urea, electrolytes and creatinine	£1.11	£1.11	18.0	18.0	18.0	18.0	0.0
Lipid test	£2.51	£2.51	-	-	-	-	0.0
GP appointment	£31.00	£31.00	3.5	3.5	3.5	3.5	0.0
Haematology	£288.00	£160.00	2.0	2.0	2.0	2.0	0.0
Radiology	£192.00	£145.00	0.4	0.4	0.4	0.4	0.0
Ophthalmology	£102.00	£98.00	2.0	2.0	2.0	2.0	0.0
Rheumatology	£245.00	£146.00	1.5	1.5	1.5	1.5	4.0
Psychology	£243.00	£170.00	0.4	0.4	0.4	0.4	0.0
Clinical Immunology	£219.00	£269.00	1.5	1.5	1.5	1.5	4.0
Occupational therapy	£73.00	£73.00	3.5	3.5	3.5	3.5	0.0
Physiotherapy	£55.00	£55.00	3.5	3.5	3.5	3.5	0.0
Inpatient stay (days)	£339.00	£339.00	1.7	1.7	1.7	1.7	0.0

AOSD=adult-onset Still's disease; Biologic=biologic disease-modifying anti-rheumatic drug; BNF=British National Formulary; C=systemic corticosteroid; DM=conventional synthetic disease-modifying anti-rheumatic drug; GP=general practitioner; NSAID=non-steroidal anti-inflammatory drug; Rem=remission health states; SJIA=systemic juvenile idiopathic arthritis
*=values apply to biologic agents. Additional cost of four lipid tests per year is applied to tocilizumab
Source: adapted from CS, Section B.3.5 (Table 63 and Table 64)

Other costs

The company estimated that the costs of each episode of MAS were £22,482 and £27,031 for patients with SJIA and AOSD respectively. Details of the estimation method used by the company are provided in Table 20.

Table 20 Summary of costs associated with MAS

Item	SJIA	AOSD	Description and source
LOS in ICU (days)	7	7	Assumption based on clinical expert opinion
LOS in HDU (days)	7	7	Assumption based on clinical expert opinion
Cost per day (ICU)	£1,957.81	£1,466.60	NHS Reference Costs (2017/18).[105] CCU17 High dependency unit for children and young people; CCU01 Non-specific, general adult critical care patients predominate
Cost per day (HDU)	£909.48	£1,466.60	NHS Reference Costs (2017/18).[105] CCU04 Paediatric intensive care unit (paediatric critical care patients predominate); CCU01 Non-specific, general adult critical care patients predominate
Methylprednisolone	£14.45	£43.34	Assumed 30mg/kg for 3 days, cost per mg
Ciclosporin	£4.46	£13.37	Assumed 4mg/kg for 3 days, cost per mg
Anakinra	£367.22	£367.22	Assumed 100mg/day for 14 days, cost per injection
IVIG	£4,050.00	£12,150.00	Assumed 1.5g/kg for 2 days, cost per gram from BNF[100]
Patients requiring IVIG	50%	50%	Assumption based on clinical expert opinion
Total hospital costs	£20,071.01	£20,532.38	Calculation
Total drug costs	£2,411.12	£6,498.92	Calculation
Total costs	**£22,482.13**	**£27,031.30**	Calculation

AOSD=adult onset Still's disease; BNF=British national formulary; HDU=high dependency unit; ICU=intensive care unit; IVIG=intravenous immunoglobulin; kg=kilogram; LOS=length of stay; mg=milligram; MAS=macrophage activation syndrome; MRU=medical resource use; SJIA=systemic juvenile idiopathic arthritis
Note: Drug costs calculated assuming average weights of 25kg (SJIA) and 75kg (AOSD)
Source: adapted from CS, Section B.3.5.8 (Table 65)

5.3.9 Cost effectiveness results

The company base case cost effectiveness results were generated using a mixed population of patients with SJIA (62.5%) and ASOD (37.5%). Subgroup analyses were carried out to generate separate results for the two populations (see CS, Section 5.2.13). Total and incremental costs, life years gained (LYG) and QALYs are shown in Table 21 (pairwise analysis) and Table 22 (fully incremental analysis) for the company's three base case treatment strategies: per-label arm, post-csDMARD arm and no-anakinra arm. In the company base case, an 'assumed PAS discount' was applied to the list price of tocilizumab whilst list prices were used for other treatments. Company model results show that the per-label arm dominates the other two arms by being cheaper and delivering more QALYs.

The net monetary benefit (NMB) for the comparison of no anakinra versus per-label anakinra is £70,102. In a fully incremental analysis, no-anakinra dominates both post-csDMARDs and per-label anakinra. The NMB for the fully incremental analysis is £29,285.

Table 21 Base case results, pairwise analysis versus no-anakinra arm

Model arm	Total			Incremental (versus no-anakinra)			ICER per QALY gained
	Costs	QALYs	LYG	Costs	QALYs	LYG	
No-anakinra	£258,107	11.304	28.202				
Post-csDMARD	£224,343	11.657	28.509	-£33,764	0.353	0.307	Dominant
Per-label	£201,317	11.970	28.774	-£56,790	0.666	0.572	Dominant

csDMARD=conventional synthetic disease-modifying anti-rheumatic drug; ICER=incremental cost effectiveness ratio; LYG=life years gained; QALY=quality adjusted life year
Source: adapted from CS, Table 70

Table 22 Base case results, fully incremental analysis

Model arm	Total			Fully incremental			ICER per QALY gained
	Costs	QALYs	LYG	Costs	QALYs	LYG	
No-anakinra	£258,107	11.304	28.202				
Post-csDMARD	£224,343	11.657	28.509	-£33,764	0.353	0.307	Extendedly dominated
Per-label	£201,317	11.970	28.774	-£23,026	0.313	0.265	Dominant

csDMARD=conventional synthetic disease-modifying anti-rheumatic drug; ICER=incremental cost effectiveness ratio; LYG=life years gained; QALY=quality adjusted life year
Source: adapted from CS, Table 70

5.3.10 Sensitivity analyses

The company's deterministic base case results showed that the per-label anakinra strategy dominated the other two strategies and, therefore, the summary results presented by the company are NMBs rather than incremental cost effectiveness ratios (ICERs) per QALY gained.

Deterministic sensitivity analyses

The company identified model parameters that they considered were subject to uncertainty and ran the model using upper and lower bound values (within a plausible range) for each of those parameters. The NMB results generated using the values from the ten most influential parameters are shown in Figure 5 (per-label arm versus no-anakinra arm) and Figure 6 (post-csDMARD arm versus no-anakinra arm). For both comparisons, the NMB is most sensitive to the assumptions around the probability of maintaining or achieving remission and discontinuing treatments. None of the analyses generated a negative NMB.

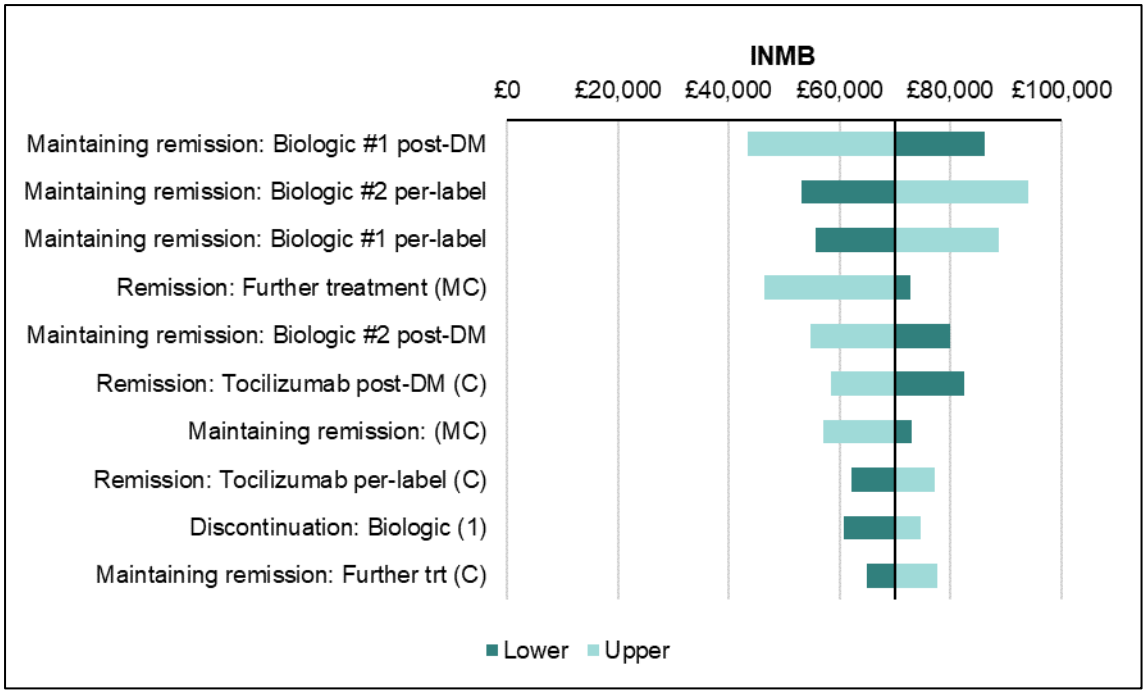


Figure 5 Tornado diagram – per-label arm versus no-anakinra arm

C=chronic; DM=(conventional synthetic) disease-modifying anti-rheumatic drug; INMB=incremental net monetary benefit; MC=monocyclic; trt=treatment
Source: CS, Figure 14

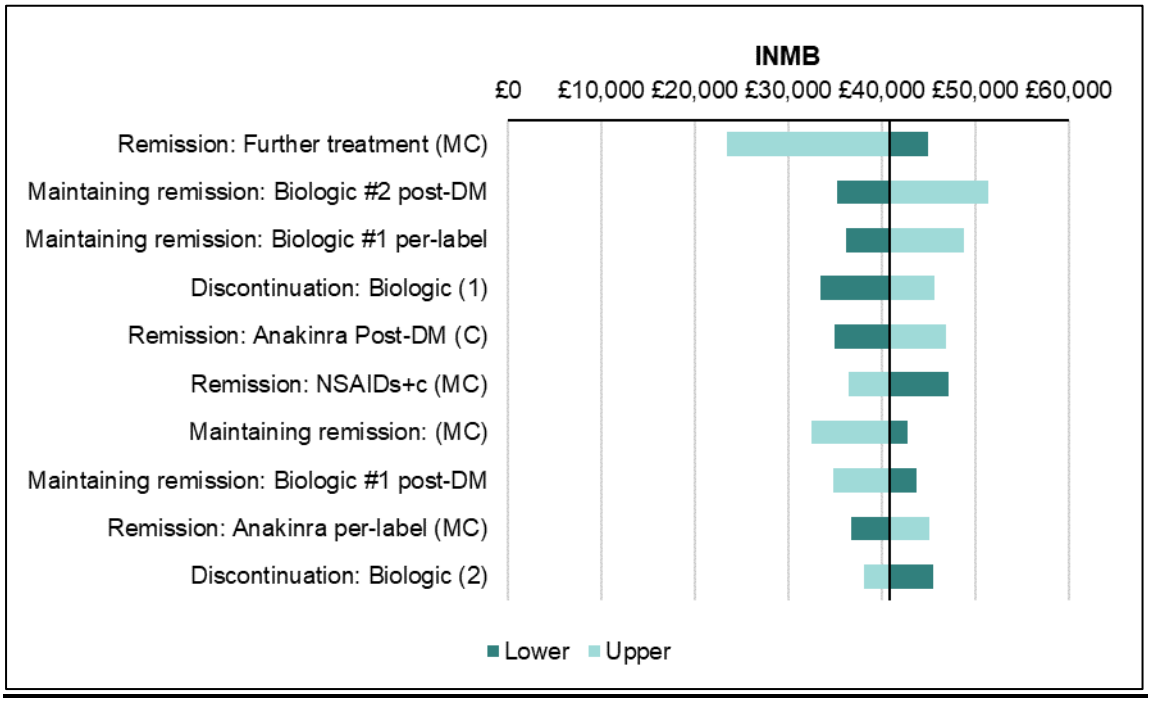


Figure 6 Tornado diagram – post-csDMARD arm versus no-anakinra arm

c=systemic corticosteroid; C=chronic; DM=conventional synthetic disease-modifying anti-rheumatic drug; INMB=incremental net monetary benefit; MC=monocyclic; NSAIDs=non-steroidal anti-inflammatory drugs
Source: CS, Figure 15

Probabilistic sensitivity analysis

The company undertook a probabilistic sensitivity analysis (PSA) to derive mean costs, QALYs and LYG. Model parameters were randomly sampled within bounds that the company deemed plausible and the model was run 1,000 times. The results from the company PSA (Table 23) are similar to the company's base case deterministic analysis results. The scatter plot is provided in Figure 7. The company did not provide a cost effectiveness acceptability curve as in each of the 1,000 probabilistic scenarios the use of per-label anakinra was shown to be the cheapest and, in all but approximately 5.5% of iterations, provided the most QALYs.

Table 23 Average results based on the probabilistic sensitivity analysis

Model arm	Total			Incremental		
	Costs	QALYs	LYG	Costs	QALYs	LYG
No-anakinra	£254,330	11.419	28.364			
Post-csDMARD	£218,425	11.778	28.644	-£35,905	0.359	0.280
Per-label	£195,913	12.074	28.865	-£22,512	0.296	0.221

csDMARD=conventional synthetic disease-modifying anti-rheumatic drug; LYG=life years gained; QALY=quality adjusted life year; ICER=incremental cost effectiveness ratio
Source: CS, Table 71

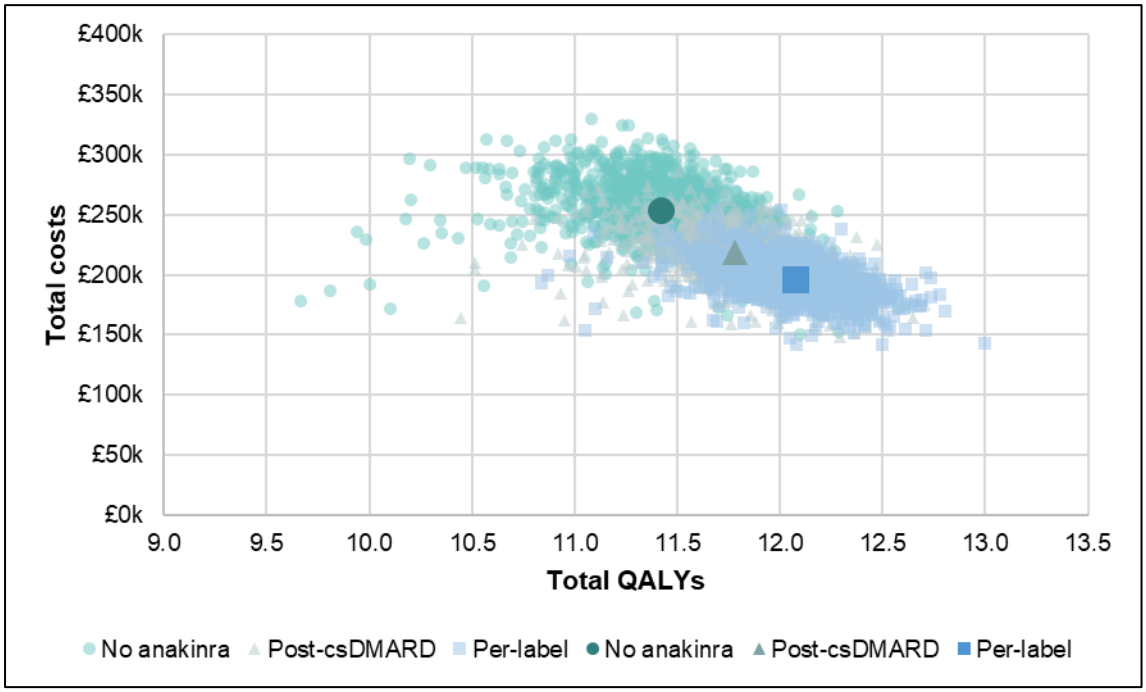


Figure 7 Probabilistic sensitivity analysis scatterplot

csDMARD=conventional synthetic disease-modifying anti-rheumatic drug; QALY=quality adjusted life year
Source: CS, Figure 16

5.3.11 Scenario analyses

The company undertook 48 scenario analyses to explore the impact of changes to key model parameters on cost effectiveness results. A list and description of all the scenario analyses is provided in Table 24. Full results are provided in the CS (Tables 73-92) and results from the

scenarios that led to the highest and lowest costs, QALYs and NMBs are provided in Table 25. For all treatment strategies, the lowest costs and QALYs were achieved when the time horizon was set to 5 years and the highest costs and QALYs were achieved when the discount rate for costs and QALYs was set to 0%. Further, the highest and lowest NMBs were also achieved for these scenarios, except for the comparison of post-csDMARD arm versus no-anakinra arm when the highest NMB occurred when patients who were no longer in remission returned to their first treatment.

Table 24 Scenario analyses performed

Scenario	Description
Analysis perspective	
Time horizon	Varied time horizon from 5 to 30 years
Discounting	Varied discount rates for costs and QALYs
Patient characteristics	
% Female	Assume % female per clinical studies of anakinra
Age	Vary average age for SJIA and AOSD patients
Weight	Vary average weight for SJIA and AOSD patients
Disease course	Vary ratio of monocyclic to chronic patients
Treatment pathway	
Loss of remission	Assume patients return to first treatment or progress to next treatment after loss of remission
First biologic	For per-label and post-csDMARD arms, vary proportion of patients that first receive anakinra or tocilizumab
Duration of treatment	Assume lifelong use of anakinra and/or tocilizumab
Clinical inputs and assumptions	
Anakinra efficacy	Use alternative source for remission probability
Utility source	Apply different utility equations from TA238[48]
Age-adjustment	Disable age-adjusted utility values
AE disutilities	Disable disutility due to ISRs and double its impact
Unresolved utility	Vary utility value for patients in ‘unresolved’ state
Macrophage activation syndrome	
Baseline risk of MAS	Uplift probability of experiencing MAS
Relative risk of MAS	Vary relative risk of developing MAS if receiving anakinra
MAS-related death	Increase probability MAS is fatal and disutility
Duration of MAS	Vary duration over which MAS impacts utility
Costs	
Other treatment	Vary cost of other treatment used
Tocilizumab PAS	Vary volume of assumed simple PAS discount for tocilizumab

AE=adverse event; AOSD=adult-onset Still’s disease; csDMARD=conventional synthetic disease-modifying anti-rheumatic drug; ISR=injection site reaction; MAS=macrophage activation syndrome; PAS=patient access scheme; QALY=quality adjusted life year; SJIA=systemic juvenile idiopathic arthritis; TA=technology appraisal
Source: CS, Table 72

Table 25 Highest and lowest result from company scenario analyses

Totals						Incremental NMBs		
No-anakinra		Per-label anakinra		Post-csDMARD		Per-label versus		Post-csDMARDs
Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	No-anakinra	Post-csDMARDs	No-anakinra
Time horizon: 5 years								
£41,647	3.03	£33,381	3.14	£35,540	3.09	£10,469	£3,280	£7,189
Discount rate: 1.5%								
£345,775	14.42	£270,867	15.30	£302,293	14.88	£92,601	£39,803	£52,798
Treatment given following loss of remission: return to first treatment								
£219,376	11.55	£138,228	12.35	£160,798	12.04	£97,179	£28,637	£68,542

csDMARDs=conventional synthetic disease-modifying anti-rheumatic drugs; ICER=incremental cost effectiveness ratio; ITT=intention to treat; OS=overall survival; NMB=incremental net monetary benefit;PD=progressed disease; PFS=progression-free survival; QALY=quality adjusted life year
Source: CS, Table 73, Table 74 and Table 79

5.3.12 Subgroup analyses

Subgroup analyses were carried out to generate separate cost effectiveness results for the SJIA and AOSD subpopulations. Due to age-adjusted utilities being used in the base case, patients with SJIA gained more QALYs than those with AOSD. In addition, total costs for patients with SJIA were slightly higher than those for patients with AOSD. The company explained that for this patient group, slightly higher health care costs (due to the increased cost of paediatric appointments) offset lower drug costs (due to differences in weight and dosing).

Table 26 Company's subgroup analyses, fully incremental analysis

Treatment strategy	Total			Incremental			ICER	
	Costs	QALYs	LYs	Costs	QALYs	LYs	versus Post-csDMARD	versus no-anakinra
Base case analysis (62.5% patients with SJIA and 37.5% patients with AOSD)								
No-anakinra	£258,107	11.304	28.202				Dominated	-
Post-csDMARD	£224,343	11.657	28.509	-£33,764	0.353	0.307	-	Dominant
Per-label	£201,317	11.970	28.774	-£23,026	0.313	0.265	Dominant	Dominant
100% AOSD patients								
No-anakinra	£254,071	10.698	27.549				Dominated	-
Post-csDMARD	£217,673	11.024	27.843	-£36,399	0.327	0.294	-	Dominant
Per-label	£196,782	11.322	28.102	-£20,891	0.297	0.259	Dominant	Dominant
100% SJIA patients								
No-anakinra	£260,529	11.668	28.593				Dominated	-
Post-csDMARD	£228,345	12.036	28.909	-£32,184	0.368	0.316	-	Dominant
Per-label	£204,038	12.359	29.178	-£24,307	0.322	0.269	Dominant	Dominant

AOSD=adult-onset Still's disease; csDMARD=conventional synthetic disease-modifying anti-rheumatic drug; ICER=incremental cost effectiveness ratio; LY=life year; QALY=quality-adjusted life year; SJIA=systemic juvenile idiopathic arthritis
Source: CS, Table 93

5.3.13 Model validation and face validity check

To validate the model, the company carried out internal quality control checks. In addition, independent quality control checks were conducted by a research consultancy not involved with model development. The modelling assumptions were presented at two advisory board meetings. The purpose of the advisory boards was to gain insight into the treatment of Still's disease within modern UK clinical practice.

5.4 ERG detailed critique of company economic model

5.4.1 NICE Reference Case checklist

Table 27 NICE Reference Case checklist completed by ERG

Attribute	Reference case	Does the de novo economic evaluation match the reference case?
Decision problem	The scope developed by NICE	Partially. The company's cost effectiveness results relate to treatment with anakinra in place of, or after, treatment with csDMARDs
Comparator(s)	As listed in the scope developed by NICE	Yes
Perspective costs	NHS and PSS	Partially. NHS only
Perspective benefits	All direct health effects, whether for patients or, when relevant, carers	Yes
Form of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies	No. 30 years is not sufficiently long to reflect the full differences in costs or outcomes between the technologies being compared
Synthesis of evidence on outcomes	Based on systematic review	Not applicable
Outcome measure	Health effects should be expressed in QALYs	Yes
Health states for QALY	Standardised and validated instrument. The EQ-5D is the preferred measure of health-related quality of life in adults	Partially. Mean CHAQ scores used in a previous NICE appraisal (TA238)[48] were converted to EQ-5D-3L utility values using a mapping algorithm
Benefit valuation	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Yes
Discount rate	The same annual rate for both costs and health effects (3.5%)	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Sensitivity analysis	Probabilistic sensitivity analysis	Yes

CHAQ=Childhood Health Assessment Questionnaire; csDMARDs=conventional synthetic disease-modifying anti-rheumatic drugs; EQ-5D-3L=EuroQol-5 Dimensions-3 levels; NMA=network meta-analysis; NSAIDs=non-steroidal anti-inflammatory drugs; QALY=quality adjusted life year; HRQoL=health-related quality of life; PSS=personal social services; TA=technology appraisal

5.4.2 Drummond checklist

Table 28 Critical appraisal checklist for the economic analysis completed by the ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	No	Published evidence for the effectiveness of treatments was only established over a maximum follow-up period of 24 weeks in small numbers of patients who were not relevant to the decision problem described in the final scope[1] issued by NICE
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	No	The ERG has concerns about the reliability of the algorithm that was used to map CHAQ mean scores onto EQ-5D-3L mean scores
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	
Did the presentation and discussion of study results include all issues of concern to users?	Partly	The company has provided extensive scenario and sensitivity analysis; however, discussion of results was limited

CHAQ=Childhood Health Assessment Questionnaire; EQ-5D-3L=EuroQol-5 Dimensions-3 levels

5.4.3 Overview

The ERG commends the company for attempting to produce an economic model that addresses the complex decision problem set out in the final scope[1] issued by NICE. The ERG confirms that the model parameters accurately reflect the parameter values described in the CS.

The ERG considers that the cost effectiveness results generated by the company model are of limited use to decision makers. This is primarily due to the absence of relevant robust clinical effectiveness evidence (see Section 4.5). However, even if relevant and robust clinical effectiveness evidence were available, the ERG considers that inherent structural flaws mean that the company model cannot be used to generate meaningful cost effectiveness results.

5.4.4 Structural limitations of the company model

Within the model, treatment switching is set at a fixed probability per weekly cycle for patients who have not achieved remission. This means that it is possible for patients to remain on a treatment that is achieving remission for the whole of the model time horizon. For example, as only 1.12% of patients receiving their first bDMARD treatment are assumed to stop treatment during each cycle, after 1 year, if the treatment has not resulted in remission, over 55.7% of these patients will still be receiving this treatment. Further, after 2 years, 33.0% of these patients will still be receiving their first bDMARD treatment despite no remission. The ERG considers that this is unrealistic.

The company model also allows patients to remain in the following pathway loop for the whole model time horizon: start a treatment, achieve remission, experience relapse and return to the same treatment before entering remission again. Whilst this loop is clinically plausible for patients who are in remission for prolonged periods, there is nothing in the model to stop this loop happening 26 times per year for the whole model time horizon. Clinical advice to the ERG is that this latter scenario is implausible.

In addition, in the company model, it is assumed that 50% of patients who are prescribed a bDMARD will remain on that treatment during remission. However, when these patients relapse, it is assumed that they will return to treatment with the same bDMARD that they were taking prior to relapse and that they will have the same probability of achieving remission as they had prior to the relapse. This assumption is illogical given that these patients had been receiving the treatment continuously whilst in remission and had relapsed whilst on that treatment.

The patient pathway loop previously described also means that, over time, patients in specific health states become increasingly heterogeneous. However, the model health state transition probabilities are invariant to the changing nature of the health state populations. This means that the extent to which health state transition probabilities reflect the transition probabilities for the health state population decrease over time. For example, during the early model cycles, patients in the remission states will, predominantly, be those who have achieved remission for the first time. However, during later model cycles, patients in these states are a mix of patients who maintained remission after initial treatment and patients with a history of a high, or low, number of relapses.

The structural issues mean that no robust ICERs per QALY gained can be generated by the company model for any treatment comparison. The solution would be to greatly increase the number of health states or, more appropriately, given the complexity of the disease course, to model the disease using a patient level simulation model. Developing a patient level simulation model is beyond the remit of the ERG and, even if it were within the ERG's remit, there is insufficient relevant robust clinical evidence to populate such a model.

5.4.5 Other model issues

In addition to the structural issues described in Section 5.4.4, the company has made a number of parameter assumptions and modelling choices that the ERG considers are inaccurate or implausible. Whilst it would be possible to generate revised ICERs per QALY gained using accurate and/or more plausible data, making these changes to the current company model would, potentially, lead to misleading results as the impact of these changes in an appropriately structured model is not known. The ERG has described the non-structural issues to highlight the additional uncertainty associated with the ICERs per QALY gained presented in the CS.

Underestimation of the effectiveness of prior treatments in the post-csDMARD arm

The company has obtained the remission rate for patients with monocyclic Still's disease who are treated with csDMARDs from the Nordstrom[57] publication. The company has calculated this rate to be 0.93% and has assumed that the equivalent probability for patients with chronic Still's disease is 0%. However, in the publication by Nordstrom,[57] it is not stated whether patients in the trial had monocyclic, polycyclic or chronic disease. Since patients with monocyclic Still's disease represent only 25% of the Still's disease population, the company's assumption means that treatment with csDMARDs is completely ineffective in 75% of patients with Still's disease. Clinical advice to the ERG suggests that this assumption is implausible.

Differences in effectiveness of bDMARDS in the second- and third-line setting

Treatment with csDMARDs and bDMARDs leads to remission in some patients. If the availability of either of these treatments is limited then this leads to an increase in the rate at which patients run out of available efficacious treatments, which is the definition provided in the CS for unresolved Still's disease (CS, p111). So, removing either csDMARDs or bDMARDs as a treatment option from the model results in an increase in the proportion of patients in the unresolved health state. However, at every point in the model, the proportion of patients in the unresolved health state is lower in the per-label arm (where csDMARD is removed) than in the post-csDMARD arm (where no treatment is removed). Thus, the removal of a potentially efficacious treatment (csDMARD) from the pathway leads to an increase in the proportion of patients having prolonged remission. The ERG notes that this can only be the case if earlier treatment with bDMARDs results in higher remission rates (4.4% in the model) than later treatment (2.9%). Given that the evidence presented by the company to support this assumption is not robust, the ERG considers that the differential effectiveness of bDMARDs by treatment line should not have been modelled in the base case, rather it should have been explored using a scenario analysis.

Canakinumab as a treatment option in the third-line setting and for patients with unresolved disease

The company's base case analysis does not include canakinumab as a treatment option in the third-line setting, or as an option for patients with unresolved disease. The company's justification is that canakinumab is not recommended in current NHS Clinical Commissioning policies for treating SJIA or AOSD.[21,47] The ERG notes that the final scope[1] issued by NICE includes canakinumab as a comparator in the third-line setting, therefore, treatment with canakinumab should have been considered by the company. Clinical advice to the ERG is that canakinumab would be considered once all other treatment options had been exhausted.

Appropriateness of the model time horizon

The ERG considers that the 30-year model time horizon is not long enough to reflect all the important differences in costs and outcomes. The ERG notes that 89% and 78% of patients with SJIA and AOSD respectively are alive at the end of the 30-year time horizon. The health state occupancy of patients who are still alive at 30 years varies across the model arms (for the SJIA and AOSD subpopulations), so the accrued costs and QALYs across the model arms would also vary if the time horizon were extended beyond 30 years.

5.5 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

In the company base case analysis, the per-label arm is estimated to dominate the post-csDMARD arm by generating an additional 0.313 QALYs and leading to a cost saving of £23,026. The ERG, however, considers that the weaknesses of the available clinical evidence and model structural issues mean that company's cost effectiveness results are not a suitable basis for decision making.

As it is beyond the remit of the ERG to address the structural issues, and as any changes to the model to resolve areas of inaccuracy or implausibility would, potentially, lead to misleading results, the ERG has not undertaken any additional or exploratory analyses using the company model. However, the ERG has undertaken cost minimisation analyses (CMAs) comparing treatment of SJIA and AOSD with anakinra versus tocilizumab and versus canakinumab in the third-line setting. The ERG has used an approach that is similar to that used to generate results for consideration as part of the Scottish Medicines Consortium[106] assessment of anakinra for treating Still's disease. The ERG considers that there is insufficient evidence to undertake a CMA of anakinra in the first- or second-line settings.

5.5.1 Cost minimisation analysis for the use of anakinra versus tocilizumab and canakinumab in the third-line setting

To undertake a CMA of the bDMARDs, the following assumptions of equivalence between the three treatments (anakinra, tocilizumab and canakinumab) are necessary:

- effectiveness in achieving and maintaining remission
- AE rates
- treatment discontinuation rates.

Evidence for SIJA

Tarp[58] carried out a NMA to investigate the efficacy (measured using ACR Pedi 30[76]) and safety (SAEs) of bDMARDs for treating JIA (see Table 10). The ERG considers the Tarp[58] findings to be limited due to differences in trial methods, the outcome reported is not a relevant measure of remission and sample sizes were small (see Section 4.2.3). The ERG does not consider that the authors' conclusions i.e., that their study showed that the three bDMARDs were equivalent in efficacy and safety) are robust. However, clinical advice to the ERG is that experience of using bDMARDs in the NHS is that it is likely that the efficacy, SAE and discontinuation rates associated with the three treatment are very similar.

Table 29 Results of the Tarp NMA: anakinra versus tocilizumab and canakinumab

Comparison (anakinra versus)	Events/patients (%)			Relative, OR (95% CI)	Quality of trial
	Anakinra	Tocilizumab	Canakinumab		
Modified ACR Pedi 30					
Canakinumab	11/12 (92)	-	35/43 (81)	0.55 (0.04 to 6.83)	Low
Tocilizumab	11/12 (92)	57/75 (76)	-	0.69 (0.06 to 8.18)	Low
Serious adverse events					
Canakinumab	0/12 (0)	-	2/43 (5)	Not estimable	Very low
Tocilizumab	0/12 (0)	3/75 (4)	-	Not estimable	Very low

ACR Pedi 30=American College of Rheumatology 30% improvement; CI=confidence interval; OR=odds ratio
Source: CS, Table 46 (corrected by the ERG)

Evidence for AOSD

There is no published evidence for relative efficacy, SAEs or discontinuation rates for the comparison of the effectiveness of anakinra versus tocilizumab or anakinra versus canakinumab for patients with AOSD. Clinical advice to the ERG is the same as the advice given for SJIA, i.e., that there is unlikely to be any difference in efficacy, SAEs or discontinuation rates between anakinra, tocilizumab and canakinumab.

Company's assumptions that apply to both SJIA and AOSD

The company has assumed that treatment with anakinra, tocilizumab and canakinumab are equivalent in terms of efficacy, SAE and discontinuation rates (CS, Section B.3.3.1.3, Section B.3.3.1.4, Table 53 and Table 55). Assuming equivalence in efficacy, SAE rates and discontinuation rates for anakinra, tocilizumab and canakinumab means that, for the CMA, the only costs that need to be considered for each treatment are drug related costs (purchase, administration and monitoring). In the company model, the administration costs for SC and IV treatments are £0 and £154 per administration respectively (CS, Section B.3.5.4). In terms of monitoring costs, the company assumed that the only difference between the three treatments was that patients receiving tocilizumab require lipid tests (at a cost of £2.51[105]) 18 times per year. Clinical advice to the ERG is that this is a reasonable assumption for some patients, however, the frequency of lipid tests for the average patient is likely to be lower than 18 times per year.

Costs of drugs for treating SJIA

Anakinra and canakinumab are administered subcutaneously, whilst tocilizumab can be administered by either SC injection or via IV infusion. Clinical advice to the ERG suggests that 80% of SJIA patients who are prescribed tocilizumab will receive IV tocilizumab, whilst the remaining 20% will receive tocilizumab via SC injection. The cost of SC administration was estimated to be zero and £154 for IV administration (patients with SJIA patients receiving IV tocilizumab).

The SmPC[107] for treatment with anakinra specifies a different dosing regimen for patients with SJIA weighing less than 50kg (1-2mg/kg subcutaneous injection every day) and for those weighing 50kg or more (100mg subcutaneous injection every day). The SmPC[108] for tocilizumab specifies different dosing regimens for patients with SJIA weighing less than 30kg (162mg SC injection every 2 weeks or 12mg/kg IV infusion every 2 weeks) and for those weighing 30kg or more (162mg SC injection every week or 8mg/kg IV infusion every 2 weeks). The ERG has, therefore, undertaken two CMAs for patients with SJIA, one for patients weighing 25kg and one for patients weighing 50kg. Each analysis has been undertaken assuming that, in line with the instructions in the SmPCs,[107-109] unused medication left in a syringe is wasted.

Using list prices for anakinra, tocilizumab and canakinumab, the results presented in Table 30 show that weekly treatment with anakinra costs £106.67 less than treatment with tocilizumab (80% receiving IV tocilizumab) and £2,298.34 less than treatment with canakinumab in patients weighing 25kg. Weekly treatment with anakinra costs £129.50 less per week than treatment with tocilizumab (80% receiving IV tocilizumab) and £4,780.29 less than treatment with canakinumab in patients weighing 50kg.

Table 30 Mean drug cost per week for patients with SJIA, using list prices for anakinra, tocilizumab and canakinumab

		Anakinra (SC)	Tocilizumab (IV)	Tocilizumab (SC)	Canakinumab (SC)
Unit costs	Vials/syringes per pack	7	1	4	1
	Cost per pack	£183.61 (100mg/vial)	£256.00 (200mg/vial)	£913.12 (162mg/ syringe)	£9,927.80 (150mg/vial)
	Cost per vial/syringe	£26.23	£256.00	£228.28	£9,927.80
	Cost of administration	-	£154.46	-	-
	Cost of lipid test	-	£2.51	£2.51	-
Drug costs (weight=25kg)	Administrations per week	7.0 (once per day)	0.5 (once every 14 days)	0.5 (once every 14 days)	0.25 (once every 28 days)
	Units per administration	1.5mg per kg (<50kg)	12.0mg per kg (<30kg)	162.0mg fixed dose (<30kg)	4.0mg per kg (up to 300mg max)
	Vials/syringes per administration	1.00	2.00	1.00	1.00
	Cost per week	**£183.61**	**£256.00**	**£114.14**	**£2,481.95**
Drug costs (weight=50kg)	Administrations per week	7.0 (once per day)	0.5 (once every 14 days)	1.0 (once every 7 days)	0.25 (once every 28 days)
	Units per administration	100mg fixed dose (50kg+)	8.0mg per kg (30kg+)	162.0mg fixed dose (30kg+)	4.0mg per kg (up to 300mg max)
	Vials/syringes per administration	1.00	2.00	1.00	2.00
	Cost per week	**£183.61**	**£256.00**	**£228.28**	**£4,963.90**
Administration costs	% incurring cost	-	100.0%	-	-
	Cost per week	£0.00	£77.23	£0.00	£0.00
Monitoring costs	Lipid tests per year	-	18.00	18.00	-
	Lipid tests per week	-	0.34	0.34	-
	Cost per week	**-**	**£0.87**	**£0.87**	**-**
Total cost per week (weight=25kg)		**£183.61**	**£334.10**	**£115.01**	**£2,481.95**
Total cost per week (weight=50kg)		**£183.61**	**£334.10**	**£229.15**	**£4,963.90**
Total cost per week (weight=25kg): assuming 80% of patients receive IV tocilizumab		**£183.61**	**£290.28**		**£2,481.95**
Total cost per week (weight=50kg): assuming 80% of patients receive IV tocilizumab		**£183.61**	**£313.11**		**£4,963.90**

IV=intravenous; kg=kilogram; mg=milligram; SC=subcutaneous
Note: intravenous tocilizumab is available as 80mg/4ml syringe at £102.40, 200mg/10ml syringe at £256.00 and 400mg/20ml syringe at £512.00; subcutaneous tocilizumab is available as 4 syringes of162mg/0.9ml at £913.12 (BNF).[100] Clinical advice to the ERG suggests that, although some patients may require up to 18 lipid tests per year, the average number of tests per patient is less than 18; Source: ERG calculations

Cost of drugs for treating AOSD

To calculate the mean drug cost of treatment with anakinra, tocilizumab and canakinumab, the ERG has assumed, in line with the SmPC for each treatment,[107-109] that the remaining contents of used syringes are discarded after each treatment administration. Patient weight only affects the dose of canakinumab; patients should be treated with 4.0mg/kg, up to a maximum of 300mg (the dose for a 75kg patient), every 4 weeks. As vials cannot be stored or shared, any adult weighing over 37.5kg will require two vials and no patient will require more than two vials. The ERG has, therefore, assumed that all patients will require two vials of canakinumab per administration regardless of their weight.

Anakinra and canakinumab are only administered subcutaneously and whilst tocilizumab may be administered by either SC injection or via IV infusion, clinical advice to the ERG is that all patients with AOSD will receive SC tocilizumab. As a consequence, the cost of drug administration has been set to zero for all treatments.

Using list prices for anakinra, tocilizumab and canakinumab, the results presented in Table 31 show that weekly treatment costs with anakinra are £45.54 less than treatment with tocilizumab and £4,780.29 less than treatment with canakinumab.

Table 31 Mean drug cost per week for patients with AOSD, using list prices for anakinra, tocilizumab and canakinumab

		Anakinra (SC)	Tocilizumab (SC)	Canakinumab (SC)
Unit costs	Syringes per pack	7	1	1
	Cost per pack	£183.61 (100mg fixed dose per syringe)	£913.12 (162mg per syringe)	£9,927.80 (150mg per syringe)
	Cost per syringe	£26.23	£228.28	£9,927.80
	Cost of lipid test	-	£2.51	-
Drug costs	Administrations per week	7.0 (i.e., once per day)	1.0 (i.e., once every 7 days)	0.25 (i.e., once every 28 days)
	Units per administration	100mg fixed dose (50kg+)	162mg fixed dose (30kg+)	4.0mg per kg (up to 300mg max)
	Vials/syringes per administration	1.00	1.00	2.00
	Cost per week	**£183.61**	**£228.28**	**£4,963.90**
Monitoring costs	Lipid tests per year	-	18.00	-
	Lipid tests per week	-	0.34	-
	Cost per week	-	£0.87	-
Total cost per week (weight=75kg)		**£183.61**	**£229.15**	**£4,963.90**

AOSD=adult onset Still's disease; kg=kilogram; mg=milligram; SC=subcutaneous
Note: clinical advice to the ERG suggests that, although some patients may require up to 18 lipid tests per year, the average number of tests per patient is less than 18
Source: ERG calculations

5.6 Conclusions of the cost effectiveness section

The ERG commends the company for producing a model that is easy to understand and acknowledges that the company has made significant efforts to use the limited clinical effectiveness evidence available. However, the available clinical effectiveness evidence is not only weak, it also does not directly relate to any of the treatment comparisons specified in the final scope[1] issued by NICE. Furthermore, the ERG identified a number of structural assumptions that render modelled treatment pathways implausible and considers that a number of parameter assumptions and modelling choices made by the company are inaccurate or implausible. Whilst it would have been possible for the ERG to generate alternative cost effectiveness results using ERG preferred parameter assumptions and modelling choices, the model structural flaws mean that such results would, at best, be uninformative and, at worst, misleading.

The ERG considers that company model results cannot be used to inform decisions on the cost effectiveness of treatment with anakinra in the first-, second- or third-line settings. A discrete event simulation model would be needed to model the complexities of the Still's disease pathway but data to populate such a model are not available. In the absence of a robust economic model, the ERG has undertaken CMAs. Clinical advice to the ERG suggests that treatment with anakinra, tocilizumab or canakinumab can be assumed to be equally effective and be associated with the same SAE profiles and discontinuation rates in the third-line setting. Results from the ERG's CMAs show that, using list prices, treatment with anakinra is cheaper than treatment with tocilizumab and canakinumab. No conclusions can be drawn on the cost effectiveness of anakinra in the first-line setting (versus NSAIDs and/or steroids) or in the second-line setting (versus csDMARDs).

6 REFERENCES

1. National Institute for Health and Care Excellence (NICE). Anakinra for treating Still's disease [ID1463]; Final Scope. London: NICE 2019.
2. Kearsley-Fleet L, Beresford MW, Davies R, De Cock D, Baildam E, Foster HE*, et al.* Short-term outcomes in patients with systemic juvenile idiopathic arthritis treated with either tocilizumab or anakinra. Rheumatology (Oxford). 2019; 58:94-102.
3. Singh-Grewal D, Schneider R, Bayer N, Feldman BM. Predictors of disease course and remission in systemic juvenile idiopathic arthritis: significance of early clinical and laboratory features. Arthritis Rheum. 2006; 54:1595-601.
4. Bywaters EG. Still's disease in the adult. Ann Rheum Dis. 1971; 30:121-33.
5. Deslandre J. Systemic-onset juvenile idiopathic arthritis. 2007; Available from: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=85414. Accessed November 2019.
6. Bhargava J, Panginikkod S. Still Disease 2019; Available from: https://www.ncbi.nlm.nih.gov/books/NBK538345/#_NBK538345_pubdet_. Accessed November 2019.
7. Vercruysse F, Barnetche T, Lazaro E, Shipley E, Lifermann F, Balageas A*, et al.* Adult-onset Still's disease biological treatment strategy may depend on the phenotypic dichotomy. Arthritis Research & Therapy. 2019; 21:53.
8. Maria AT, Le Quellec A, Jorgensen C, Touitou I, Riviere S, Guilpain P. Adult onset Still's disease (AOSD) in the era of biologic therapies: dichotomous view for cytokine and clinical expressions. Autoimmunity reviews. 2014; 13:1149-59.
9. Gerfaud-Valentin M, Jamilloux Y, Iwaz J, Seve P. Adult-onset Still's disease. Autoimmunity reviews. 2014; 13:708-22.
10. Pruunsild C, Uibo K, Liivamagi H, Tarraste S, Talvik T, Pelkonen P. Incidence of juvenile idiopathic arthritis in children in Estonia: a prospective population-based study. Scand J Rheumatol. 2007; 36:7-13.
11. Pelkonen PM, Jalanko HJ, Lantto RK, Makela AL, Pietikainen MA, Savolainen HA*, et al.* Incidence of systemic connective tissue diseases in children: a nationwide prospective study in Finland. J Rheumatol. 1994; 21:2143-6.
12. Modesto C, Anton J, Rodriguez B, Bou R, Arnal C, Ros J*, et al.* Incidence and prevalence of juvenile idiopathic arthritis in Catalonia (Spain). Scand J Rheumatol. 2010; 39:472-9.
13. Malleson PN, Fung MY, Rosenberg AM. The incidence of pediatric rheumatic diseases: results from the Canadian Pediatric Rheumatology Association Disease Registry. J Rheumatol. 1996; 23:1981-7.
14. Kaipiainen-Seppanen O, Savolainen A. Changes in the incidence of juvenile rheumatoid arthritis in Finland. Rheumatology (Oxford). 2001; 40:928-32.
15. Huemer C, Huemer M, Dorner T, Falger J, Schacherl H, Bernecker M*, et al.* Incidence of pediatric rheumatic diseases in a regional population in Austria. J Rheumatol. 2001; 28:2116-9.
16. Berntson L, Andersson Gare B, Fasth A, Herlin T, Kristinsson J, Lahdenne P*, et al.* Incidence of juvenile idiopathic arthritis in the Nordic countries. A population based study with special reference to the validity of the ILAR and EULAR criteria. J Rheumatol. 2003; 30:2275-82.
17. National Institute for Health and Care Excellence (NICE). Evidence summary [ESNM36]: Systemic juvenile idiopathic arthritis: canakinumab. London: NICE; 2014; Available from: https://www.nice.org.uk/advice/esnm36/chapter/Key-points-from-the-evidence. Accessed Nov 2019.
18. SOBI. Data on File: Advisory Board Meeting Minutes (September 2019)2019.
19. Mahroum N, Mahagna H, Amital H. Diagnosis and classification of adult Still's disease. J Autoimmun. 2014; 48-49:34-7.

20. Gerfaud-Valentin M, Maucort-Boulch D, Hot A, Iwaz J, Ninet J, Durieu I*, et al.* Adult-onset Still disease: manifestations, treatment, outcome, and prognostic factors in 57 patients. Medicine (Baltimore). 2014; 93:91-9.
21. NHS England. Clinical Commissioning Policy: Anakinra/tocilizumab for the treatment of Adult-Onset Still's Disease refractory to second-line therapy (adults). 2018; Available from: https://www.england.nhs.uk/publication/clinical-commissioning-policy-anakinra-tocilizumab-for-the-treatment-of-adult-onset-stills-disease-refractory-to-second-line-therapy-adults/. Accessed November 2019.
22. Ruscitti P, Cipriani P, Masedu F, Iacono D, Ciccia F, Liakouli V*, et al.* Adult-onset Still's disease: evaluation of prognostic tools and validation of the systemic score by analysis of 100 cases from three centers. BMC Med. 2016; 14:194.
23. Lebrun D, Mestrallet S, Dehoux M, Golmard JL, Granger B, Georgin-Lavialle S*, et al.* Validation of the Fautrel classification criteria for adult-onset Still's disease. Seminars in arthritis and rheumatism. 2018; 47:578-85.
24. Efthimiou P, Paik PK, Bielory L. Diagnosis and management of adult onset Still's disease. Annals of the rheumatic diseases. 2006; 65:564-72.
25. Svantesson H, Akesson A, Eberhardt K, Elborgh R. Prognosis in juvenile rheumatoid arthritis with systemic onset. A follow-up study. Scand J Rheumatol. 1983; 12:139-44.
26. Spiegel LR, Schneider R, Lang BA, Birdi N, Silverman ED, Laxer RM*, et al.* Early predictors of poor functional outcome in systemic-onset juvenile rheumatoid arthritis: a multicenter cohort study. Arthritis Rheum. 2000; 43:2402-9.
27. Packham JC, Hall MA. Long-term follow-up of 246 adults with juvenile idiopathic arthritis: functional outcome. Rheumatology. 2002; 41:1428-35.
28. Calabro JJ, Holgerson WB, Sonpal GM, Khoury MI. Juvenile rheumatoid arthritis: a general review and report of 100 patients observed for 15 years. Seminars in arthritis and rheumatism. 1976; 5:257-98.
29. Bowyer SL, Roettcher PA, Higgins GC, Adams B, Myers LK, Wallace C*, et al.* Health status of patients with juvenile rheumatoid arthritis at 1 and 5 years after diagnosis. J Rheumatol. 2003; 30:394-400.
30. Ansell BM. Long-term follow-up of juvenile chronic polyarthritis. Verhandlungen der Deutschen Gesellschaft fur Rheumatologie. 1976; 4:1-3.
31. Modica RF, Lomax KG, Batzel P, Cassanas A. Impact of systemic juvenile idiopathic arthritis/Still's disease on adolescents as evidenced through social media posts. Open Access Rheumatol. 2018; 10:73-81.
32. Gledhill J, Rangel L, Garralda E. Surviving chronic physical illness: psychosocial outcome in adult life. Arch Dis Child. 2000; 83:104-10.
33. Mitrovic S, Fautrel B. Complications of adult-onset Still's disease and their management. Expert Review of Clinical Immunology. 2018; 14:351-65.
34. Arthritis Foundation. Systemic Juvenile Idiopathic Arthritis treatment. 2019; Available from: https://www.arthritis.org/about-arthritis/types/juvenile-idiopathic-arthritis-jia/treatment.php. Accessed November 2019.
35. Ferrara G, Petrillo MG, Giani T, Marrani E, Filippeschi C, Oranges T*, et al.* Clinical use and molecular action of corticosteroids in the pediatric age. Int J Mol Sci. 2019; 20:444.
36. Benjamin O, Lappin SL. Disease Modifying Anti-Rheumatic Drugs (DMARD). StatPearls Publishing; 2019; Available from: https://www.ncbi.nlm.nih.gov/books/NBK507863/. Accessed November 2019.
37. Shenoi S, Horneff G, Cidon M, Ramanan AV, Kimura Y, Quartier P*, et al.* The burden of systemic juvenile idiopathic arthritis for patients and caregivers: an international survey and retrospective chart review. Clin Exp Rheumatol. 2018; 36:920-8.
38. Strand V, Khanna D. The impact of rheumatoid arthritis and treatment on patients' lives. Clin Exp Rheumatol. 2010; 28:S32-40.
39. Brouwer WB, van Exel NJA, Van De Berg B, Dinant HJ, Koopmanschap MA, van den Bos GA. Burden of caregiving: evidence of objective burden, subjective burden, and

quality of life impacts on informal caregivers of patients with rheumatoid arthritis. Arthritis Care & Research. 2004; 51:570-7.
40. Bojke L, Spackman E, Hinde S, Helliwell P. Capturing all of the costs in NICE appraisals: the impact of inflammatory rheumatic diseases on productivity. Rheumatology. 2012; 51:210-5.
41. Angelis A, Tordrup D, Kanavos P. Socio-economic burden of rare diseases: A systematic review of cost of illness evidence. Health policy (Amsterdam, Netherlands). 2015; 119:964-79.
42. Angelis A, Kanavos P, Lopez-Bastida J, Linertova R, Serrano-Aguilar P. Socioeconomic costs and health-related quality of life in juvenile idiopathic arthritis: a cost-of-illness study in the United Kingdom. BMC Musculoskelet Disord. 2016; 17:321.
43. Bracaglia C, Prencipe G, De Benedetti F. Macrophage activation syndrome: different mechanisms leading to a one clinical syndrome. Pediatr Rheumatol. 2017; 15 (1).
44. Kumakura S, Murakawa Y. Clinical characteristics and treatment outcomes of autoimmune-associated hemophagocytic syndrome in adults. Arthritis Rheumatol. 2014; 66:2297-307.
45. Ruscitti P, Rago C, Breda L, Cipriani P, Liakouli V, Berardicurti O*, et al.* Macrophage activation syndrome in Still's disease: analysis of clinical characteristics and survival in paediatric and adult patients. Clin Rheumatol. 2017; 36:2839-45.
46. Ruscitti P, Iacono D, Ciccia F, Emmi G, Cipriani P, Grembiale RD*, et al.* Macrophage Activation Syndrome in Patients Affected by Adult-onset Still Disease: Analysis of Survival Rates and Predictive Factors in the Gruppo Italiano di Ricerca in Reumatologia Clinica e Sperimentale Cohort. J Rheumatol. 2018; 45:864-72.
47. NHS England. Clinical Commissioning Policy Statement: Biologic Therapies for the treatment of Juvenile Idiopathic Arthritis (JIA) (E03X04). London: NHS England; 2015; Available from: https://www.england.nhs.uk/wp-content/uploads/2018/08/Biologic-therapies-for-the-treatment-of-juvenile-idiopathic-arthritis.pdf. Accessed November 2019.
48. National Institute for Health and Care Excellence (NICE). Tocilizumab for the treatment of systemic juvenile idiopathic arthritis: Technology appraisal guidance [TA238]. 2011; Available from: https://www.nice.org.uk/guidance/ta238. Accessed November 2019.
49. National Institute for Health and Care Excellence (NICE). Canakinumab for treating systemic juvenile idiopathic arthritis (terminated appraisal) (TA302). London: NICE; 2013; Available from: https://www.nice.org.uk/search?q=TA302. Accessed November 2019.
50. Pardeo M, Pires Marafon D, Insalaco A, Bracaglia C, Nicolai R, Messia V*, et al.* Anakinra in systemic juvenile idiopathic arthritis: A single-center experience. J Rheumatol. 2015; 42:1523-7.
51. Nigrovic PA. Review: is there a window of opportunity for treatment of systemic juvenile idiopathic arthritis? Arthritis Rheumatol. 2014; 66:1405-13.
52. Ter Haar NM, van Dijkhuizen EHP, Swart JF, van Royen-Kerkhof A, El Idrissi A, Leek AP*, et al.* Treatment to target using recombinant interleukin-1 receptor antagonist as first-line monotherapy in new-onset systemic juvenile idiopathic arthritis: results from a five-year follow-up study. Arthritis Rheumatol. 2019; 71:1163-73.
53. Vastert SJ, de Jager W, Noordman BJ, Holzinger D, Kuis W, Prakken BJ*, et al.* Effectiveness of first-line treatment with recombinant interleukin-1 receptor antagonist in steroid-naive patients with new-onset systemic juvenile idiopathic arthritis: results of a prospective cohort study. Arthritis Rheumatol. 2014; 66:1034-43.
54. Nigrovic PA, Mannion M, Prince FH, Zeft A, Rabinovich CE, van Rossum MA*, et al.* Anakinra as first-line disease-modifying therapy in systemic juvenile idiopathic arthritis: report of forty-six patients from an international multicenter series. Arthritis Rheum. 2011; 63:545-55.

55. Quartier P, Allantaz F, Cimaz R, Pillet P, Messiaen C, Bardin C*, et al.* A multicentre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial). Ann Rheum Dis. 2011; 70:747-54.
56. Ilowite N, Porras O, Reiff A, Rudge S, Punaro M, Martin A*, et al.* Anakinra in the treatment of polyarticular-course juvenile rheumatoid arthritis: safety and preliminary efficacy results of a randomized multicenter study. Clin Rheumatol. 2009; 28:129-37.
57. Nordstrom D, Knight A, Luukkainen R, van Vollenhoven R, Rantalaiho V, Kajalainen A*, et al.* Beneficial effect of interleukin 1 inhibition with anakinra in adult-onset Still's disease. An open, randomized, multicenter study. J Rheumatol. 2012; 39:2008-11.
58. Tarp S, Amarilyo G, Foeldvari I, Christensen R, Woo JM, Cohen N*, et al.* Efficacy and safety of biological agents for systemic juvenile idiopathic arthritis: a systematic review and meta-analysis of randomized trials. Rheumatology (Oxford). 2016; 55:669-79.
59. Zeft A, Hollister R, LaFleur B, Sampath P, Soep J, McNally B*, et al.* Anakinra for systemic juvenile arthritis: the Rocky Mountain experience. J Clin Rheumatol. 2009; 15:161-4.
60. Pascual V, Allantaz F, Arce E, Punaro M, Banchereau J. Role of interleukin-1 (IL-1) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical response to IL-1 blockade. J Exp Med. 2005; 201:1479-86.
61. Ohlsson V, Baildam E, Foster H, Jandial S, Pain C, Strike H*, et al.* Anakinra treatment for systemic onset juvenile idiopathic arthritis (SOJIA). Rheumatology (Oxford). 2008; 47:555-6.
62. Marvillet I, Penadés IC, Montesinos BL, Puche AM. Anakinra treatment in patients with systemic-onset juvenile idiopathic arthritis: “The Valencia Experience”. Pediatric Rheumatology Online Journal. 2011; 9:P71-P.
63. Lequerre T, Quartier P, Rosellini D, Alaoui F, De Bandt M, Mejjad O*, et al.* Interleukin-1 receptor antagonist (anakinra) treatment in patients with systemic-onset juvenile idiopathic arthritis or adult onset Still disease: preliminary experience in France. Ann Rheum Dis. 2008; 67:302-8.
64. Irigoyen P, Olson J, Hom C, Ilowite N. Treatment of systemic onset juvenile idiopathic arthritis with anakinra. Ped Rheum Online J. 2006; 4:123-34.
65. Gattorno M, Piccini A, Lasiglie D, Tassi S, Brisca G, Carta S*, et al.* The pattern of response to anti-interleukin-1 treatment distinguishes two subsets of patients with systemic-onset juvenile idiopathic arthritis. Arthritis Rheum. 2008; 58:1505-15.
66. Ortiz-Sanjuan F, Blanco R, Riancho-Zarrabeitia L, Castaneda S, Olive A, Riveros A*, et al.* Efficacy of Anakinra in Refractory Adult-Onset Still's Disease: Multicenter Study of 41 Patients and Literature Review. Medicine (Baltimore). 2015; 94:e1554.
67. Naumann L, Feist E, Natusch A, Langen S, Krause A, Buttgereit F*, et al.* IL1-receptor antagonist anakinra provides long-lasting efficacy in the treatment of refractory adult-onset Still's disease. Ann Rheum Dis. 2010; 69:466-7.
68. Laskari K, Tzioufas AG, Moutsopoulos HM. Efficacy and long-term follow-up of IL-1R inhibitor anakinra in adults with Still's disease: a case-series study. Arthritis Res Ther. 2011; 13:R91.
69. Iliou C, Papagoras C, Tsifetaki N, Voulgari PV, Drosos AA. Adult-onset Still's disease: clinical, serological and therapeutic considerations. Clin Exp Rheumatol. 2013; 31:47-52.
70. Giampietro C, Ridene M, Lequerre T, Costedoat Chalumeau N, Amoura Z, Sellam J*, et al.* Anakinra in adult-onset Still's disease: long-term treatment in patients resistant to conventional therapy. Arthritis Care Res (Hoboken). 2013; 65:822-6.
71. Giampietro C, Ridene M, Fautrel B, Bourgeois P. Long term treatment with anakinra in patients with adult-onset still disease. Arthritis Rheum. 2010; 62:S902.

72. Dall'Ara F, Frassi M, Tincani A, Airo P. A retrospective study of patients with adult-onset Still's disease: is pericarditis a possible predictor for biological disease-modifying anti-rheumatic drugs need? Clin Rheumatol. 2016; 35:2117-23.
73. Colafrancesco S, Priori R, Valesini G, Argolini L, Baldissera E, Bartoloni E*, et al.* Response to Interleukin-1 Inhibitors in 140 Italian Patients with Adult-Onset Still's Disease: A Multicentre Retrospective Observational Study. Front Pharmacol. 2017; 8:369.
74. Cavalli G, Franchini S, Aiello P, Guglielmi B, Berti A, Campochiaro C*, et al.* Efficacy and safety of biological agents in adult-onset Still's disease. Scand J Rheumatol. 2015; 44:309-14.
75. European Medicines Agency. European Public Assessment Report: CHMP extension of indication variation assessment report. . London: EMA; 2018; Available from: https://www.ema.europa.eu/en/documents/variation-report/kineret-h-c-363-ii-0056-epar-assessment-report-variation_en.pdf. Accessed November 2019.
76. Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. Arthritis And Rheumatism. 1997; 40:1202-9.
77. Ruperto N, Brunner HI, Quartier P, Constantin T, Wulffraat N, Horneff G*, et al.* Two Randomized Trials of Canakinumab in Systemic Juvenile Idiopathic Arthritis. New England Journal of Medicine. 2012; 367:2396-406.
78. Lovell DJ, Giannini EH, Reiff AO, Kimura Y, Li S, Hashkes PJ*, et al.* Long-term safety and efficacy of rilonacept in patients with systemic juvenile idiopathic arthritis. Arthritis Rheum. 2013; 65:2486-96.
79. Ilowite NT, Prather K, Lokhnygina Y, Schanberg LE, Elder M, Milojevic D*, et al.* Randomized, double-blind, placebo-controlled trial of the efficacy and safety of rilonacept in the treatment of systemic juvenile idiopathic arthritis. Arthritis Rheumatol. 2014; 66:2570-9.
80. Clinicaltrials.gov. A study to evaluate efficacy and safety of anakinra in the treatment of Still's disease (SJIA and AOSD) (anaSTILLs). 2019; Available from: https://clinicaltrials.gov/ct2/show/NCT03265132. Accessed November 2019.
81. Saccomanno B, Tibaldi J, Minoia F, Bagnasco F, Pistorio A, Guariento A*, et al.* Predictors of effectiveness of anakinra in systemic juvenile idiopathic arthritis. The Journal of Rheumatology. 2019; 46:416-21.
82. SOBI. Data on File: Summary of clinical efficacy – Still´s disease: SOBI 2017/18.
83. Hong D, Yang Z, Han S, Liang X, Ma K, Zhang X. Interleukin 1 inhibition with anakinra in adult-onset Still disease: a meta-analysis of its efficacy and safety. Drug design, development and therapy. 2014; 8:2345.
84. Centre for Reviews and Dissemination (CRD). Systematic Reviews: CRD's guidance for undertaking reviews in healthcare. University of York; 2009; Available from: https://www.york.ac.uk/crd/SysRev/!SSL!/WebHelp/SysRev3.htm. Accessed.
85. Sterne JAC, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M*, et al.* ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. BMJ. 2016; 355:i4919
86. De Benedetti F, Brunner HI, Ruperto N, Kenwright A, Wright S, Calvo I*, et al.* Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. The New England journal of medicine. 2012; 367:2385-95.
87. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992; 30:473-83.
88. Grevich S, Shenoi S. Update on the management of systemic juvenile idiopathic arthritis and role of IL-1 and IL-6 inhibition. Adolescent Health, Medicine and Therapeutics. 2017; 8:125.
89. Horneff G, Schulz AC, Klein A, Eising K. THU0575 Anakinra for first line steroid free treatment in systemic onset juvenile idiopathic arthritis. Annals of the Rheumatic Diseases. 2018; 77:489-.

90. Sota J, Rigante D, Ruscitti P, Insalaco A, Sfriso P, de Vita S*, et al.* Anakinra drug retention rate and predictive factors of long-term response in systemic juvenile idiopathic arthritis and adult onset Still disease. Frontiers in Pharmacology. 2019; 10.

91. Yamada H, Kaneko Y, Takeuchi T. FRI0664 Biomarkers for relapse in patients with adult onset still's disease treated with il-6 inhibitor. Annals of the Rheumatic Diseases. 2018; 77:853.

92. Grom AA, Ilowite NT, Pascual V, Brunner HI, Martini A, Lovell D*, et al.* Rate and clinical presentation of macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis treated with canakinumab. Arthritis Rheumatol. 2016; 68:218-28.

93. Roche. RoActemra® (tocilizumab) for the treatment of systemic juvenile idiopathic arthritis (sJIA). TA238 Company submission. National Institute for Health and Care Excellence,; 2011; Available from: https://www.nice.org.uk/guidance/ta238/history. Accessed November 2019.

94. Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Alecock E*, et al.* Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. Lancet (London, England). 2008; 371:987-97.

95. Fleischmann RM, Halland AM, Brzosko M, Burgos-Vargas R, Mela C, Vernon E*, et al.* Tocilizumab inhibits structural joint damage and improves physical function in patients with rheumatoid arthritis and inadequate responses to methotrexate: LITHE study 2-year results. The Journal Of Rheumatology. 2013; 40:113-26.

96. Ara R, Brazier JE. Using health state utility values from the general population to approximate baselines in decision analytic models when condition-specific data are not available. Value in Health. 2011; 14:539-45.

97. Restelli U, Rizzardini G, Antinori A, Lazzarin A, Bonfanti M, Bonfanti P*, et al.* Cost-effectiveness analysis of dolutegravir plus backbone compared with raltegravir plus backbone, darunavir+ritonavir plus backbone and efavirenz/tenofovir/emtricitabine in treatment naive and experienced HIV-positive patients. Ther Clin Risk Manag. 2017; 13:787-97.

98. Beauchemin C, Letarte N, Mathurin K, Yelle L, Lachaine J. A global economic model to assess the cost-effectiveness of new treatments for advanced breast cancer in Canada. Journal of medical economics. 2016; 19:619-29.

99. M F Silva J, Ladomenou F, Carpenter B, Chandra S, Sedlacek P, Formankova R*, et al.* Allogeneic hematopoietic stem cell transplantation for severe, refractory juvenile idiopathic arthritis. Blood advances. 2018; 2:777-86.

100. British National Formulary. Drug search. 2019; Available from: https://bnf.nice.org.uk/drug/. Accessed 2019 December 05.

101. Department of Health and Social Care. Drugs and pharmaceutical electronic market information tool (eMIT). 2019; Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit. Accessed November 2019.

102. Fujii T, Akizuki M, Kameda H, Matsumura M, Hirakata M, Yoshida T*, et al.* Methotrexate treatment in patients with adult onset Still's disease—retrospective study of 13 Japanese cases. Annals of the Rheumatic Diseases. 1997; 56:144.

103. Frosch M, Roth J. New insights in systemic juvenile idiopathic arthritis—from pathophysiology to treatment. Rheumatology. 2007; 47:121-5.

104. Hayward K, Wallace CA. Recent developments in anti-rheumatic drugs in pediatrics: treatment of juvenile idiopathic arthritis. Arthritis research & therapy. 2009; 11:216-.

105. NHS Improvement. National Schedule of Reference Costs - Year 2017-18 - NHS trust and NHS foundation trusts. NHS Improvement; 2018; Available from: https://improvement.nhs.uk/resources/reference-costs/#rc1718. Accessed November 2019.

106. Scottish Medicines Consortium. Detailed Advice Document: Anakinra 100mg/0.67mL solution for injection in prefilled syringe (Kineret®) - Swedish Orphan Biovitrum Ltd (SOBI). Glasgow: SMC; 2018.
107. Swedish Orphan Biovitrum Ltd. electronic Medicines Compendium (eMC): SmPC-anakinra. Kineret 100 mg/0.67 ml solution for injection in pre-filled syringe. 20 March 2007. 2007; Available from: https://www.medicines.org.uk/emc/product/559/smpc. Accessed 2019 November 19.
108. Roche Products Limited. electronic Medicines Compendium (eMC): SmPC-tocilizumab. RoActemra 162 mg solution for injection in pre-filled syringe. 25 September 2013. 2013; Available from: https://www.medicines.org.uk/emc/product/5357/smpc. Accessed 2019 November 19.
109. Novartis Pharmaceuticals UK Ltd. electronic Medicines Compendium (eMC): SmPC-canakinumab. Ilaris® 150 mg/ml solution for injection. 19 June 2014. 2014; Available from: https://www.medicines.org.uk/emc/product/8874/smpc. Accessed 2019 November 19.

7 APPENDICES

7.1 Appendix 1

Classification criteria for SJIA and AOSD

Table 32 Classification criteria for the diagnosis of SJIA

Inclusion criteria	Arthritis in 1 or more joints Fever (with or preceding arthritis) ≥2 weeks duration that is daily for ≥ 3 days One or more of the following: • Evanescent erythematous rash • Generalised lymph node enlargement • Hepatomegaly and/or splenomegaly • Serositis
Exclusion criteria	• Psoriasis or history of psoriasis in the patient or first-degree relative • Arthritis in the HLA-B27-positive male beginning after 6th birthday • Ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis, or a history of one of these disorders in a first degree relative • The presence of IgM rheumatoid factor on at least two occasions, at least 3 months apart

HLA-B27=human leucocyte antigen B27; IgM=immunoglobulin M; SJIA=systemic juvenile idiopathic arthritis
Source: CS, Table 3

Table 33 Classification criteria for the diagnosis of AOSD

Cush 1987	Yamaguchi 1992	Fautrel 2002
Probable AOSD: 10 points during 12 weeks observation Definite AOSD: 10 points during 6 months of observation	5 criteria at least 2 major Exclusion criteria: infections, malignancies, rheumatic diseases	4 major criteria or 3 major and 2 minor
2 points each: • Quotidian fever >39°C • Transient rash • WBC >12,000/mL and ESR >40 mm/h • Negative ANA/RF • Carpal ankylosis	Major criteria: • Fever >39°C (intermittent, 1 week or longer) • Arthralgia >2 weeks • Typical rash • WBC >10,000/mL(>80% neutrophil granulocytes)	Major criteria: • Spiking fever >39°C • Arthralgia • Transient rash • Neutrophil granulocytes >80% • Glycosylated ferritin <20%
1 point each: • Onset age >35 years • Arthritis • Sore throat • RES involvement or liver abnormalities • Serositis • Cervical or tarsal ankylosis	Minor criteria: • Sore throat • Lymphadenopathy and/or splenomegaly • Liver abnormalities • Negative ANA/RF	Minor criteria: • Maculopapular rash • WBC >10,000/mL

ANA=antinuclear antibody; AOSD=adult-onset Still's disease; ESR=erythrocyte sedimentation rate; RF=rheumatoid factor; WBC=white blood cell count
Source: CS, Table 4

7.2 Appendix 2

Uncontrolled studies reported in the CS

Table 34 Uncontrolled studies in SJIA

Primary study	Study design	N	Anakinra dose, mg/day	Used in economic model
Gattorno 2008[65]	Prospective	22	1 (100)	No[a]
Irigoyen 2006[64]	Retrospective	14	NR	No[a]
Lequerre 2008[64] [b]	Prospective	20	1 to 2 (100)	No[a]
Marvillet 2011[62]	Retrospective	22	3 (100)	No[a]
Nigrovic 2011[54]	Retrospective	46	Median starting dose 1.5 (IQR 1.1 to 2.0)	No[a]
Ohlsson 2008[61]	Retrospective	7	1 to 2 (100)	No[a]
Pardeo 2015[50]	Retrospective	25	Median starting dose 2.0 (IQR 1.3 to 2.0); up to 5	Yes
Pascual 2005[60]	Prospective	9	2 (100)	No[a]
Vastert 2014[53] [c]	Prospective	20	2 (100)	No[a]
Ter Haar 2019[52] [c]	Prospective	42	2 (100)	No[a]
Zeft 2009[59]	Retrospective	33	Median 1.6 (0.8 to 9.1)	No[a]

IQR=interquartile range; NR=not reported; SJIA=systemic juvenile idiopathic arthritis
[a] No relevant outcomes reported; [b] The study also described 15 patients with AOSD treated with anakinra; [c] Long-term follow-up of prospective study. (In addition, to the 20 patients included in Vastert [2014], the present study also included patients who presented since January 2012 and patients who were seen with arthralgia but without overt arthritis at diagnosis from the start of the cohort in 2008. The latter were only included if the clinical picture (e.g., spiking fever, rash) and laboratory values (e.g., ferritin and IL-18 levels) indicated a suspected diagnosis of systemic JIA and other diagnoses had been excluded)
Source: CS, Table 8

Table 35 Uncontrolled studies in AOSD

Primary study	Study design	N	Anakinra dose, mg/day	Used in economic model
Cavalli 2015[74]	Retrospective	20	100	No
Colafrancesco 2017[73]	Retrospective	140	100	No
Dall'Ara 2016[72]	Retrospective	13	NR	No
Gerfaud-Valentin 2014[20]	Retrospective	6	NR	No
Giampietro 2013[70]	Retrospective	28	100	No
Giampietro 2010[71]	Retrospective	19	100	No
Iliou 2013[69]	Retrospective	10	100	No
Laskari 2011[68]	Prospective	25	100	No
Lequerre 2008[63] a	Prospective	15	100	No
Naumann 2010[67]	Prospective	8	NR	No
Ortiz-Sanjuan 2015[66]	Retrospective	41	100	No

AOSD=adult-onset Still's desease; NR=not reported; N=number of patients
[a] The study also described 20 patients with SJIA treated with anakinra
Source: CS, Table 10

7.3 Appendix 3

Table 36 Values derived from RCTs and used in the company economic model

Trial	Outcome	Value in economic model
Quartier[55]	Probability of injection site reaction for treatment with anakinra in people with SJIA (CS, Table 54)	0.42% per administration
	Baseline age of people with SJIA	8.5 years
Nordstrom[57]	Baseline age of people with AOSD	39 years
Nordstrom[57]	Remission rate for treatment with csDMARD	0.93% per week
	Treatment discontinuation rate with csDMARD: assuming 95% of patients would have achieved remission or discontinued treatment at 16 weeks	16.23% per week
Nordstrom[57]	Remission rate for treatment with anakinra and tocilizumab (post-csDMARD)	2.85% per week
Nordstrom[57]	Probability of injection site reaction for treatment with anakinra in people with AOSD (CS, Table 54)	0.16% per administration
Ilowite[56]	none	Not applicable

AOSD=adult onset Still's disease; csDMARD=conventional synthetic disease-modifying anti-rheumatic drug; SJIA=systemic juvenile idiopathic arthritis