NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Anakinra for treating Still's disease [ID1463]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Anakinra for treating Still's disease [ID1463]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission** from **Swedish Orphan Biovitrum Ltd**

2. **Clarification questions and company responses**
   a. Clarification response
   b. Additional clarification response
   c. ERG comments on company's additional clarification response

3. **Patient group, professional group and NHS organisation submission** from:
   a. Rare Autoinflammatory Conditions Community – UK (RACC-UK)

4. **Expert personal perspectives** from:
   a. Eslam Al-Abadi – clinical expert, nominated by Swedish Orphan Biovitrum Ltd
   b. Lisa Dunkley – clinical expert, nominated by the Royal College of Physicians
   c. Amanda Jones – patient expert, nominated by Rare Autoinflammatory Conditions Community – UK (RACC-UK)
   d. Rachel Rimmer – patient expert, nominated by Rare Autoinflammatory Conditions Community – UK (RACC-UK)

5. **Evidence Review Group report** prepared by Liverpool Reviews and Implementation Group (LRiG)

6. **Evidence Review Group – factual accuracy check**

7. **Technical Report sent out for engagement**

8. **Technical engagement response** from **Swedish Orphan Biovitrum Ltd**

9. **Technical engagement responses from experts:**
   a. Eslam Al-Abadi – clinical expert, nominated by Swedish Orphan Biovitrum Ltd
   b. Lisa Dunkley – clinical expert, nominated by the Royal College of Physicians

10. Technical engagement response from consultees and commentators:

a. British Society for Rheumatology
b. Royal College of Physicians
c. Novartis Pharmaceuticals

11. Evidence Review Group critique of company response to technical engagement prepared by Liverpool Reviews and Implementation Group (LRiG).

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Anakinra for the treatment of Still's disease (including Systemic Juvenile Idiopathic Arthritis and Adult-Onset Still's Disease) [ID1463]

Document B

Company evidence submission

October 2019

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Abbreviations

ACR	American College of Rheumatology
ACRPedi 30	American College of Rheumatology Paediatric Response Criteria
A&E	Accident and emergency
AE	Adverse events
AKA	Anakinra
ALT	Alanine transaminase
ANA	Antinuclear antibody
ANC	Absolute neutrophil count
AOSD	Adult-onset Still's disease
AST	Aspartate aminotransferase
AZA	Azathioprine
BCRD	Biologics for Children with Rheumatic Diseases
BMT	Bone marrow transplant
BNF	British national formulary
BNFc	British National Formulary for children
CAN	Canakinumab
CHAQ	Childhood health assessment questionnaire
CI	Confidence interval
CID	Clinically inactive disease
CRP	C-reactive protein
csDMARD	conventional synthetic disease modifying antirheumatic drug
CyA	Cyclosporine a
D	Day
DAH	Diffuse alveolar haemorrhage
Det	Deterministic
DIC	Disseminated intravascular coagulopathy
DMARD	Disease-modifying anti-rheumatic drug
eMIT	Electronic Marketing information tool
ENT	Ear, nose and throat
EPAR	European Public Assessment Report
ESR	Erythrocyte sedimentation rate
EQ-5D	Euroqol-5 dimensions
FT	Further treatment
GP	General practitioner
HAQ	Health assessment questionnaire
Hb	Haemoglobin
HDU	High dependency unit
HLA	Human leukocyte antigens
HLH	Haemophagocytic lymphohistiocytosis
HR	Hour
HRQL	Health-related quality of life
IC	Intravascular coagulopathy
ICU	Intensive care unit

IgM	Immunoglobulin M
IL	Interleukin
IL-1RI	Interleukin-1 type I receptor
IL-1Ra	Recombinant Interleukin-1 receptor antagonist
ILAR	International League of Associations for Rheumatology
IQR	Interquartile range
ISR	Injection site reaction
ITT	Intent-to-treat
IV	Intravenous
JADAS-71	71-joint juvenile arthritis disease activity score
JAK	Janus kinase inhibitor
JIA	Juvenile idiopathic arthritis
JIA ACR 30	Modified American College of Rheumatology Paediatric 30 response criteria
JRA	Juvenile rheumatoid arthritis
kg	Kilogram
KOL	Key opinion leader
LEF	Leflunomide
LOM	Joints with limitation of passive motion
LY	Life year
M	Month
m^2	Metres squared
M1F	Macrophage migration inhibitory factor
MAA	Marketing authorisation application
MAS	Macrophage activation syndrome
MASAC	Medical and Scientific Advisory Council
MDA	Minimal disease activity
mg	Milligram
MHC	Major histocompatibility component
MRU	Medical resource use
MTA	Multiple technology appraisal
MTX	Methotrexate
NHS	National health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analyses
NMB	Net monetary benefit
NR	Not reported
NSAID	Nonsteroidal anti-inflammatory
NSAIDs+C	Nonsteroidal anti-inflammatory drug + corticosteroids
OLE	Open label extension
ONS	Office for National Statistics
OWSA	One-way sensitivity analysis
OR	Odds ratio
PAS	Patient access scheme
PBO	Placebo
PGA	Physician global assessment of disease activity

PGE	Patient global evaluation of wellbeing
PK	Pharmacokinetic
PrC	Prospective controlled
Prob	Probabilistic
PSA	Probabilistic sensitivity analysis
PSSRU	Personal social services research unit
PTSD	Post-traumatic stress disorder
QALY	Quality-adjusted life year
QC	Quality control
RCT	Randomised controlled trial
Rem	Remission
RES	Reticuloendothelial system
RF	Rheumatoid factor
RR	Relative risk
SAA	Serum amyloid A
SAE	Serious adverse events
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SF-36	Short form 36
SJC	Swollen joint count
SSZ	Sulfasalazine
sJIA	Systemic juvenile idiopathic arthritis
sJRA	Systematic juvenile rheumatoid arthritis
SLR	Systematic literature review
SmPC	Summary of product characteristics
STA	Single technology appraisal
TA	Technology appraisal
TJC	Tender joint count
TMPT	Thiopurine methyltransferase
TOC	Tocilizumab
TNF-α	Tumour necrosis factor alpha
TTP	Thrombotic thrombocytopenic purpura
VAS	Visual analogue scale
Vs	Versus
WBC	White blood cell
WK	Week

B.1. Decision problem, description of the technology and clinical care pathway

Decision problem

- The decision problem is concerned with an evaluation of the clinical and cost-effectiveness of anakinra (Kineret®) for the treatment of Still's disease (including sJIA and AOSD)
- Still's disease is a severe, rare systemic inflammatory disorder associated with a range of debilitating clinical manifestations, including a daily spiking fever, joint pain and inflammation, muscle pain and rash. Poorly managed disease is associated with an elevated risk of developing macrophage activation syndrome (MAS) – a serious and potentially fatal complication.
- sJIA is associated with significant and severe morbidity that can persist into adult life and which has profound consequences for the patients' quality of life.

Description of the technology

- Anakinra is a recombinant Interleukin-1 receptor antagonist that neutralises the biologic activity of IL-1α and IL-1β by competitively inhibiting their binding to IL-1RI. Interleukin-1 is a pivotal pro-inflammatory cytokine mediating many cellular responses including those important in synovial inflammation
- Anakinra is indicated in adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg 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 NSAIDs or glucocorticoids. It can be given as monotherapy or in combination with other anti-inflammatory drugs and DMARDs
- Clinical studies of anakinra, and over a decade of use in NHS practice have shown it is an effective therapy to reduce clinical signs and symptoms of Still's disease, including normalisation of laboratory parameters, and allowing a clinically meaningful tapering of glucocorticoids in many patients. Reduced steroid use leads to a lower risk of a number of steroid-related complications, including stunted growth, coronary and renal impairment. The use of IL-1 blockade as first-line therapy has advantages; prevention of chronic arthritis, reduced risk of developing arthritis, and enabling withdrawal or tapering of glucocorticoids

Clinical care pathway

- There is growing acceptance in the clinical community that sJIA and AOSD are one single disease (Still's disease), with onset at different ages. However, historically these have been considered separately in national policy documents
- NSAIDs are almost always used to ease symptoms during the differential diagnostic process, particularly when joint symptoms are absent or limited. Glucocorticoids are commonly used following diagnosis (±NSAIDs). If insufficient, DMARDs such as methotrexate may then be considered, although there is conflicting evidence concerning their efficacy in Still's disease.
- In current NHS practice, two biologic therapies are used for both sJIA and AOSD – anakinra and tocilizumab (RoActemra, Roche). Anakinra is the only biological therapy recommended in children aged 8 months to 2 years, and is the only reimbursed, licensed treatment option in AOSD. Anakinra has vastly improved clinical outcomes in Still's disease and confirmed the pathogenic role of IL-1 in the disease process.

Key: AOSD, adult-onset Still's disease; DMARDs, disease-modifying antirheumatic drugs; NSAIDs, nonsteroidal anti-inflammatory drugs; sJIA, systemic juvenile idiopathic arthritis

B.1.1. Decision problem

The decision problem for this technology appraisal as defined in the final NICE scope (1) is an evaluation of the clinical and cost-effectiveness of anakinra (Kineret®) for the treatment of Still's disease (systemic juvenile idiopathic arthritis [sJIA] and adult onset Still's disease [AOSD]).

Anakinra is licensed for use in the EU as follows:

- In adults for the treatment of the signs and symptoms of rheumatoid arthritis (RA) in combination with methotrexate, with an inadequate response to methotrexate alone.
- In adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg or above for the treatment of cryopyrin-associated periodic syndromes (CAPS), including: neonatal-onset multisystem inflammatory disease (NOMID) / chronic infantile neurological, cutaneous, articular syndrome (CINCA), Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndrome (FCAS).
- In adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg 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.[1]

Anakinra can be given as monotherapy or in combination with other anti-inflammatory drugs and (conventional synthetic) disease-modifying antirheumatic drugs (csDMARDs).[1] The final scope issued by NICE and the decision problem addressed in this submission is shown in Table 1.

Table 1. Decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with Still's disease, including sJIA and AOSD.	People with active Still's disease, including sJIA and AOSD.	Aligned with the NICE final scope
Intervention	Anakinra as monotherapy or in combination with other anti-inflammatory drugs and DMARDs	Anakinra as monotherapy or in combination with other anti-inflammatory drugs and DMARDs	Aligned with the NICE final scope
Comparator(s)	For previously untreated disease: • NSAIDs and systemic corticosteroids For disease previously treated with NSAIDs or systemic corticosteroids: • DMARDs For disease previously treated with DMARDs: • tocilizumab (only for systemic juvenile idiopathic arthritis that has responded inadequately to methotrexate) • canakinumab	For previously untreated disease: • NSAIDs and systemic corticosteroids For disease previously treated with NSAIDs or systemic corticosteroids: • DMARDs For disease previously treated with DMARDs: • tocilizumab (only for systemic juvenile idiopathic arthritis that has responded inadequately to methotrexate) • canakinumab	Anakinra is indicated in adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg 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. The anticipated clinical usage of anakinra is per its current license in sJIA and AOSD – following failure of NSAIDs +/- corticosteroids ('per-label'). A second scenario following DMARDs ('post-DMARD') is also considered. Clinical practice guidelines recommend the use of anakinra in patients with continued disease activity (sJIA or AOSD) after treatment with NSAIDs, current NHS commissioning policies limit its use at this stage of the pathway restricting to use in patients who have failed to achieve remission with csDMARDs. In contrast to the well-known progressive disease course of Still's disease, complete remission was achieved in 50-100% anakinra-treated patients and a consistently high proportion of patients markedly improved and associated with a reduction in the use of glucocorticoids, as well as affecting the natural course of the disease and reducing the risk of developing persistent arthritis.

			The use of anakinra aligned with indication provides the increased possibility for patients to achieve remission earlier than would otherwise be possible. This has the potential to lead a reduced number of patients having unresolved disease (associated with greater costs, poorer quality-of-life, and an increased risk of developing the potentially fatal complication of MAS).
Outcomes	The outcome measures to be considered include: • disease activity (including disease flares and remission) • fever • physical function • blood markers (including markers for inflammation) • glucocorticoid tapering • rash • mortality • adverse effects of treatment • health-related quality of life (HRQL)	sJIA • Clinical response according to ACRPedi criteria • Study specific response, including: − fever − rash − active joints − pain − laboratory tests (CRP-levels, ESR, WBC, Hb, albumin, platelets) • Glucocorticoid-sparing effect • Adverse effects of treatment AOSD • Clinical response according to ACR criteria • Study specific response, including: − ACR response − responder rate − systemic signs and symptoms of inflammation and arthritis − laboratory tests (ESR, CRP) • Glucocorticoid-sparing effect • Adverse effects of treatment	The outcome measures to be considered are those reported in the trials that were conducted in support of the marketing authorisation application. Of note, the outcomes measures for response vary between studies and the definition of response and remission varied. With regards to remission, at the time the majority of identified studies were conducted, remission was not considered a relevant endpoint (given that remission had not been achieved for patients prior to study entry, and the studies were planned to be conducted for only a limited time horizon). In the sJIA trials none of the studies reported HRQL

		• Health-related quality of life	
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • People with sJIA or AOSD • People with Macrophage Activation Syndrome (MAS) • Level of disease activity	• People with sJIA or AOSD	There is a growing acceptance that sJIA and AOSD are one single disease - Still´s disease, with onset at different ages; childhood in sJIA (most often between 3 and 5 years of age) and adulthood (aged 16 years-plus) in AOSD. The current split definition and cut-off of 16 years of age may cause an issue in the transition from child to adult care which one definition would potentially solve (Still's disease). Evidence in efficacy and safety has been evaluated in trials in the respective populations – sJIA and AOSD – and this is reflected in the submission. Note that there are no trials using MAS as inclusion criteria and it is therefore typically treated as an adverse event rather than a subgroup.

Key: ACRPedi 30, American College of Rheumatology Paediatric Response Criteria; AOSD, adult onset Still's disease; CRP, c-reactive protein; DMARD, disease-modifying anti-rheumatic drug, ESR, erythrocyte sedimentation rate; Hb, haemoglobin; HRQL, health-related quality of life; NSAID, nonsteroidal anti-inflammatory drug; sJIA, systemic juvenile idiopathic arthritis; WBC, white blood cell

B.1.2. Description of the technology being appraised

Anakinra (Kineret®, Swedish Orphan Biovitrum Ltd) is a recombinant Interleukin-1 receptor antagonist (IL-1Ra) that blocks the biological activity of cytokine IL-1, thereby controlling active inflammation. It is administered by subcutaneous (SC) injection. A description of the technology being appraised is presented in Table 2.

The summary of product characteristics (SmPC) is included in Appendix C.

The Scottish Medicines Consortium (SMC) has accepted the use of anakinra for use within NHS Scotland: "… treatment of adults, adolescents, children and infants aged 8 months or older (who weigh at least 10kg) with Still's disease (including AOSD and sJIA) who have active systemic features of moderate to high disease activity or who still have symptoms after treatment with anti-inflammatory medicines. Anakinra can be used by itself or with other medicines such as other anti-inflammatory medicines and disease modifying anti-rheumatic drugs (DMARDs)."[2]

Table 2. Description of anakinra

UK approved name and brand name	• Anakinra (Kineret®)
Mechanism of action	Anakinra neutralises the biologic activity of IL-1α and IL-1β by competitively inhibiting their binding to IL-1RI. Interleukin-1 is a pivotal pro-inflammatory cytokine mediating many cellular responses including those important in synovial inflammation.
Marketing authorisation/CE mark status	Anakinra is licenced for use in the EU as follows: • In adults for the treatment of the signs and symptoms of rheumatoid arthritis (RA) in combination with methotrexate (MTX), with an inadequate response to MTX alone. • In adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg or above for the treatment of CAPS, including: NOMID / CINCA, MWS, FCAS. • In adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg or above for the treatment of Still's disease, including systemic juvenile idiopathic arthritis (sJIA) and adult-onset Still's disease (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. Marketing authorisation for RA granted on 8 March 2002 and was extended on 30 October 2012 to include CAPS (including CINCA, MWS, FCAS). On 11 April 2018 the licence was extended to include Still's disease.
Indications and any restriction(s) as described in	**Indication** Anakinra is indicated in adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg or above for the treatment of

the summary of product characteristics (SmPC)	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 NSAIDs or glucocorticoids. Anakinra can be given as monotherapy or in combination with other anti-inflammatory drugs and DMARDS. **Restriction** Anakinra must not be initiated in patients with neutropenia (ANC <1.5 x 10^9/l)
Method of administration and dosage	Anakinra is supplied in pre-filled syringe of 100 mg/0.67 ml solution. The recommended dose for patients weighing 50 kg or more is 100 mg/day by subcutaneous (SC) injection. Patients weighing less than 50 kg should be dosed by body weight with a starting dose of 1-2 mg/kg/day. Children weighing less than 50 kg are dosed by body weight with a starting dose of 1-2 mg/kg/day, patients weighing 50 kg or more are dosed with 100 mg/day. In children with inadequate response the dose can be escalated up to 4 mg/kg/day. However, in this submission, the trial protocols are restricted to 1-2 mg/kg/day.[3;4] Response to treatment should be evaluated after 1 month: In case of persistent systemic manifestations dose may be adjusted in children or continued treatment with anakinra should be reconsidered by the treating physician.
Additional tests or investigations	Routine testing of hepatic enzymes during the first month should be considered, especially if the patient has pre-disposing factors or develops symptoms indicating liver dysfunction. Neutrophil counts are recommended prior to initiating anakinra treatment, and while receiving anakinra, monthly during the first 6 months of treatment and quarterly hereafter. Patients should also be tested for latent tuberculosis and viral hepatitis, in accordance with published guidelines on the use of Kineret and on management of patients receiving biological anti-inflammatory treatments.
List price and average cost of a course of treatment	Kineret 100 mg/0.67ml solution for injection pre-filled syringes (pack size 7), £183.61.[5] Assuming one injection per day (i.e. one pack per week), the average course for one year of treatment is approximately £9,580.51. The average cost of a course of treatment is difficult to estimate, as the disease duration and severity varies between patients.
Patient access scheme (if applicable)	There is no patient access scheme (PAS) for this technology.

Key: ANC, absolute neutrophil count; AOSD, adult onset Still's disease; DMARDs, disease-modifying anti-rheumatic drug; IL, interleukin; IL-1RI, interleukin-1 type I receptor; NSAID, nonsteroidal anti-inflammatory drug; PAS, patient access scheme; SC, subcutaneous; sJIA, systemic juvenile idiopathic arthritis.

B.1.3. Health condition and position of the technology in the treatment pathway

B.1.3.1. Disease overview

B.1.3.1.1. Clinical features

Systemic juvenile idiopathic arthritis (sJIA) is 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. Onset of sJIA typically occurs between 3 and 5 years of age. 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).[6]

Bywaters described 14 adult patients with the same symptoms as those seen in sJIA, establishing the diagnosis AOSD (referred to as AOSD when it begins in patients over the age of 16 years).[7] Signs and symptoms of AOSD are highly variable between individuals with episodes of disease occurring at variable frequencies and durations. Based on which symptoms predominate, the disease activity and evolution, 2 different AOSD phenotypes have been described; a systemic form (characterised by an acute onset which is characterised by fever, weight loss and other systemic manifestations) and the arthritis predominant form (characterised by indolent onset and systems mainly affecting the joints).[7-9] Within the systemic phenotype, the disease may be monocyclic or chronic (polycyclic [intermittent] or persistent)[9;10] (refer to Section B.1.3.1.4).

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 of regular daily activities.[6;7] Patients with peripheral joint involvement will require time off school or work for a period because of joint disability. The joints affected are frequently the knees, fingers and wrists and less frequently shoulders and ankles.[7] [6] Still's disease (including sJIA and AOSD) is generally a progressive disease that leads to significant pain, joint destruction and functional decline, and has a substantial economic impact both for patients and society.[6;7]

The 2 groups of patients are typically treated by paediatric rheumatologists/immunologists (sJIA) and by adult rheumatologists/immunologists (AOSD) separately. Their pathogenesis is still not completely understood but is believed to be of 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.

B.1.3.1.2. Epidemiology

AOSD and sJIA are rare diseases. Published data indicate the incidence of sJIA in Europe to range between 0.4 and 0.9 per 100,000 per year.[11-17] The estimated incidence of sJIA in the UK is 0.1 per 10,000 children per year (equivalent to 100 children diagnosed per year),[18] 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).[19] Onset of sJIA typically occurs between 3 and 5 years of age.[20] Experts considered that the proportion of males to females in sJIA was 1:1.[21] However, the experts also noted that there is some evidence which points to there being more female than male patients.[21]

There are limited data on the epidemiology of AOSD. AOSD is a rare, systemic, inflammatory disorder of unknown aetiology with an estimated incidence of 0.14 to 0.40 cases per 100,000 people and a prevalence of 1 to 34 cases per million people.[22;23] In England, there is an estimated incidence of 55 to 110 cases of AOSD per year, and prevalence is estimated at 400 to 800 patients.[24] AOSD has bimodal age distribution, the first peak between the ages of 15 to 25 years and the second between 36 to 46 years. However, about three-quarters of the patients report the onset of disease between 16 and 35 years of age.[25] Published literature suggests that females are affected by AOSD slightly more than males: estimates in the literature suggest that women represent up to 70% of patients.[10;26-28] However, clinical advice has suggested that it could more closely resemble a 1:1 split.[21]

B.1.3.1.3. Diagnosis

The clinical presentation of Still's disease can differ substantially.[26] It is difficult to diagnose as there are no specific tests or laboratory findings which may differentiate it from similar disorders, therefore diagnosis is usually based on clinical evaluation, patient history, identification of characteristic findings, and exclusion of other possible disorders. However, some blood tests may reveal characteristic changes associated with Still's disease such as: elevated white blood cells and/or platelets, low levels of red blood cells, elevated erythrocyte

sedimentation rate and elevated ferritin levels.[20;29] Potential differential diagnosis for sJIA include infections, connective tissue disease (e.g. lupus), acute leukaemia and other autoinflammatory diseases.[20] Potential differential diagnosis of AOSD include infections (e.g. endocarditis or occult infections), malignancies (e.g. lymphoma) or autoimmune diseases (e.g. polyarteritis nodosa, vasculitis and polymyositis).[23;30]

Time to diagnosis varies between sJIA and AOSD, with a longer run-in to diagnosis for AOSD compared with sJIA.[21] This difference arises from the fact that there is a longer list of conditions to rule out before a diagnosis can be confirmed, and for AOSD patients with monocyclic disease course this may result in resolution of symptoms in other specialties.[21] Evidence in sJIA patients suggests that misdiagnosis causes stress and suffering in sJIA patients, and clinical advice suggests that the length of time to diagnose AOSD patients also causes suffering in adult patients.[21;31]

The diagnostic criteria for sJIA are shown in Table 3 and for AOSD are shown in Table 4.

Table 3. 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

Key: HLA-B27, human leucocyte antigen B27; IgM, immunoglobulin M; sJIA, systemic juvenile idiopathic arthritis
Source: Grevich et al. 2017[32]

Table 4. 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	Major criteria: • Fever >39°C (intermittent, 1 week or longer)	Major criteria: • Spiking fever >39°C • Arthralgia

Cush 1987	Yamaguchi 1992	Fautrel 2002
• WBC >12,000/mL and ESR >40 mm/h • Negative ANA/RF • Carpal ankylosis	• Arthralgia >2 weeks • Typical rash • WBC >10,000/mL (>80% neutrophil granulocytes)	• 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

Key: ANA, antinuclear antibody; AOSD, adult onset Still's disease; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; WBC, white blood cell count

Source: Cush et al., 1987;[33] Fautrel et al., 2002;[34] Yamaguchi et al., 1992[35]

B.1.3.1.4. Clinical course

Patients with sJIA can follow variable disease courses. Patients previously diagnosed with Still's disease can be categorised as 'monocyclic', where a patient will experience one disease flare followed by life-long remission, or 'chronic', where the patient has polycyclic or persistent disease. Patients with polycyclic disease achieve remission and may discontinue treatment for long periods of time before an episode of recurrence, whereas patients with persistent disease – often associated with progressive arthritis with or without systemic symptoms and significant morbidity – may require life-long treatment; in both instances however, patients are considered to have 'chronic' disease.[6;32;36] While the proportion of patients with sJIA reported to follow each specific course has varied between studies (monocyclic 11%–40%, polycyclic 2.3%–34%, persistent 51%–66%), more than half the patients seem to follow the persistent disease course. In AOSD, the disease course is monocyclic in approximately one-third of patients and chronic in the remaining two-thirds one-third polycyclic and one-third persistent active disease).[9;10]

Studies have shown that clinical and laboratory features at 6 months after disease onset were predictive of outcome in sJIA.[37;38] Persistent systemic symptoms and thrombocytosis 6 months after disease onset were highly predictive of the development of destructive arthritis within 2 years of disease onset.[38] Moreover, fever, rash, the need for corticosteroids, and thrombocytosis 6 months after disease onset were predictive of poor functional outcome.[37]

B.1.3.1.5. Burden of disease

Patients with Still's disease (including sJIA and AOSD) 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),[37;39-43] and increased fatigue which impedes personal and social functioning.[31;44] In addition, the clinical course of Still's disease is often progressive with patients experiencing enduring disease activity, disability, and chronic morbidity.

One study in the sJIA population (Shenoi, 2018; n=61), reported mean (±SD) Child Health Questionnaire Parent-Form 50 (CHQ-PF50) physical, and psychosocial summary scores, to be substantially lower in sJIA patients than for the normative population (physical 40.0±18.2 vs. 53.0±8.8 and psychosocial 46.6±11.3 vs. 51.2±9.1).[45] It is reasonable to assume that HRQL is substantially lower in AOSD patients compared with the general population and may in fact be poorer than the sJIA population given the increased severity of the AOSD population. In addition, patients with Still's disease (including sJIA and AOSD), may also experience different complications affecting their clinical picture, management and prognosis; for example, macrophage activation syndrome (MAS) (refer to Section B.1.3.1.6).[46] The mortality rate from sJIA is higher than the mortality rate associated with other subtypes of JIA as seen in clinical practice,[47;48] and mortality rates of AOSD patients are reported to be as high as 9.3% and 10%.[49;50]

Available treatments for sJIA and AOSD patients aim to improve well-being while minimising side effects; first-line treatments for the control of inflammation usually involve non-steroidal anti-inflammatory drugs (NSAIDs) and intra-articular glucocorticoid injections.[51] However, use of high doses, particularly over a prolonged period of time, is 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.[52] 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.[52] Long-term use of high-dose corticosteroids can also lead to steroid dependency in both children and adults.[10] Second-line treatments usually include conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), such as methotrexate (MTX) or cyclosporine A (CyA), which 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. DMARDs may also be toxic to the liver or bone marrow and cause rashes and stomach disturbances).[53]

Research has indicated that the potential for school disruption in children with chronic arthritis is high, in severely affected children. Research in the JIA population has indicated that missing school can lead to problems in keeping up with schoolwork and social relationships, and a prolonged absence or multiple brief absences from school may contribute significantly to negative school performance. Shenoi et al. found that over a period of 2 months, patients with sJIA missed 2.9 school days due to sJIA (10% yearly loss).[45] 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, their work performance within and outside the home, and their participation in family, social, and leisure activities.[54] 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.[54] Disease-related reductions in productivity are not just due to the physical limitations posed by RA; mental/emotional limitations also play a key role in reducing HRQL and productivity.[54] Given the severity of AOSD it is reasonable to assume that the impact of AOSD may be similar to RA, or worse depending on the severity of symptoms.

Patients are likely to need to make frequent visits to GP, hospital, and therapists to manage the disease.[21] As well as imposing a substantial burden on patients' lives, sJIA and AOSD can also impose a substantial health burden on caregivers' and families' lives. A caregiver role can affect work productivity on several levels, including quitting the workforce, missed work time (absenteeism) and decreased productivity while at work.[55;56] In addition to absenteeism, caregiving may hamper work productivity while at work through negative health effects of caregiving (depression, anxiety) and decreased ability to concentrate on work activities.[55;56]

In caregivers' of children with sJIA the mean (±SD) 36-item short-form health survey (SF-36) mental component score was substantially lower compared with a normative population (46.2±10.7 vs. 50.0±10, respectively).[45] A total of 77% of caregivers were employed either full- or part-time; however, 36% had reduced their hours/stopped working due to their child's sJIA.[45] Productivity losses of biologic-treated patients and their families are possibly explained by the volume of sJIA-related healthcare appointments required as well as periods of symptom-related incapacity.[45] Over a period of 2 months, 11% of caregivers stated sJIA appointments caused them to miss work 'most of the time' or 'always'.[45] Caregivers lost 25 work days annually and 27.5 days of productivity (Work Productivity and Activity Impairment

questionnaire: Specific Health Problem [WPAI:SHP]: mean absenteeism 10%; presenteeism (impairment at work) 11%).[45] No evidence was identified in AOSD patients but clinical advice indicates that it is reasonable to assume that the consequence would be the same, if not worse given the severity of the condition, as for other chronic forms of arthritis.[21]

Economic burden

No data on economic burden were identified in the sJIA or AOSD populations. However, UK data from the JIA population (mean age 21.4 [SD 16.8]) were indicative of an economic burden on society due to the substantial health care costs associated with increased healthcare resource utilisation. The study estimated direct health care costs comprising 46.0 % 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 for patients not in need of assistance.[57;58]

B.1.3.1.6. Complications

Macrophage activation syndrome (MAS) is a reactive form of haemophagocytic lymphohistiocytosis (HLH), the most frequent life-threatening complication of Still's disease, both in paediatric and adult patients.[46;59] Approximately, 10% of sJIA and AOSD patients will develop MAS, and 30% to 40% have subclinical MAS.[32;60-62] MAS remains the most significant cause of mortality in sJIA. The probability of death due to MAS is associated with a range of estimates in the literature; however, experts[21] highlighted a study by Kumakura *et al.*, (2014)[62] owing to its large sample size, in which the estimated mortality rate was 12.9%. Approximately one-third of the patients requiring intensive care.[32;63]

The most common triggers of MAS are infections, drugs and flares of the disease, leading to an overproduction of cytokines, such as interleukin 1 beta (IL-1β), IL-6 and IL-18, and to an uncontrollable activation of the macrophages and CD8+ T cells.[59] The resulting clinical presentation includes continuous high fever, hepatosplenomegaly and histopathological evidence of haemophagocytosis by activated macrophages, in bone marrow as well as in other reticuloendothelial organs.[59;64] This severe clinical picture may evolve toward multiple organ failure and unfavourable outcome.[59]

Laboratory features of MAS include a drop in ESR, white blood cell (WBC) count, platelet counts, and fibrinogen levels with rising and extremely elevated ferritin levels, elevated liver

enzymes, lactate dehydrogenase, triglycerides, D-dimer, and prolonged prothrombin time, and partial thromboplastin time. Soluble IL-2 receptor and soluble CD163 are also elevated in active MAS.[27;59;65-67] In adults, evidence suggests that evidence of lymphadenopathy and liver involvement, and presence of abdominal pain may also be predictive factors.[68;69]

In 2016, classification criteria for MAS complicating sJIA were established by an expert panel at a consensus conference with a sensitivity of 73% and a specificity of 99% in preliminary validation analysis (PRINTO criteria): ferritin >684 ng/mL plus any 2 of: platelet count ≤181 x 10^9/L; aspartate aminotransferase >48 units/L; triglycerides >156 mg/dL; fibrinogen ≤360 mg/dL.[70] However, MAS is an evolving process and the patient may not meet all the criteria at onset. With regard to adults, guidelines are available but there is no real consensus: pyrexia of unknown origin in “at-risk” population; serum ferritin 500 – 10,000 µg/L (MAS possible); serum ferritin >10,000 µg/L (MAS probable). In cases where the underlying cause is not known, the investigative approach includes imaging/bone marrow biopsy for malignancy, thorough infectious screen and targeted viral serology dependent on epidemiological risk for exposure to various pathogens (EBV serology and EBV DNA is recommended in all patients).[71]

As far as the therapeutic strategies of MAS are concerned, the treatment includes the clearance of possible triggers, the suppression of the inflammatory response and supportive care.[59] Most patients would typically receive steroids, cyclosporine, anakinra and IV immunoglobulin (~50% of patients).[71]

Other severe complications reported in AOSD include disseminated intravascular coagulopathy (DIC) (non-remitting high fever and purpuric or petechial rash), thrombotic thrombocytopenic purpura (TTP) (microangiopathic haemolytic anaemia, thrombocytopenia and multiple organ failure), and diffuse alveolar haemorrhage(DAH) (haemoptysis, coughing and progressive dyspnoea), pulmonary hypertension (shortness of breath, chest pain, swelling and cyanosis), and aseptic meningitis (vomiting, headache and firm neck pain).[46;64;72]

B.1.3.2. Clinical pathway of care

B.1.3.2.1. Treatment guidelines

Clinical guidelines and consensus statements for sJIA and AOSD have recently been developed by the American College of Rheumatology (ACR).[73-75]

For sJIA patients with active systemic features and varying degrees of synovitis, the 2013 ACR Guidelines recommend anakinra, glucocorticoid monotherapy, or NSAIDs as initial therapy. If patients are prescribed NSAIDs and disease activity continues for 1 month, anakinra, glucocorticoids, or canakinumab/tocilizumab are recommended (the choice is typically determined by symptoms). For sJIA patients without active systemic features and varying degrees of synovitis, the guidelines recommend therapy with methotrexate (MTX) or leflunomide, NSAID monotherapy, or intra-articular glucocorticoid injection. Anakinra, abatacept, TNF-α inhibitors, or tocilizumab are then recommended as continued therapy if disease activity persists (though abatacept and TNF-α inhibitors are not licensed for the treatment of Still's disease). For patients with features indicative of MAS, the guidelines have a level C recommendation for anakinra, calcineurin inhibitors, or systemic glucocorticoid as initial therapies.[73]

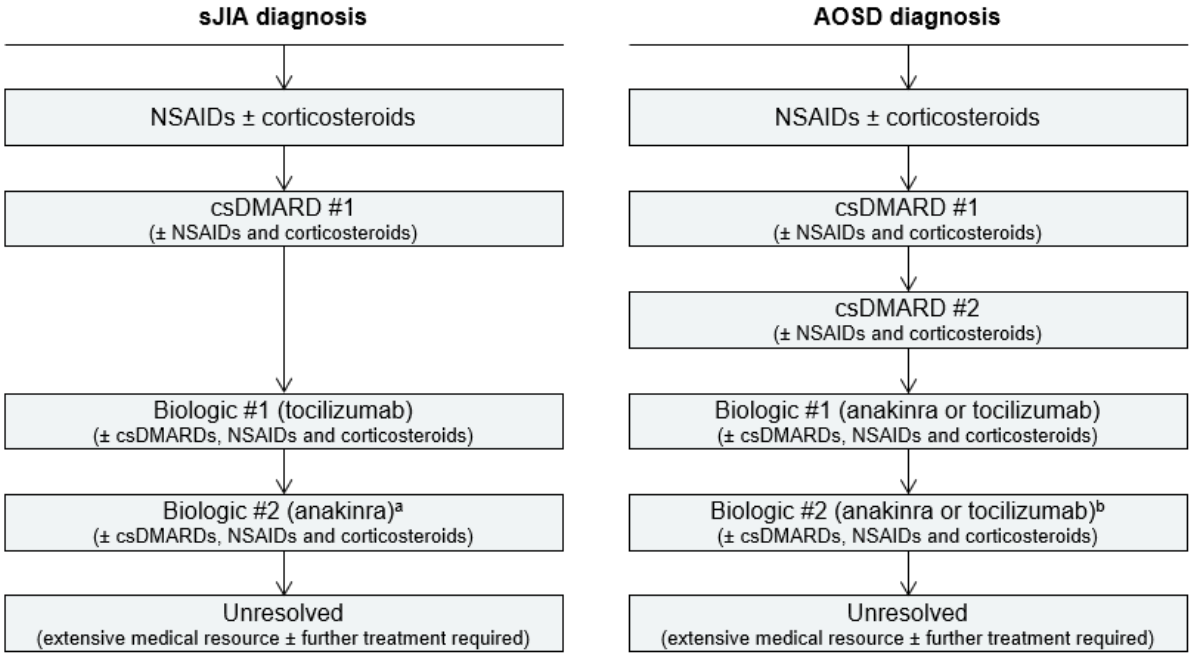
Due to a lack of guidelines for AOSD, a consensus document was created in order to help physicians dealing with new-onset AOSD.[76] The consensus document largely supports the 2012 best practice recommendations proposed by Pouchot and Arlet endorsing the use of anakinra (subcutaneous [SC] 100 mg/day) in refractory AOSD.

B.1.3.2.2. Current treatment pathway

Common fundamental features of sJIA and AOSD have resulted in the development of similar treatment approaches. The aim of treatment is to achieve remission of symptoms by minimising joint damage and controlling pain, fever and inflammation.

In the UK, the current clinical pathway of care for the pharmacological treatment of sJIA and AOSD includes sequential non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids (intra-articular, intravenous or oral) and conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) – specifically methotrexate (Figure 1).[24;77]

Figure 1. Current clinical pathway: sJIA and AOSD



Key: AOSD, adult-onset Still's disease; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; NSAIDs, non-steroidal anti-inflammatory drugs; sJIA, systemic juvenile idiopathic arthritis.
Notes: [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: NICE TA238[77]; NHS England[24]

Patients are typically first treated with NSAIDs + corticosteroids; steroids are also useful in the diagnostic work-up. After failing to achieve remission with NSAIDs + corticosteroids, patients progress to csDMARDs such as methotrexate. In accordance with NHS commissioning policy for AOSD, following methotrexate, AOSD patients are required to be treated with a second csDMARD (likely cyclosporine A [CyA]), before biologic treatment may be considered.[24] sJIA patients, however, typically only receive treatment with one csDMARD (e.g. methotrexate) prior to the use of biologic DMARDs (bDMARDs) in accordance with the NHS commissioning policy for sJIA.[78]

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 in accordance with NHS clinical commissioning policies for sJIA and AOSD.[24;78] However, csDMARDs may also be toxic to the liver or bone marrow and cause rashes and stomach disturbances.[53] csDMARDs that are beneficial in other subtypes of JIA are ineffective in sJIA.[79]

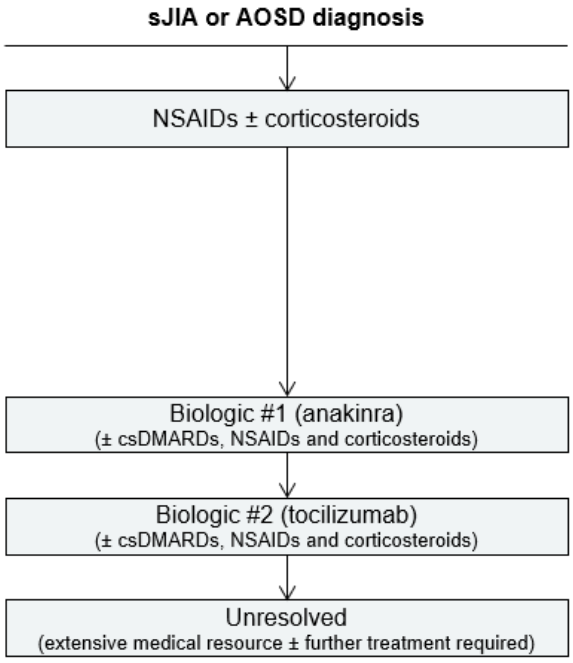
If symptoms are not adequately controlled with non-biological DMARDs, biologic therapies may be considered as per NHS England clinical commissioning policies (dated 2015 [JIA] and June 2018 [AOSD]).[24;78] AOSD patients may receive anakinra or tocilizumab first, based on clinician preference. sJIA patients currently receive tocilizumab first, based on current NICE guidance (TA238).[36] 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. Canakinumab is not recommended for the routine treatment of Still's disease in the NHS in England,[19] but may be used if refractory to other recommended treatments.

B.1.3.2.3. Proposed positioning of anakinra in the treatment pathway

The proposed positioning of anakinra is for use as per its licensed indication, specifically; Anakinra is indicated in adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg 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 NSAIDs or glucocorticoids. Anakinra can be given as monotherapy or in combination with other anti-inflammatory drugs and csDMARDs.

The use of anakinra aligned with indication (Figure 2) provides the increased possibility for patients to achieve remission earlier than would otherwise be possible. Earlier use of anakinra has the potential to reduce the number of patients with unresolved disease (associated with greater costs, poorer quality-of-life, and an increased risk of developing the potentially-fatal complication of MAS).

Figure 2. Proposed positioning of anakinra: sJIA and AOSD



Key: AOSD, adult-onset Still's disease; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; NSAIDs, nonsteroidal anti-inflammatory drugs; sJIA, systemic-juvenile idiopathic arthritis.

B.1.4. Equality considerations

There are no major equality issues concerning the use of anakinra.

B.2. Clinical effectiveness

Evidence base

- The key clinical data for anakinra comes from 3 RCTs in sJIA and AOSD populations:
  - Ilowite et al. (2009): a multicentre, blinded, placebo-controlled RCT of anakinra (1 mg/kg/day) with a subgroup of n=15 sJIA patients.
  - Quartier et al. (2011) (ANAJIS): a multicentre, double-blind, placebo-controlled RCT of anakinra (2 mg/k/day) of n=24 sJIA patients.
  - Nordström et al. (2012) (NORDIC AOSD05): a multicentre, open-label, csDMARD-controlled RCT of anakinra (100 mg/day) of n=22 AOSD patients.
- The safety and efficacy of anakinra has also been studied in a number of uncontrolled studies, in both sJIA and AOSD populations, notably including studies where anakinra was used earlier in disease course (i.e. before the use of csDMARDs).
- Anakinra has also been used extensively in NHS practice for over a decade.

Study findings

- The RCT evidence for anakinra demonstrated its efficacy across a range of outcomes:
  - In Ilowite et al. (2009), a total of 11/15 patients (73%) were ACRPedi 30 responders in the 12-week open-label run-in phase.
  - In Quartier et al. (2011) ANAJIS, 8/12 patients (67%) receiving anakinra, and 1/12 (8%) receiving placebo were modified ACRPedi 30 responders (absence of disease-related fever, and a decrease of at least 50% of CRP & ESR versus baseline). Glucocorticoid dose was reduced in 100% (anakinra) and 25% (csDMARD) patients.
  - In Nordström et al. (2012) NORDIC AOSD05, 6/12 patients (50%) receiving anakinra versus 2/10 (20%) receiving csDMARD were still in remission after 24 weeks. 17 patients completed the open-label extension phase (Week 52), of which 7/14 anakinra-treated patients, and 2/3 csDMARD patients switched to anakinra, were in remission. Mean glucocorticoid dose was reduced by 10.8 (anakinra) and 10.5 (csDMARD) prednisone equivalents in the majority of patients; or stopped entirely (3/12 [anakinra] vs 0/10 [csDMARD]).
- Evidence concerning the use of anakinra earlier in disease course (i.e. before the use of csDMARDs) demonstrated improved outcomes versus its use following csDMARDs.
  - Response was achieved in >50% of patients over 6, 12, 24, and 36 months, and that this effect was sustained over the long-term (median follow-up 5.8 years [IQR 2.9, 5.6]) with 96% of patients followed up for 5 years (24/25) having inactive disease, of which 75% (18/24) were off medication at the 5 year time point).
- The safety profile of anakinra is similar across indications, age groups, and dose levels, with the exception of injection site reactions (ISRs) which were more frequent in sJIA versus AOSD populations. However, ISRs are typically reported within the first 4 weeks of therapy, and resolved during continued treatment. The ability to adopt flexible dosing can minimise the duration of potential treatment-related adverse reactions particularly early in the course of treatment.
- Published studies in more than 600 patients, together with extensive safety data from studies in RA and CAPS, as well as more than 15 years of post-marketing experience in various indications including Still's disease, provide a substantial basis for a safety evaluation of anakinra in Still's disease and demonstrate that anakinra is an effective, well-tolerated valuable treatment option in the pathway of care for Still's disease (particularly when used early in disease course).

Key: ACRPedi, American College of Rheumatology paediatric criteria; AOSD, adult-onset Still's disease; CAPS, Cryopyrin-Associated Periodic Syndromes; CRP, C-reactive protein; csDMARDs, conventional synthetic disease-

modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; IQR, interquartile range; NHS, National Health Service; RA, rheumatoid arthritis; RCT, randomised controlled trial; sJIA, systemic juvenile idiopathic arthritis.

B.2.1. Identification and selection of relevant studies

A systematic literature review (SLR) of the clinical evidence evaluating the efficacy and safety of anakinra for the treatment of Still's disease (including sJIA and AOSD). Full methodology and results of the SLR, including PRISMA diagrams, used to identify and select clinical evidence relevant to the technology being appraised are discussed in Appendix D.

B.2.2. List of relevant clinical effectiveness evidence

Since the introduction of anakinra in 2002 in the EU for the treatment of RA, there has been substantial improvements in understanding the differences between autoimmune and autoinflammatory diseases, as well as the role of IL-1 inhibition. The benefit of anakinra in Still's disease is mainly based on bibliographic data from real-world clinical studies. The assessment of known and potential risks of anakinra treatment in Still's disease are also based on bibliographic data, but mostly on data from the use of anakinra in company-sponsored clinical studies in multiple indications, and the company post-marketing safety database, including individual case safety reports (ICSRs) from patients treated for Still's disease as well as other indications.

sJIA and AOSD share common clinical manifestations, and there is a growing understanding that these are different diagnostic names applied to one single inflammatory condition, here referred to as Still´s disease. However, the majority of published studies of treatment results are based on studies conducted by paediatric rheumatologists using the diagnostic label sJIA or by rheumatologists treating adults using the label AOSD. Therefore, the efficacy of anakinra for individual studies is summarized separately for sJIA and AOSD.

B.2.2.1. sJIA

The efficacy of anakinra in sJIA has been evaluated in:

- 1 prospective, randomised, double-blind, placebo-controlled, study to evaluate the safety, clinical response and pharmacokinetics of anakinra in polyarticular course JIA, including a subpopulation of sJIA patients (Ilowite et al. [2009]); and

- 1 prospective, multicentre, randomised, double-blind placebo-controlled study to evaluate the safety and efficacy of anakinra in patients with sJIA (Quartier et al. [2011]);

- 1 non-randomised UK registry study to evaluate the safety and efficacy of anakinra compared with tocilizumab in patients with sJIA (Kearsley-Fleet et al. 2019).[80]

Table 5. Clinical effectiveness evidence in sJIA: Ilowite et al. (2009)[a]

Study	**Ilowite (2008)**				
Study design	A randomised, multicentre, blinded, placebo-controlled trial with an open-label run-in period, followed by an open-label extension study				
Population	Patients presenting with polyarticular-course JRA between 2 and 17 years of age, with a minimum weight of 10 kg. **Note:** sJIA patients were a subgroup of the total population				
Intervention(s)	Anakinra 1 mg/kg/day (max 100 mg/day)				
Comparator(s)	Placebo				
Indicate if trial supports application for marketing authorisation	Yes	X[c]	Indicate if trial used in the economic model	Yes	
	No			No	X
Rationale for use/non-use in the model	Estimated remission[b] probabilities for anakinra are not reported within the trial. This is because at the time these studies were conducted, remission was not considered a relevant endpoint (given that remission had not been achieved for patients prior to study entry, and the studies were planned to be conducted for only a limited time horizon				

Reported outcomes specified in the decision problem	• Adverse effects of treatment
	• Disease activity:
	  • Proportion of patients with disease flares in the blinded-phase
	  • Changes in sJIA core components				

All other reported outcomes	• Pharmacokinetic assessments				

Key: sJRA, systemic juvenile rheumatoid arthritis

Notes: [a] Company sponsored study; [b] Remission defined as clinically inactive disease; [c] Ilowite study supported marking authorisation relevant to this appraisal.

Source: Ilowite et al. (2009)[3]

Table 6. Clinical effectiveness evidence in sJIA: ANAJIS (Quartier et al. [2011])

Study	**Quartier et al. (2011) (ANAJIS)**
Study design	A multicentre, randomised, double-blind, placebo-controlled trial, followed by an open-label phase
Population	Patients aged 2-20 years with sJIA. >6 months' duration
Intervention(s)	Anakinra 2 mg/kg daily via SC injection (maximum dose 100 mg)

Study	Quartier et al. (2011) (ANAJIS)				
Comparator(s)	Placebo				
Indicate if trial supports application for marketing authorisation	Yes	X	Indicate if trial used in the economic model	Yes	X
	No			No	
Rationale for use/non-use in the model	Estimated remission probabilities for anakinra are not utilised in the model. This is because at the time these studies were conducted, remission was not considered a relevant endpoint (given that remission had not been achieved for patients prior to study entry, and the studies were planned to be conducted for only a limited time horizon. Incidence of injection-site reactions is, however, reported and used in the model.				

Reported outcomes specified in the decision problem	• Disease activity defined as:
	  • response rate according to a modified ACRPedi 30 score[a]
	  • proportion of patients with inactive disease at Month 6
	• Adverse effects of treatment				

All other reported outcomes	• Pharmacokinetic assessments				

Key: ACRPedi 30, American College of Rheumatology Paediatric 30% improvement; SC, subcutaneous; sJIA, systemic juvenile idiopathic arthritis

Notes: [a] Modified ACRPedi 30: ACRPedi 30 response AND absence of disease-related fever (body temperature <38C over the past 8 years) AND 50% decrease compared with Day 1 or normalization of both CRP and ESR values; [b] Remission defined as clinically inactive disease

Source: Quartier et al (2011)[4]

Table 7. Clinical effectiveness evidence in sJIA: Kearsley-Fleet et al. (2019)

Study	Kearsley-Fleet, 2019				
Study design	Non-randomised UK registry study				
Population	Patients with systemic JIA registered starting either tocilizumab or anakinra from 1 January 2010 with baseline and 1 year data returned before 31 December 2016				
Intervention(s)	Anakinra				
Comparator(s)	Tocilizumab				
Indicate if trial supports application for marketing authorisation	Yes		Indicate if trial used in the economic model	Yes	
	No	X		No	X
Rationale for use/non-use in the model	While the study reported potentially useful information, it was not utilised in the model due to concerns over the patient population included in the analysis (e.g. history of MAS).				

Reported outcomes specified in the decision problem	• Disease activity:
	  • proportion achieving MDA
	  • proportion achieving clinically inactive disease
	  • proportion achieving ACRPedi 90 response
	  • change in active joint count, limited joint count, PGA, PGE, CHAQ, ESR and JADAS-71				

All other reported outcomes	• Treatment survival

Key: ACRPedi 90, American College of Rheumatology Paediatric 90% improvement; CHAQ, childhood health assessment questionnaire; CID, clinically inactive disease; ESR, erythrocyte sedimentation rate; JADAS-71, 71-joint juvenile arthritis disease activity score; MDA, minimal disease activity; PFA, physician global assessment of disease activity; PGE, patient (or parent) global evaluation of wellbeing; SC, subcutaneous; sJIA, systemic juvenile idiopathic arthritis

Notes: [a] Defined as 3 of the 6 JIA core outcome variables (active joint count, limited joint count, PGA, PGE, childhood HAQ (CHAQ) for functional ability, and ESR) improved by at least 90%, with a maximum of one variable worsening by >30%

Source: Kearsley-Fleet et al. (2019)[80]

In addition, the identified evidence is supported by 10 prospective and retrospective uncontrolled trials (reported in 11 publications). These trials are summarised in Table 8 and Appendix D.

Table 8. sJIA: supporting non-randomised (single arm) studies

Primary study ref.	Study design & objective	N	Anakinra dose, mg/day	Used in economic model
Gattorno, 2008	Pr	22	1 (100)	No[a]
Irigoyen, 2006	Re	14	NR	No[a]
Lequerre, 2008[b]	Pr	20	1–2 (100)	No[a]
Marvillet, 2011	Re	22	3 (100)	No[a]
Nigrovic, 2011	Re	46	Median starting dose 1.5 (IQR 1.1 to 2.0)	No[a]
Ohlsson, 2008	Re	7	1-2 (100)	No[a]
Pardeo, 2015	Re	25	Median starting dose 2.0 (IQR 1.3 to 2.0); up to 5	Yes
Pascual, 2005	Pr	9	2 (100)	No[a]
Vastert, 2014[c]	Pr	20	2 (100)	No[a]
Ter Haar, 2019[c]	Pr	42	2 (100)	No[a]
Zeft, 2009	Re	33	Median 1.6 (0.8 to 9.1)	No[a]

Key: NR, not reported; Pr, prospective Re, retrospective

Notes: [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 et al. [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: Gattorno 2008;[81] Irigoyen 2006;[82] Lequerre 2008;[83] Marvillet 2011;[84] Nigrovic 2011;[85] Ohlsson 2008;[86] Pardeo 2015;[87] Pascual 2005;[88] Ter Haar 2019;[89] Vastert 2014;[90] Zeft 2009[91]

B.2.2.2. AOSD

The efficacy of anakinra in AOSD has been evaluated in:

- 1 randomised, active-controlled, open-label study (Nordstrom et al. [2012]).[92]

Table 9. Clinical effectiveness evidence in AOSD

Study	**Nordström (2012) (NORDIC AOSD05)**				
Study design	An open, randomised (1:1), multicentre trial with 2 parallel patient groups with refractory AOSD. A 28-week open-label extension (OLE), with switching or add-on treatment with the comparator drug, was possible if improvement did not occur within 24 weeks				
Population	Patients diagnosed with AOSD according to the preliminary classification by Yamaguchi et al. 1992 and refractory to corticosteroids and DMARDs				
Intervention(s)	Anakinra 100mg/day via SC injection				
Comparator(s)	Any of the following DMARDs were included as comparators: • MTX 10−25 mg weekly oral/SC/IM • AZA 1−3 mg/kg/day oral; • LEF 20 mg/day oral • CyA 2.5−5 mg/kg/day divided into 2 oral doses • SSZ 1000−2000 mg/day oral				
Indicate if trial supports application for marketing authorisation	Yes	X	Indicate if trial used in the economic model	Yes	X
	No			No	
Rationale for use/non-use in the model	Estimated remission probabilities for anakinra over 24 weeks and incidence of injection site reactions are utilised in the model				

Reported outcomes specified in the decision problem	• Disease activity
	  • remission according to specific criteria[a]
	  • response rate
	• Adverse effects of treatment
	• HRQL (HAQ, SF-36 and global and disease-related assessments of health)				

All other reported outcomes	None				

Key: AZA, azathioprine; CyA, cyclosporine A; DMARDs, disease-modifying anti-rheumatic drugs; HAQ, health assessment questionnaire; HRQL, health-related quality of life; IM, intramuscular; LEF, leflunomide; MTX, methotrexate; OLE, open label extension; SC, subcutaneous; SSZ, sulfasalazine

Notes: [a] Defined as body temperature ≤37°C, CRP ≤10 mg/L and ferritin (≤200 mcg/l female or ≤275 mcg/l) and normal swollen joint count or tender joint count

Source: Nordstrom et al. (2012)[92]

In addition, the identified randomised controlled evidence is supported by 11 prospective and retrospective uncontrolled trials (Table 10).

Table 10. AOSD: supporting non-randomised (single arm) studies

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

Key: NR, not reported; N, number of patients

Notes: [a] The study also described 20 patients with sJIA treated with anakinra

Source: Cavalli 2015;[93] Colafrancesco 2017;[94] Dall'Ara 2016;[95] Gerfaud-Valentin 2014;[23] Giampietro 2010;[96] Giampietro 2013;[97] Ilioiu 2013;[98] Laskari 2011;[99]l Lequerre 2008;[83] Naumann 2010;[100] Ortiz-Sanjuan 2015[101]

B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1. sJIA

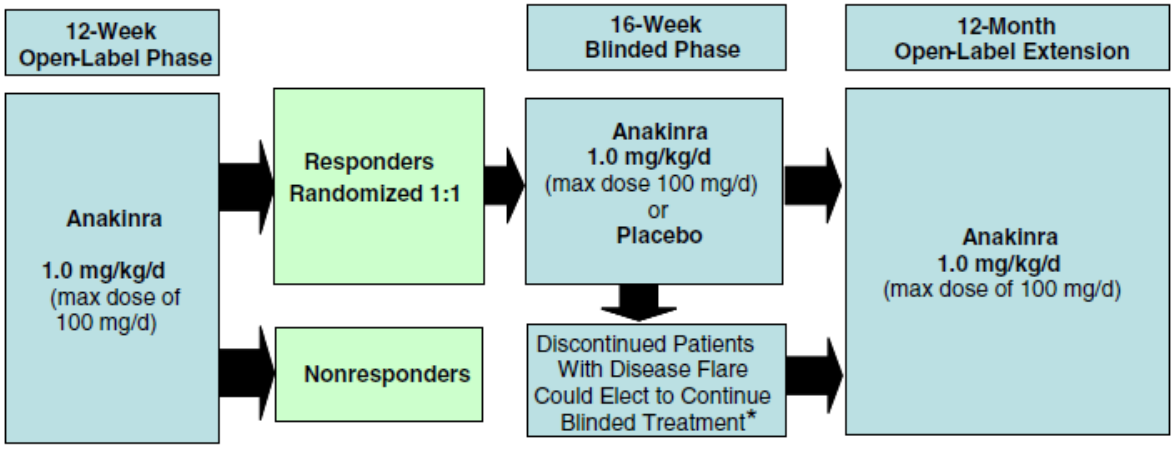
The methodological summaries of the controlled studies for anakinra in sJIA are presented in Section B.2.3.1.1, Section B.2.3.1.2 and Section B.2.3.1.3, and an overview is provided in Table 11.

B.2.3.1.1. Ilowite et al. (2009)

The study (990758/990779) reported by Ilowite et al. (2009) consisted of a 12-week open-label run-in phase (anakinra treatment 1 mg/kg/day, maximum 100 mg/day). Thereafter, patients meeting the definition of a responder (American College of Rheumatology [ACR] Juvenile Rheumatoid Arthritis [JRA] core set of criteria) were randomly assigned (1:1 ratio) to blinded doses of placebo or anakinra for an additional 16 weeks. A responder was defined as having a ≥30% improvement in 3 of any 6 JRA Core Set Criteria variables and with worsening by ≥30% in no more than 1 of the remaining variables. JRA Core Set Criteria include the following: physician global assessment of disease activity, patient/parent assessment of disease activity, Childhood Health Assessment Questionnaire (CHAQ),

number of joints with active arthritis, number of joints with limited range of motion, and ESR. Patients who experienced disease flare during the blinded phase were removed from the primary study but had the option to switch arms (if on “blinded” placebo then switched to “blinded” anakinra, and if on “blinded” anakinra then switched to “blinded” placebo) and continue blinded treatment. Disease flares were defined as (1) ≥30% worsening in at least three of the six JRA Core Set Criteria with improvement in ≤1 of the remaining six JRA Core Set Criteria or (2) a change in at least two active joints or a worsening by at least two units (based on a 0–10 scale) on either the global assessments or the visual analogue scale (VAS). Patients had the option to continue anakinra therapy in the 12-month open-label extension phase after completion of the blinded phase (Figure 3).

Figure 3. Design for study reported by Ilowite et al (2009)



Notes: * Patients switched treatment arms if they elected to continue
Source: Ilowite et al. (2009)[3]

The primary endpoint, safety, was assessed by evaluation of the incidence of treatment-emergent adverse events (including serious adverse events and infectious episodes) and laboratory values. Vital signs, blood chemistries, detection of IL-1ra antibodies, adverse events, concomitant medications, emergency room visits and/or hospitalisations, and injection site reactions (ISRs) were evaluated throughout the initial open-label phase, the blinded phase, and the extension study. Secondary endpoints included measures of efficacy and pharmacokinetics. Efficacy endpoints included the proportion of patients with disease flares in the 16-week blinded phase. Other efficacy assessments included time to disease flare and changes in the JRA core components at Week 28. Pharmacokinetics were

conducted at screening, Day 1 and Weeks 2, 4, 8, 12, 16, 20, 24, and 28 or early termination to characterize a population profile.

Note: This study assessed the safety and preliminary efficacy of anakinra in patients with polyarticular course JRA. The total of 86 patients included 15 patients with sJIA. All patients entered the 12-week open-label run-in phase (1 mg/kg anakinra daily, ≤100 mg/day). Fifty responders (including 11 in the sJIA population) were randomised to anakinra or placebo in a 16-week blinded phase, followed by a 12-month open-label extension (including 10 patients in the sJIA population). Only the data for the sJIA population are within scope of this submission.

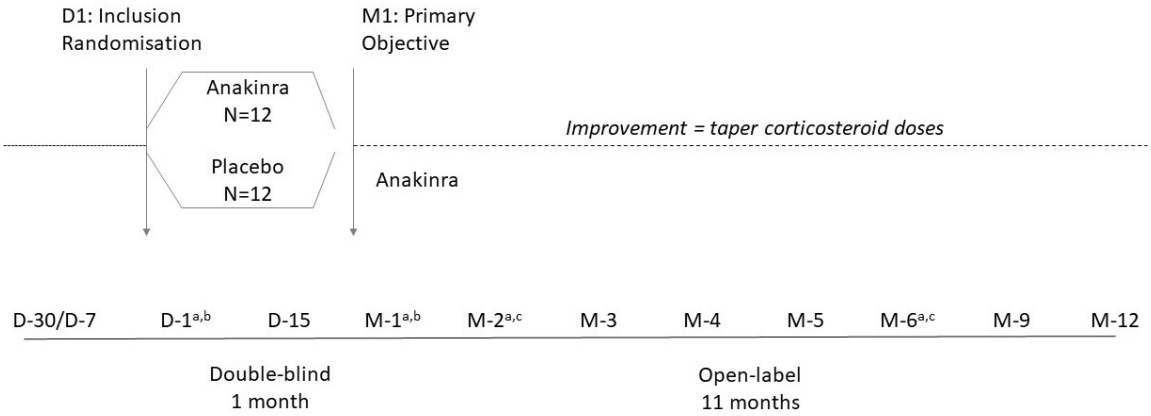
B.2.3.1.2. Quartier et al. (2011)

The study reported by Quartier et al. (2011) was a prospective, multicentre, randomized, double-blind, placebo-controlled study, in patients previously treated with glucocorticoids, DMARDs or biological agents. This study consisted of 2 parts.

- Part 1 was a randomised, double-blind, placebo-controlled phase. At Day 1, eligible patients were randomised to receive either anakinra or placebo (1:1) from Day 1 to Month 1 (M1) using a computer-generated random list.
- Part 2 was an open-label treatment period: all patients received anakinra after Month 1. Tapering the dose of corticosteroids was allowed after the Month 1 visit (reduction of 0.4–0.5 mg/kg monthly for daily doses of ≥1.5 mg/kg, 0.3–0.4 mg/kg for doses between 1 and 1.5 mg/kg, 0.2–0.3 mg/kg between 0.6 and 1 mg/kg, 0.1–0.2 mg/kg between 0.3 and 0.6 mg/kg, ≤0.10 mg/kg for doses <0.3 mg/kg).[4]

The study design is presented in Figure 4.

Figure 4. Study design: ANAJIS (Quartier et al. [2011])



Key: D, Day; M, Month

Notes: [a] Measurement of serum amyloid A and ferritin levels, assessment of the percentage of glycosylated ferritin, gene expression profiling analysis and cytokine measurements; [b] Measurement of the concentration of anakinra in plasma (pharmacokinetic analyses); [c] Measurement of serum anti-pneumococcal antibodies

Source: Quartier et al. 2011[4]

Included patients (aged 2 to 20 years) were required to have greater than 6 months of disease duration, active systemic disease (disease-related fever and / or CRP greater than 20 mg/L and / or first hour ESR greater than 20 mm/hour) and significant overall disease activity at Day 1 of the study. Patients were stratified by treatment centre then randomised equally to one month of treatment with anakinra 2 mg/kg SC daily, maximum daily dose of 100 mg (n=12) or placebo (n=12). No immunosuppressive drugs or DMARDs were allowed during the trial. Nonsteroidal anti-inflammatory drugs and corticosteroids had to be taken at stable dosage for 1 month before Day 1 and until Month 1.[4]

The primary objective was to demonstrate a higher proportion of responders to a modified American College of Rheumatology Paediatric Response Criteria 30 (ACRPedi 30) score after 1 month of treatment with anakinra compared to placebo. The modified ACRPedi 30 was developed specifically for this trial, in which a responder was required to fulfil the following 3 conditions:

- ACRPedi 30 response

AND

- Absence of disease-related fever (body temperature <38ºC over the previous 8 days)

AND

- 50% decrease compared with Day 1 or normalisation of both CRP and ESR values.[4]

During the open-label phase of the trial, the objective was to assess the number of patients who reached Month 6 with inactive disease, as defined by Wallace et al. (2004),[102] under a daily dose of prednisone <0.3 mg/kg or 10 mg, whichever was lower.[4]

B.2.3.1.3. Kearsley-Fleet et al. (2019)

The study was a non-randomised UK registry study. It included patients with sJIA registered in the UK Biologics for Children with Rheumatic Diseases study starting either tocilizumab or anakinra from 1 January 2010 with baseline and 1-year data returned before 31 December 2016.[80] Patients are recruited to the study at the point of starting a new biologic therapy but do not have to be biologic naïve.[80]

The objectives of this analysis were to (1) investigate and compare baseline characteristics in all children and young people in the UK between 2010 and 2016 starting either tocilizumab or anakinra for sJIA, (2) measure and compare short-term outcomes, including treatment response, treatment survival and stop reasons by one year of treatment between children starting (a) tocilizumab vs anakinra, and (b) either tocilizumab or anakinra as a first-line vs subsequent-line biologic therapy, and (3) investigate associations between baseline characteristics and outcomes at 1 year.[80]

At registration, the start of biologic therapy, the treating physician or affiliated clinical research nurse completed a detailed questionnaire on patient demographics, disease characteristics, ILAR classification and disease activity, and all current and past anti-rheumatic therapies, including prior biologics, and other medications.[80] Follow-up questionnaires were completed at 6 months, 1 year and then annually thereafter.[80] Details of changes to drug therapy, as well as current disease activity measures, were documented.[80] The occurrence of any adverse events or new health diagnoses were recorded.[80]

Three primary outcome measures were investigated at one year after start of biologic; proportion achieving minimal disease activity (MDA), proportion achieving clinically inactive disease (CID), and proportion achieving ACRPedi 90 response.[80] Both the MDA and CID criteria assess disease activity at a single time point. Patients with systemic JIA were defined as achieving MDA if the physician global assessment of disease activity (PGA) was no >3.4

cm, the patient (or parent) global evaluation of well-being (PGE) was no >2.1 cm, with a maximum of 1 active joint.[80] Patients were defined as achieving CID if they had no active joints, no systemic features, no active uveitis, PGA of zero, and a normal ESR defined in this study as 20mg/mm or less.[80] The ACR paediatric response criterion assesses change in disease activity over time and can be assessed with differing percentages of achievement.[80] A patient was defined as achieving an ACR Pedi 90 if three of the six JIA core outcome variables (active joint count, limited joint count, PGA, PGE, CHAQ for functional ability, and ESR) improved by at least 90%, with a maximum of one variable worsening by >30%.[80] Patients with a baseline core outcome variable of zero who worsen over time were classified to worsen that variable by >30%.[80] Patients who improved core outcome variable down to zero over time were classified to improve that variable by 100%.[80] Patients with a baseline core outcome variable of zero and remained at zero over time improved by 0% (neither improved nor worsened).[80] Patients who stopped biologic therapy before one year were classified as failing to achieve these outcomes, unless the stop reason was remission, in which case they were classified as achieving all outcomes.[80] Primary outcomes were compared between patients starting tocilizumab vs anakinra, and also between patients starting anakinra or tocilizumab as a first-line biologic vs patients starting as a subsequent biologic therapy.[80]

Secondary effectiveness outcomes studied included the change in active joint count, limited joint count, PGA, PGE, CHAQ, ESR and 71-joint juvenile arthritis disease activity score (JADAS-71), using regression models adjusted for baseline values.[80] A drug survival analysis was performed using a Kaplan-Meier curve to present the proportion of patients who stopped biologic therapy by 1 year.[80] The stop reasons of therapy given by the treating physician were categorised and described for each drug cohort: inefficacy, remission, adverse event. Secondary effectiveness outcomes and drug survival were compared between patients starting tocilizumab vs. anakinra, and between patients starting either drug as first-line biologic vs subsequent biologic.[80]

B.2.3.1.4. Supporting studies: uncontrolled evidence

The methodological summaries of the uncontrolled studies for anakinra in sJIA are provided in Table 12.

Table 11. Summary of methodology for sJIA studies

Study	Ilowite (2008)	ANAJIS, Quartier (2011)	Kearsley-Fleet (2019)
Location	The trial was conducted in 17 centres in the USA, Canada, Australia, New Zealand, and Costa Rica	6 centres located in France.	This study used data collected from the UK's Biologics for Children with Rheumatic Diseases (BCRD) study (1 January 2010 to 31 December 2016)
Trial design	A randomised, multicentre, blinded, placebo-controlled study with an open-label run-in period, followed by an open-label extension study.	A one-month multicentre, randomised, double-blind, placebo-controlled trial, followed by an open-label phase up to M12.	Non-randomised, prospective controlled study
Eligibility criteria for participants	**Key inclusion criteria:** • polyarticular-course JRA independent • ≥5 swollen joints due to active arthritis (not bony overgrowth) • three joints with limitation of motion at screening and the D1 visit • age 2 -17 years • minimum weight of 10 kg • receiving stable dose of methotrexate for 6 weeks before study entry • no biologic therapy within 4 weeks of initiating study drug. **Key exclusion criteria:** • ALT or AST>2.0 times the upper limit of normal, creatinine >1.5 times the upper limit of normal, WBC count <2.0×109/L, neutrophil count <1.5×109/L, or a platelet count of <150×109/L. • patients receiving a DMARD other than methotrexate • patients receiving intra-articular or systemic corticosteroid injections within 4 weeks before study entry.	**Key inclusion criteria:** • age 2–20 years • a diagnosis of sJIA with more than 6 months' disease duration despite oral prednisone or prednisolone ≥0.3 mg/kg or 10 mg/day (whichever is lower), patient displays active systemic disease (disease-related fever and/or CRP>20 mg/l and/or first hour ESR >20) and significant overall disease activity at D1 with at least three of the following criteria: − physician global assessment of disease activity ≥20/100 − parent/patient assessment of disease effect on overall wellbeing ≥20/100 − Childhood Health Assessment Questionnaire score ≥0.375/3 − ≥2 joints with active arthritis − ≥2 joints with non-irreversible limited range of motion − ESR ≥30) **Key exclusion criteria:** • previous treatment with an IL-1 inhibitor or any condition contraindicating immunosuppressive treatment • intravenous or intra-articular steroids, immunosuppressive drugs and DMARDs	**Key inclusion criteria** Patients with systemic JIA registered starting either tocilizumab or anakinra from 1 January 2010 with baseline and 1-year data returned before 31 December 2016 were included in this study.

Study	Ilowite (2008)	ANAJIS, Quartier (2011)	Kearsley-Fleet (2019)
		to be stopped at least 1 month before study onset or longer depending on half-life,	
Settings and locations where data were collected	Investigators and their research teams collected all data	The trial was hospital-based. Investigators and their research teams collected all data	UK's BCRD study
Trial drugs	Anakinra 1 mg/kg/day (max 100 mg/day) Placebo	Anakinra 2 mg/kg daily via SC injection (maximum dose 100 mg) Placebo	Anakinra Tocilizumab
Permitted and disallowed concomitant medication	The following medication was permitted throughout the study: • Methotrexate • Corticosteroids • NSAIDs.	No immunosuppressive drugs or DMARDs were allowed during the trial. NSAIDs and corticosteroids had to be taken at stable dosage for 1 month before Day 1 and until Month 1. Tapering the dose of corticosteroids was allowed after the M1 visit with reduction of: • 0.4–0.5 mg/kg monthly for daily doses of ≥1.5 mg/kg • 0.3–0.4 mg/kg for doses between 1 and 1.5 mg/kg • 0.2–0.3 mg/kg between 0.6 and 1 mg/kg • 0.1–0.2 mg/kg between 0.3 • 0.6 mg/kg, ≤0.10 mg/kg for doses <0.3 mg/kg	Unclear; however, concomitant steroid (64%) and methotrexate (83%) reported
Primary outcomes (including scoring methods and timings of assessments)	The incidence of treatment-emergent adverse events	Proportion of responders according to a modified ACRPedi 30 score which includes: • ACRPedi 30 response − absence of disease-related fever (body temperature <38°C over the previous 8 days) − 50% decrease compared with D1 or normalisation of both CRP and ESR values	• Proportion achieving MDA − assessed disease activity at a single timepoint − patients with sJIA were defined as achieving MDA if the PGA was ≤3.4 cm, PGE was ≤2.1 cm, & maximum of 1 active joint • Proportion achieving CID − assessed disease activity at a single timepoint

Study	Ilowite (2008)	ANAJIS, Quartier (2011)	Kearsley-Fleet (2019)
			− no active joints, no systemic features, no active uveitis, PGA of zero & ESR ≤20 mg/mm • Proportion achieving ACRPedi 90 response − defined as 3 of the 6 JIA core outcome variables active joint count, limited joint count, PGA, PGE, childhood HAQ (CHAQ) for functional ability, and ESR) improved by at least 90%, with a maximum of one variable worsening by >30% Patients with a baseline core outcome variable of zero who worsen over time were classified to worsen that variable by >30%. Patients who improved core outcome variable down to 0 over time were classified to improve that variable by 100%. Patients with a baseline core outcome variable of 0 and remained at zero over time improved by 0% (neither improved nor worsened). Patients who stopped biologic therapy before 1 year were classified as failing to achieve these outcomes, unless the stop reason was remission, in which case they were classified as achieving all outcomes.
Other outcomes used in the economic model/specified in the scope	• The proportion of patients with disease flares in the 16-week blinded phase. • Time to disease flare • Changes in the JRA core components at Week 28 • Pharmacokinetic assessments	• Modified ACRPedi 30, 50, 70 and 100 responses, included an improvement of 30%, 50%, 70% or more and 100% respectively, in at least three of the six core criteria for juvenile rheumatoid arthritis and a worsening of 30% or more in no more than one of the following criteria: − PGA − PGE − number of joints with active arthritis	• Change in active joint count • Change in limited joint count • Change in PGA • Change in PGE • Change in CHAQ • Change in ESR • Change in JADAS-71 • Drug survival (patients who stopped biologic therapy by 1 year. The stop reasons of therapy were categorised as inefficacy, remission, adverse event)

Study	Ilowite (2008)	ANAJIS, Quartier (2011)	Kearsley-Fleet (2019)
		− number of joints with limited range of motion − CHAQ − ESR • Proportion of patients at Month 6 with inactive disease as defined by Wallace et al. (2004)[102] under a daily dose of prednisone <0.3 mg/kg or 10 mg, whichever is lower. • Adverse effects of treatment	
Pre-planned subgroups	NR	NR	NR

Key: ACRPedi, American College of Rheumatology paediatric; AEs, adverse events; AKA, anakinra; BCRD, Biologics for Children with Rheumatic Diseases CHAQ; childhood health assessment questionnaire; CID, clinical inactive disease; CRP, C-reactive protein; D, day; DMARD, disease-modifying anti-rheumatic drug; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; HRQL, health-related quality of life; IL, interleukin; ISR, injection site reaction; JADAS-71, juvenile arthritis disease activity score; JRA, juvenile rheumatoid arthritis; M, month; MAS, macrophage activation syndrome; MDA, minimal disease activity; NR, not reported; PGA, physician's global assessment of disease activity; PGE, patient's or the parents' global assessment of overall wellbeing; PK, pharmacokinetic; PrC, prospective controlled; RCT, randomised controlled trial; SC, subcutaneous; SF-36, short form 36; sJIA, systemic-onset juvenile idiopathic arthritis; TOC, tocilizumab; vs, versus; WBC, white blood cell

Source: Ilowite et al. (2009);[3] Kearsley-Fleet et al. (2018);[80] Quartier et al. (2011)[4]

Table 12. Summary of methodology: uncontrolled studies (sJIA)

Author, year	Location, no. of centres	Study design	Population	Intervention	Key outcomes	Follow-up
Gattorno, 2008	Italy, NR	Prospective, open-label study	Patients with sJIA receiving long-term steroid therapy, plus six additional patients with active sJIA who had not received steroid treatment.	Starting dosage of anakinra was 1 mg/kg/day, subcutaneously (maximum 100 mg). Doses could be increased to 3 or 4 mg/kg.	Clinical response: clinical parameters (fever, rash, number of active joints) and laboratory parameters (CRP, ESR, haemoglobin, WBC) Corticosteroid requirement.	Patients were treated for a mean of 1.36 years (range 0.3 to 2.59 years).
Irigoyen, 2006	USA, 5 centres	Retrospective chart review	Patients with refractory sJIA.	Anakinra (dose NR)	Clinical response: clinical parameters (fever, rash, number of active joints) and laboratory parameters (ESR, haemoglobin, platelets, WBC).	Length of follow-up NR
Lequerre, 2008[a]	France, multicentre (number NR)	Prospective, open-label study	35 patients were included, 20 with sJIA and 15 with AOSD.	All patients treated with corticosteroids prior to anakinra (1 to 2 mg/kg/day; maximum 100 mg/day)	Systemic features: fever, skin rash, ESR or CRP levels, and other disease markers (TJC, SJC, physician's and patient's or parent's assessment of disease activity or pain on a VAS)	14.7 months (range 2-27 months)
Marvillet, 2011	Belgium, single centre	Retrospective chart review	Patients with sJIA treated with anakinra	Anakinra (1-3 mg/kg/day)	Clinical response: clinical parameters (fever, rash, arthritis joint count, assessment of disease activity by physician and parent/patient, pain by parent/patient) and laboratory parameters (ESR, CRP).	11-56 months
Nigrovic, 2011	11 centres in 4 countries (Countries NR)	Retrospective chart review	Patients with sJIA receiving treatment with anakinra as part of the initial DMARD regimen	Dose: NR Anakinra alone:22% Anakinra plus DMARDs without corticosteroid:11% Anakinra plus corticosteroids without other DMARDs:46% Anakinra plus DMARDs plus corticosteroids:22%.	Clinical response: clinical parameters (fever, rash, number of active joints) and laboratory parameters (CRP and ESR, haemoglobin, platelets). Corticosteroid requirement.	Median, months (IQR): 14.5 (7.5-26)
Ohlsson, 2008	UK, 3 tertiary, paediatric rheumatology centres	Retrospective chart review	Patients with sJIA who had received anakinra	Anakinra median daily dose of 1 mg/kg (range 0.4–2mg/kg)	Juvenile arthritis core set criteria, clinical and laboratory findings were recorded.	Median, years (range): 1 (0.75-2.3)
Pardeo, 2015	NR, single centre	Retrospective chart review	Patients with sJIA treated with anakinra for at least 6 months	Anakinra 2 mg/kg/day	The number of patients who achieved clinically inactive disease at 6 months, defined as absence of active arthritis and specific sJIA features (i.e.	Median 2.8 years (range 1.6-7.3)

Author, year	Location, no. of centres	Study design	Population	Intervention	Key outcomes	Follow-up
					absence of fever, rash, serositis, splenomegaly, and generalized lymphadenopathy), and normal ESR and CRP.	
Pascual, 2005	USA, NR	Prospective, open-label study	Patients with sJIA	Anakinra 2 mg/kg, up to 100 mg.	Clinical response: clinical parameters (fever, rash, arthritis score) and laboratory parameters (CRP, ESR, haemoglobin, platelets).	Mean, months (range): 6.6 (2-12)
Vastert, 2014	Holland, single centre	Prospective, observational cohort study	Patients with new-onset sJIA	Anakinra 2 mg/kg (max 100 mg) Anakinra was used as initial therapy after failure to respond to NSAIDs, but before the use of DMARDs, systemic corticosteroids, or other biologic agents.	Clinical response to treatment was evaluated according to the adapted ACRpedi 30, 50, 70, and 90 criteria.	Mean, months (range): 32 (12-54)
Ter Haar, 2019[c]	Holland, single centre	Prospective, observational cohort study	Patients with new-onset sJIA	Anakinra 2 mg/kg (max 100 mg) Anakinra was used as initial therapy after failure to respond to NSAIDs, but before the use of DMARDs, systemic corticosteroids, or other biologic agents.	Clinical response to treatment was evaluated according to the adapted ACRpedi 30, 50, 70, and 90 criteria.	Median of 5.8 years (IQR 2.9, 7.6 years)
Zeft, 2009	3 Paediatric Rheumatology centres	Retrospective case series	Patients with sJIA resistant to conventional aggressive immunosuppressive treatments	Anakinra median dose of 1.6 mg/kg/day (range 0.8 to 9.1 mg/kg/day)	Clinical response: clinical parameters (fever, rash, number of active joints) and laboratory parameters (ESR, haemoglobin, platelets).	NR

Key: ACRPedi, American College of Rheumatology paediatric; AOSD, adult-onset Still's disease; CRP, C-reactive protein; DMARD, disease-modifying anti-rheumatic drug; ESR, erythrocyte sedimentation rate; IQR, interquartile range; NR, not reported; NSAID, nonsteroidal anti-inflammatory; sJIA, systemic-onset juvenile idiopathic arthritis; SJC, swollen joint count; TJC, tender joint count; WBC, white blood cell

Notes: [a] The study also described 15 patients with AOSD treated with anakinra; [b] Study is a retrospective study of patients treated with IL-1-INH, study reported data for anakinra and canakinumab but only anakinra data were reported in this submission as canakinumab is not recommended for the treatment of Still's (including sJIA and AOSD) in the UK NHS; [c] Long-term follow-up of prospective study Vastert 2014 Long-term follow-up of prospective study. (In addition, to the 20 patients included in Vastert et al. [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: Gattorno et al. 2008[81]; Irigoyen et al., 2006[82]; Lequerre et al., 2008[83]; Marvillet et al., 2011[84]; Nigrovic et al., 2011 [85]; Ohlsson et al, 2008[86]; Pardeo et al., 2015[87]; Pascual et al., 2005[88]; Ter Haar et al., 2019;[89] Vastert et al.,2014[90]; Zeft et al., 2009[91]

B.2.3.2. AOSD

The methodological summaries of the controlled studies for anakinra in AOSD are presented in Section B.2.3.2.1 and an overview is provided in Table 13.

B.2.3.2.1. Nordstrom et al. (2012)

NordicAOSD05 (Nordstrom et al. [2012])[92] was a 24-week, open-label, multicentre trial in adults with refractory corticosteroid-dependent AOSD who were randomised to receive either anakinra 100 mg/day or csDMARDs. An option of a 28-week extension was available if no improvement occurred during the first phase of the trial.

The study enrolled adults with a diagnosis of AOSD, according to Yamaguchi et al.[35] criteria, and treated with a corticosteroid and possibly a csDMARD for at least two months prior to randomisation. Patients had to be considered refractory to corticosteroids and csDMARD, defined as need for prednisone at least 10 mg/day (or equivalent) with or without concomitant use of csDMARD, and unacceptable disease activity as determined by the investigator. Doses of NSAID and oral corticosteroid had to have been stable for at least two weeks, and doses of csDMARD had to be stable for at least four weeks, prior to randomisation. Study medicines were daily anakinra 100 mg SC injection, or methotrexate 10 mg to 25 mg weekly oral/SC/intramuscular, azathioprine 1 to 3 mg/kg/day oral, leflunomide 20 mg/day oral, cyclosporine 2.5 to 5 mg/kg/day in two divided oral doses or sulfasalazine 1,000 to 2,000mg/day oral. Increases in csDMARD dose was allowed following the Week 4 assessment. Corticosteroid dosages had to be kept constant for four-weeks following randomisation, and any increases implied treatment failure. Patients were allowed two intra-articular corticosteroid injections in 24 weeks and patient could receive NSAIDs if needed.4

The primary endpoint was remission of AOSD following 8 weeks of treatment with study medicine in all randomised patients. The criteria for AOSD remission required patients to be afebrile (≤37°C body temperature) in the absence of NSAIDs 24 hours prior to measurement, and to have a decrease of CRP and ferritin to within reference limits, to have normal swollen joint counts and normal tender joint counts.[92]

After 4 weeks, the effect of anakinra therapy was assessed. Enhancement of csDMARD dose was allowed, but escalation of corticosteroids implied treatment failure. Efficacy was then assessed at Weeks 8, 12 and 24.[92]

Table 13. Summary of methodology for AOSD trial

Study	Nordström (2012) (NORDIC AOSD05)
Location	10 centres in Finland, Norway, and Sweden.
Trial design	An open, randomised (1:1), multicentre trial with 2 parallel patient groups with refractory AOSD. A 28-week open-label extension (OLE), with switching or add-on treatment with the comparator drug, was possible if improvement did not occur within 24 weeks
Eligibility criteria for participants	**Key inclusion criteria:** • Diagnosed with AOSD according to Yamaguchi, et al. 1992.[35] • Exposed to a corticosteroid and possibly a csDMARD for ≥2 months prior to randomisation because of diagnosed AOSD. • Considered refractory to corticosteroids and csDMARD[a] • Doses of NSAID and oral corticosteroid had been stable for ≥2 weeks before randomisation. • If using csDMARD, doses had been stable for ≥ 4 weeks before randomisation. • If previously treated with anti-TNF agents, patients had discontinued etanercept ≥ 4 weeks and infliximab or adalimumab ≥ 8 weeks prior to starting the study medication. **Key exclusion criteria:** • Use of corticosteroids below prednisolone equivalent of 10 mg/day • Total WBC count < 2.0 H 10^9/l, neutrophil count < 1.0 H 10^9/l, or platelet count <100 H 10^9/l • Elevated serum creatinine (≥ 1.5 H upper limit of normal). • Elevated serum ALT or AST (≥ 3 H upper limit of normal) • Abnormal haemoglobin or erythrocyte count (outside 30% of the upper/lower limits of normal). • Severe comorbidities (e.g., diabetes mellitus, cardiovascular or pulmonary diseases, history of cancer). • Use of anti-TNF agents ≤ 4 weeks (etanercept) or ≤ 8 weeks (infliximab or adalimumab) prior to randomisation or need for using them during the entire study. • Treatment in the past with anakinra.
Settings and locations where data were collected	Hospital-based setting. Investigators and their research teams collected all data.
Trial drugs	Anakinra 100mg/day via SC injection plus corticosteroids Any of the following csDMARDs were included as comparators plus corticosteroids: • MTX 10−25 mg weekly oral/SC/IM • AZA 1−3 mg/kg/day oral; • LEF 20 mg/day oral • CyA 2.5−5 mg/kg/day divided into 2 oral doses

	• SSZ 1000−2000 mg/day oral
Permitted and disallowed concomitant medication	All patients initially received prednisolone ≥ 10 mg/day and NSAID if required. Corticosteroid dosage had to be kept constant for 4 weeks from randomisation. Two intraarticular corticosteroid injections in 24 weeks were allowed.
Primary outcomes (including scoring methods and timings of assessments)	The primary endpoint was remission according to specific criteria at 8 weeks: • afebrile (≤ 37°C body temperature, measured twice from armpit), in the absence of NSAID 24 hours prior to measurement • decrease of CRP and ferritin to reference limits and normal SJC and TJC.
Other outcomes used in the economic model/specified in the scope	HAQ SF-36 Global and disease-related assessments Adverse events
Pre-planned subgroups	NR

Key: ALT, alanine transaminase; AOSD, adult-onset Still's disease; AST, aspartate aminotransferase; AZA, azathioprine; CRP, C-reactive protein; CyA, cyclosporine; csDMARD, conventional synthetic disease modifying antirheumatic drug; HAQ, health assessment questionnaire; LEF, leflunomide; MTX, methotrexate; NR, not reported; NSAID, nonsteroidal anti-inflammatory; SC, subcutaneous; SJC, swollen joint count; SSZ, sulfasalazine; TJC, tender joint count; WBC, white blood cell; Wk, week

Notes: [a] Refractory state defined as need for prednisolone≥ 10 mg/day (or equivalent) with or without concomitant use of DMARD, and unacceptable disease activity as determined by the investigator.

Source: Nordström et al. 2012[92]

B.2.3.2.2. Supporting studies: uncontrolled evidence

The methodological summaries of the uncontrolled studies for anakinra in AOSD are provided in Table 14.

Table 14. Summary of methodology: uncontrolled studies (AOSD)

Author, year	Location, no. of centres	Study design	Population	Intervention	Key outcomes	Follow-up
Cavalli, 2015	Italy, single centre	Retrospective chart review	Severe or refractory AOSD	Anakinra 100 mg/day	**Complete response** - absence of articular and systemic manifestations of AOSD with normalisation of the inflammatory markers CRP and ESR, and with a reduction of the corticosteroid dose of at least 50% for at least 2 months. **Partial response** - a clinical improvement without normalisation of inflammatory markers, or without a 50% reduction in the corticosteroid dose.	Patients followed up ≥12 months
Colafrancesco, 2017	Italy, 18 centres	Retrospective chart review	Refractory AOSD fulfilling Yamaguchi criteria	Anakinra 100 mg/day at baseline	**Complete response** - signs of active disease absent and inflammatory markers normalised. **Partial response** - when complete response was not achieved although there were clear signs of clinical improvement according to the attending physician.	Mean follow-up 56.8±54 months
Dall'Ara, 2016	Italy, single centre	Retrospective chart review	Patients who received a diagnosis of AOSD between 1997 and 2014, and fulfil the Yamaguchi criteria	NR	**Complete response** - the normalisation of inflammatory markers (CRP and ESR), and the absence of articular and systemic manifestation for at least 6 months.	Median follow-up 61 months (range 41-100)
Gerfaud-Valentin, 2014	Patients identified via Medical Information Department of Hospices Civils de Lyon	Retrospective chart review	Patients fulfilling either the Yamaguchi or Fautrel criteria for AOSD	NR	**Controlled disease** – clinically asymptomatic AOSD **Complicated AOSD** – 1 or more of the following conditions: acute fulminant hepatitis, disseminated intravascular coagulation, thrombotic microangiopathy, reactive haemophagocytic syndrome, shock, multiple organ failure, myocarditis, complicated pericarditis, severe sepsis, acute respiratory distress syndrome, AA amyloidosis	Mean follow-up 27.8 months (range 14-36)

Author, year	Location, no. of centres	Study design	Population	Intervention	Key outcomes	Follow-up
Giampietro, 2013	France, national survey, multicentre	Retrospective, chart review using standardised questionnaire	Refractory AOSD patients defined by Yamaguchi diagnostic criteria	Anakinra daily dose of 100 mg	**Complete remission** - disappearance of all AOSD symptoms, and a partial response was defined as persistence of some general or articular signs	NR
Giampietro, 2010	France, Multicentre	Retrospective, chart review using standardised questionnaire	Refractory AOSD patients defined by Yamaguchi diagnostic criteria	Anakinra daily dose of 100 mg	**Complete remission** - disappearance of all AOSD symptoms **Partial response** - persistence of some general or articular signs.	NR
Iliou, 2013	Greece, single centre	Retrospective, observational study	Patients diagnosed with AOSD	Anakinra daily dose of 100 mg	**Response** - remission of systemic manifestations (fever, rash, raised inflammatory markers) and arthritis.	Median follow-up 7 years (range 2-19)
Laskari, 2011	NR, single centre	Prospective, open-label study	Patients with refractory AOSD	Anakinra daily dose of 100 mg	**ACR20, 50, and 70 scores**. **Complete response** - complete resolution of all disease-related symptoms, except for joint erosion. **Partial clinical response or partial laboratory response** - improvement (at least 10% when measurement was feasible) in one or more related clinical or laboratory, respectively, manifestations, but without complete resolution of disease activity.	≥ 6 months
Lequerre, 2008[a]	France, multicentre number NR)	Prospective, open-label study	Patients with AOSD diagnosed according to the Yamaguchi criteria	Anakinra daily dose of 100 mg	**Response** - resolution of systemic symptoms and an improvement of the ACR score by at least 20 %.	Mean 14.7 months (range 2-27 months)
Naumann 2010	Germany, single centre	Prospective open-label case series	Patients with refractory AOSD	Anakinra daily dose of 100 mg	**Sustained remission** (assumed to be the absence of clinical symptoms e.g. rash and arthritis although not explicitly stated) Inflammatory laboratory markers – CRP, ESR, neutrophils, ferritin Glucocorticoid use	Treatment period 6 to 48 months

Author, year	Location, no. of centres	Study design	Population	Intervention	Key outcomes	Follow-up
Ortiz-Sanjuan, 2015	Spain, multicentre	Retrospective, open-label study	Refractory AOSD patients	Anakinra daily dose of 100 mg	Outcomes not specified – clinical and laboratory data collected	Median 16 months (IQR 5-50)

Key: AOSD, adult-onset Still's disease; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; ESR, erythrocyte sedimentation rate; IQR, interquartile range; NR, not reported

Notes: [a] The study also described 15 patients with AOSD treated with anakinra; [b] The study also described 15 patients with AOSD treated with anakinra; [h] Patients enrolled in the present study are almost overlapping with those included in Colafrancesco et al., 2017

Source: Cavalli et al. 2015[93]; Colafrancesco et al. 2017[94]; Dall'Ara et al. 2016[95]; Gerfaud-Valentin et al. 2014[23]; Giampietro et al. 2013[97] Giampietro et al. 2010[96]; Iliou et al. 2013[98]; Laskari et al. 2011;[99] Lequerre et al. 2008;[83] Naumann et al., 2010;[100] Ortiz-Sanjuan et al. 2015[101]

B.2.4. Baseline characteristics

B.2.4.1. sJIA

B.2.4.1.1. Ilowite et al. (2008)

Baseline demographics and clinical characteristics of the sJIA patients are presented (Table 15).

Table 15. Baseline demographics and clinical characteristics for sJIA trials: Ilowite et al. (2008)

Characteristics	Anakinra (n=15)[b]
Female, n (%)	7 (47)
Age, mean value, years (SD)	10.6 (4.29)
Disease duration, mean value, years (SD)	5.3 (3.34)
Starting dose of anakinra (mg/kg)	1
Baseline steroid dose, mean value (SD), mg/kg	0.2 (max 10)[a]

Key: SD, standard deviation

Notes: [a] If administered, kept stable for 4 weeks before study; [b] sJIA patients

Source: Ilowite et al. (2009)[3]; Data on File, 2013[103]

B.2.4.1.2. Quartier et al. (2011)

Baseline demographics and clinical characteristics of patients enrolled in the study reported by Quartier et al (2011) are presented in Table 16. Although not tested for statistically significant difference, systemic features are generally lower for the anakinra group. The anakinra group had a mean duration of 1 more year of treatment with steroids, compared to placebo. However, the disease mean duration was also greater by one year. In contrast, the placebo group had higher numbers of patients who had received previous treatments with DMARDs (67% vs. 92% in the anakinra and placebo groups, respectively).[4]

The global assessments, which are widely used in rheumatoid arthritis practice (Table 16) were considered to be generally well balanced between arms. These assessments often incorporate a single question with a 0–10 or 0–100 response, where higher is worse.[4]

Table 16. Baseline demographics and clinical characteristics for sJIA trials: ANAJIS (Quartier et al. [2011])

	Quartier (2011) (ANAJIS)	
Characteristics	**Anakinra (n=12)**	**Placebo (n=12)**
Demographic features		
Female, n (%)	7 (58)	8 (67)
Age, mean value, years (SD)	9.5 (5.19)	7.5 (3.73)
Disease mean duration, years (SD)	4.2 (3.33)	3.2 (1.95)
Systemic features		
Fever (>38°C), no. of patients (%)	4 (33.3)	5 (41.7)
CRP, mg/l (n≤6), mean value (SD)	66 (64.40)	84 (65.74)
ESR first hr (n≤10), mean value (SD)	44 (23.37)	57 (27.85)
SAA, mg/l (n≤6.4), mean value (SD)	366 (262)	368 (229)
High serum ferritin[a], no. of patients	2	3
Joint assessment		
Active joints, mean no. (SD)	16 (13.12)	16 (15.84)
Joints with LOM, mean no. (SD)	16 (14.88)	17 (14.91)
Global assessments		
Physician's VAS, mean value (SD)	63 (20.57)	57 (29.74)
Parent's global VAS, mean value (SD)	50 (24.39)	55 (26.51)
Parent's pain VAS, mean value (SD)	50 (25.73)	53 (25.89)
CHAQ, mean value (SD)	1.67 (0.845)	1.44 (0.625)
Treatment with steroids		
Duration, mean, years (SD)	3.9 (2.93)	2.7 (2.10)
Daily dose, mean, mg/kg (SD)	0.52 (0.237)	0.66 (0.373)
Previous treatment with DMARDs		
DMARD and/or biological agent, no. of patients	8	11
DMARD, no biological agent, no. of patients	3	3
DMARD and biological agent, no. of patients	5	8
Methotrexate, no. of patients	8	11
Etanercept, no. of patients	5	8
Others, no. of patients (no. of DMARDs)	4 (7[b])	4 (6[c])

Key: CHAQ, Childhood Health Assessment Questionnaire (0–3); CRP, C-reactive protein; DMARDs, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; hr, hour; LOM, joints with limitation of passive motion; SAA, serum amyloid A; VAS, visual assessment (0–100 mm scale) of disease activity by the physician, disease effect on overall wellbeing and pain by the parents

Notes: [a] Ferritin levels were highly variable. Data showed elevated levels as follows, >100 µg/l in patients <13 years, >200 in female patients >13 years and >300 in male patients >13 years) in only five patients (range 347–3135 µg/l), with low glycosylated ferritin (<40%) in these five patients (range 14–30%); [b] thalidomide (n=2), tocilizumab (n=2, one single infusion, phase II trial), azathioprine (n=1), cyclosporine (n=1), leflunomide (n=1); [c] azathioprine (n=2), thalidomide (n=1), tocilizumab (n=1, one single infusion, phase II trial), cyclosporine (n=1), intravenous immunoglobulins (n=1).

Source: Quartier et al. (2011)[4]

B.2.4.1.3. Kearsley-Fleet et al. (2019)

Baseline demographics and clinical characteristics of patients enrolled in the non-randomised (UK registry) study reported by Kearsley-Fleet et al. (2019) are presented in Table 17 In total, 57% were female, and 70% were starting a biologic for the first time. The majority of patients had prior exposure to methotrexate: 98% of tocilizumab and 86% of anakinra (p=0.04). Approximately 59% of patients had systemic features present when starting either tocilizumab or anakinra and 16% had a history of MAS.

More patients starting anakinra as their first biologic compared with tocilizumab (86% vs 63%; p=0.04), with shorter disease duration (1 vs 2 years; p=0.003) and higher frequency of prior macrophage activation syndrome (37% vs 8%; p=0.004).[80]

Table 17. Baseline demographics and clinical characteristics for sJIA trials: Kearsley-Fleet et al. (2019)

Characteristics	Anakinra N=22	Tocilizumab N=54	P value
Female, n (%)	28 (52)	15 (68)	0.2
First biologic, n (%)	19 (86)	34 (63)	0.04
Previous biologic, n	20	23	0.2
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, 13)	7 (4, 11)	1.0
Disease duration, years, median (IQR)	1 (0, 1) [n=21]	2 (1,3)	0.003
Systemic features present, n (%)	24 (53) [n=45]	11 (79) [n=14]	0.09
MAS history, n (%)	7 (37) [n=19]	4 (8) [n=49]	0.004
Prior MTX exposure, n (%)	19 (86)	53 (98)	0.04
Concomitant MTX, n (%)	19 (86)	44 (81)	0.5
Prior steroid exposure, n (%)	22 (100)	53 (98)	0.5
Concomitant steroids, n (%)	13 (59)	36 (67)	0.5
Disease activity, median IQR			
Active joint count, 71 joints	4 (1, 8) [n=48]	5 (1, 11) [n=17]	0.8
Limited joint count, 71 joints	3 (0, 11) [n=18]	3 (1,7) [n=48]	0.9
CHAQ, range 0-3	0.9 (0.4, 1.8) [n=34]	1.1 (0.5, 2.0) [n=13]	0.5
PGA, 0-10 cm VAS	4 (1, 6) [n=34]	2 (2, 6) [n=15]	0.6
PGE, 0-10 cm VAS	4 (1,6) [n=16]	4 (2, 7) [n=34]	0.9

Characteristics	Anakinra N=22	Tocilizumab N=54	P value
Pain VAS, 0-10 cm VAS	4 (1, 6) [n=16]	4 (1, 6) [n=32]	0.9
ESR, mm/h	55 (27, 86) [n=17]	26 (10, 58) [n=49]	0.3
CRP, mm/h	18 (4, 63) [n=53]	64 (19, 95) [n=18]	0.2
JADAS-71	20 (11, 26) [n=22]	19 (6, 30) [n=11]	0.9

Key: CHAQ, Childhood HAQ; IQR, interquartile range; JADAS-71, 71-joint juvenile arthritis disease activity score; MAS, macrophage activation syndrome; MTX, methotrexate; PGA, physician global assessment of disease; PGE, patient (or parent) global evaluation of wellbeing; VAS, visual analogue scale

Source: Kearsley-Fleet et al (2019)[80]

B.2.4.1.4. Supporting studies: uncontrolled evidence

The baseline demographics and clinical characteristics of the uncontrolled studies for anakinra in sJIA are provided in Table 18.

Table 18. Summary of baseline characteristics: uncontrolled studies (sJIA)

Study, year	Number of patients (female/male)	Age at study (anakinra) start (SD or range)	Disease duration (SD or range)	Refractory to previous treatment	MTX n (%)	anti-TNF n (%)	Glucocorticoid treatment n (%)
Gattorno, 2008	22 (11F/11M)	Mean 10.3 (4.60) yrs	Mean 3.4 (0.3, 10.9) yrs	NR	12 (55)	9 (41)	22 (100)
Irigoyen, 2006	14 (NR)[d]	Mean 7 (1, 15) yrs	NR	Yes	NR	NR	NR
Lequerre, 2008[a]	20 (12F/8M)	Mean 12.4 (5.2) yrs)	Mean 7.0 (4) yrs	Yes	19 (95)	14 (70)	20 (100)
Marvillet, 2011	22 (NR)[d]	Mean 8.6 (1.8, 15.6) yrs	Mean 2.4 (0, 10.2) yrs	NR (firstline treatment)	NR	NR	NR
Nigrovic, 2011	46 (27F/19M)	Median 7.6 (0.75, 15.7) yrs[b]	Mean 0.2 (0.12, 0.47) yrs	NR (post steroids) (firstline treatment)	0	0	31 (67)
Ohlsson, 2008	7 (NR)[d]	Median 8.5 (5.2, 15) yrs	NR	Yes	6 (86)	4 (57)	7 (100)
Pardeo, 2015	25 (12F/13M)	Median 7.3 (4.8, 10.8) yrs	Median 4.9 (IQR 1.6, 24.5) mths	Yes	6 (24)	6 (24)	14 (56)
Pascual, 2005	9 (7F/2M)	Mean 8.4 (4.8) yrs	Mean 4.6 (3.8) yrs	Yes	7 (78)	4 (44)	9 (100)
Vastert, 2014	20 (7F/13M)	Mean 7.9 (1.1, 15.3) yrs	Newly diagnosed	Non-responders to NSAIDs (firstline treatment)	0	0	0
Ter Haar, 2019[e]	42 (25F/17M)	Median 7.1 (IQR 3.9, 11.8)	Newly diagnosed	Non-responders to NSAIDs (firstline treatment)	0	0	0
Zeft, 2009	33 (18F/15M)	Median 6 (1, 17) yrs[c]	Median 29 mths (1, 252) mths	Yes	20 (61)	10 (30)	27 (82)

Key: anti-TNFα, anti-tumour necrosis factor alpha; F, female; IQR, interquartile range; M, male; mths, months; MTX, methotrexate; NR, not reported; SD, standard deviation; yrs, years

Notes: [a] The study also described 15 patients with AOSD treated with anakinra; [b] At disease onset; [c] At symptom onset; [d] Gender not stated; [e] Long-term follow-up of prospective study Vastert 2014. (In addition, to the 20 patients included in Vastert et al. [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: Gattorno et al. 2008[81]; Irigoyen et al., 2006[82]; Lequerre et al., 2008;[83] Marvillet et al., 2011[84]; Nigrovic et al., 2011 [85]; Ohlsson et al, 2008[86]; Pardeo et al., 2015[87]; Pascual et al., 2005[88]; Ter Haar et al., 2019;[89] Vastert et al 2014;[90]; Zeft et al., 2009[91]

B.2.4.2. AOSD

B.2.4.2.1. Nordstrom et al. (2012)

Baseline demographic and disease characteristics were generally well balanced. Imbalances were noted in the blood markers, with ESR slightly higher and ferritin levels substantially higher in the anakinra group compared to the csDMARD group.

Table 19. Baseline characteristics for AOSD trials: NordicAOSD05 (Nordstrom et al. [2012])

Characteristics	Nordström (2012) (NORDIC AOSD05)	
	Anakinra (n=12)	csDMARD (n=10)
Age, mean (SD) years	39 (18)	39 (17)
Women/men, n	6/6	5/5
Duration of disease, months, median (range)	14 (2-240)	19 (3-204)
CRP, mg/l, mean (range)	25 (0.5-104)	25 (0.2-116)
Ferritin, µg/l, mean (range)	354 (18-1740)	186 (17-680)[a]
ESR, mm/h, mean (range)	24 (5-84)	17 (1-37)
WBC count, mean (range)	10.6 (3.6-22.4)	13.2 (7.4-21.4)
Platelet count, mean (range)	355 (158-573)	298 (234-417)
Physician global, mm, mean (range)	21 (6-45)	21 (2-43)
Patient global, mm, mean (range)	25 (3-60)	28 (0-65)
SJC, mean (range)	2 (0-13)	2 (0-10)
TJC, mean (range)	4 (0-20)	3 (0-14)
Fever, n (%)	1 (8)	1 (10)
Rash, n (%)	9 (75)	8 (80)
Prednisolone dose, mg, mean (range)	22.5 (10-60)	18.5 (10-25)[a]
Drug therapy	AKA	MTX 6, AZA 3, LEF 1

Key: AKA, anakinra; AOSD, adult-onset Still's disease; AZA, azathioprine; CRP, C-reactive protein; LEF, leflunomide; MTX, methotrexate; SJC, swollen joint count; SSZ, sulfasalazine; TJC, tender joint count;

Notes: a, significant difference (p<0.001)

Source: Nordstrom et al. (2012)[92]; Data on File, 2013[103]

B.2.4.2.2. Supporting studies: uncontrolled evidence

The baseline demographics and clinical characteristics of the uncontrolled studies for anakinra in AOSD are provided in Table 20.

Table 20. Summary of baseline characteristics: uncontrolled studies (AOSD)

Study, year	Number of patients (female/male)	Age at study (anakinra) start (SD or range)	Disease duration (SD or range)	Refractory to previous treatment	MTX n (%)	anti-TNF n (%)	Glucocorticoid treatment n (%)
Cavalli 2015	20 (11F/9M)	Mean 41 (18, 71) yrs	Mean 9 yrs	Yes	15 (75)[b]	6 (30)	20 (100)
Colafrancesco 2017	140 (93F/47M)	Mean 37.4 (16.1) yrs	NR	Yes	106 (75.8)	NR	137 (97.8)
Dall'Ara 2016	13 (9F/4M)	Mean 32.8 (17, 59) yrs	NR	Yes	12 (92)	3 (23)	13 (100)
Gerfaud-Valentin 2014	6 (NR)[d]	NR	NR	Yes	NR	NR	NR
Giampietro 2010	19 (NR)	Mean 40.6 (23, 73) yrs	Mean 9.4 yrs	Yes	NR	10 (52.6)	19 (100)
Giampietro 2013	28 (19F/9M)	Mean 40.3 yrs (23 to 73) yrs	Mean 9.3 (1 to 22) yrs	Yes	25 (89)	23 (82)	28 (100)
Iliou 2013	10 (NR)	NR	NR	Yes	NR	NR	10 (100)
Laskari 2011	25 (12F/13M)	Median 32 yrs (18 to 71 yrs)	Median 7 mths (1, 228 mths)	Yes	NR	NR	12 (100)
Lequerre 2008[a]	15 (11F/4M)	Mean 38.1 (12.8) yrs)	Mean 7.8 (6.4) yrs	Yes	15 (100)	10 (67)	12 (80)
Naumann 2010	8 (7F/1M)	Age range 25 to 66 years	Mean 5.7 (3.7) yrs	Yes	8 (100)	6 (75)	8 (100)
Ortiz-Sanjuan 2015	41 (36F/15M)	Mean 34.4 (14) yrs	Median (IQR) 3.5 (2 to 6) yrs	Yes	32 (78)[b]	20 (49)	40 (97.6)[c]

Key: anti-TNFα, anti-tumour necrosis factor alpha; F, female; IQR, interquartile range; M, male; mths, months; MTX, methotrexate; NR, not reported; SD, standard deviation; yrs, years

Notes: [a] The study also described 20 patients with sJIA treated with anakinra; [b] Before anakinra treatment; [c] Concomitant treatment with anakinra at baseline; [d] Gender not stated; [e] Study population included other indications; [f] Of the total population, 35 patients were treated with anakinra; [g] The study also described 15 patients with AOSD treated with anakinra; [h] Patients enrolled in the present study are almost overlapping with those included in Colafrancesco et al., 2017

Source: Cavalli et al. 2015[93]; Colafrancesco et al. 2017[94]; Dall'Ara et al. 2016[95]; Gerfaud-Valentin et al. 2014[23]; Giampietro et al. 2013;[97] Giampietro et al. 2010;[96] Iliou et al. 2013[98]; Laskari et al. 2011[99]; Lequerre et al. 2008;[83] Naumann et al., 2010;[100] Ortiz-Sanjuan et al. 2015[101]

B.2.5. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.5.1. sJIA

Table 21 describe the primary objectives, statistical methodology and data handling techniques used in the identified sJIA studies (Ilowite et al. [2009]; Kearsley-Fleet et al. [2019];[80] Quartier et al. [2011]).[3;4] Where available participant flow data for the included studies are shown in Appendix D.

B.2.5.1.1. Supporting studies: uncontrolled evidence

The statistical analysis methods of the uncontrolled studies for anakinra in sJIA are provided in Table 22

Table 21. Summary of statistical analysis for sJIA trials

Trial	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Ilowite (2009)[a]	To assess the safety of anakinra in patients with JRA.[a]	No information reported for the sJIA subgroup [[All study population: Safety results were summarised for all patients who received at least one dose of study medication. Descriptive statistics were used to summarise all data. The analysis of time-to-disease flare from randomisation during the 16-week blinded phase in the intent-to-treat subset was assessed using the log-rank test (p value=0.05)]]	Study not powered to detect a difference between treatments in the sJIA subgroup [[All study population: Due to good responses to anti-tumour necrosis factor-α therapy among patients with JRA and the desire of patients and their families to avoid daily injections, enrolment was not sufficient to meet sample size requirements (n=204) that could adequately power, at 80% or higher, the efficacy analyses. Study objectives were amended primarily to assess the safety of anakinra, with an adjusted enrolment goal of 50 patients.]]	NR
Quartier (2011) (ANAJIS)	The primary objective was to compare the efficacy after 1 month's treatment with anakinra or placebo in the two groups of patients.	To explore whether each variable from the ACRPedi score, CRP, SAA and/or parent/patient assessment of pain were associated with response to treatment, the ratio (value at inclusion − value at M1)/value at inclusion, was compared in both groups. Qualitative and quantitative data were compared using Wilcoxon test and Fisher exact test, respectively. The R statistical software was used for statistical analysis.	At least a 60% difference was anticipated in the percentage of patients obtaining improvement in the anakinra-treated group compared with the control group (DMARD), with no more than 10% patients improving in group 2. Given a 5% type I error, a 20% type II error and a two-sided Fisher exact test, 12 patients per group were required.	An intention-to-treat analysis was performed. No further details provided.

Trial	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Kearsley-Fleet (2019)	The objectives of this analysis were to (1) investigate and compare baseline characteristics in all children and young people in the UK between 2010 and 2016 starting either TOC or AKA for sJIA, (2) measure and compare short-term outcomes, including treatment response, treatment survival and stop reasons by one year of treatment between children starting (a) TOC vs AKA, and (b) either TOC or anakinra as a first-line vs subsequent-line biologic therapy, and (3) investigate associations between baseline characteristics and outcomes at one year	Categorical baseline characteristics were compared used Pearson's chi-squared test, and continuous variables were compared between groups using nonparametric K-sample test on the equality of medians. Primary outcome: Statistical significance between cohorts was assessed using logistic regression which was also adjusted using a propensity score[b] to compare outcomes in patients treated with TOC vs AKA. Secondary effectiveness outcomes: Statistical significance between cohorts was assessed using logistic regression for secondary effectiveness outcomes and a log-rank test for equality of survivor functions for the drug survival. Univariable logistic regression was used to assess the associations of baseline characteristics with the primary outcomes at 1 year Multiple imputation was used to account for missing data.[c] From the imputed values, the outcome variables could be calculated: JADAS-71 (at baseline and one year), change in JADAS-71 from baseline, change in CHAQ from baseline, MDA at one year, CID at one year, and ACR Pedi 90 response at 1 year. Drug survival analysis was performed using a Kaplan-Meier curve to present the proportion of patients who stopped biologic therapy by 1 year. Baseline characteristics and primary and secondary outcomes were compared between patients starting TOC vs AKA,	NR	NR

Trial	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		and between patients starting either drug as first-line biologic vs subsequent biologic.		

Key: ACRPedi 90, American College of Rheumatology 90% improvement; AKA, anakinra; CHAQ, childhood HAQ; CID, clinically important difference; ESR, erythrocyte sedimentation rate; JADAS-71, 71-joint juvenile arthritis disease activity score; JRA, polyarticular-course juvenile rheumatoid arthritis; MDA, minimal disease activity; PGA, physician global assessment of disease activity; PGE, patient (or parent) global evaluation of well-being; SAA, serum amyloid A, TOC, tocilizumab; vs, versus

Notes: [a] Applicable for the total population, only the sJIA population is within scope of this submission; [b] The propensity score included: whether the patient was starting it as a first-biologic, gender, age, disease duration, concomitant methotrexate use, concomitant steroid use, active joint count, limited joint count, PGA, PGE, CHAQ, ESR and JADAS-71 ; [c] Complete variables included biologic therapy (anakinra or tocilizumab), whether the patient was starting it as a first-biologic, age at biologic start, gender, concomitant methotrexate use, concomitant steroid use, discontinuation of biologic in the first year (not for remission). Imputed values included disease duration at start of biologic, disease activity measures at the start of therapy and at 1 year (active joint count, limited joint count, PGA, PGE, CHAQ, ESR) and whether patient had systemic features at 1 year

Source: Ilowite et al.(2009);[3] Kearsley-Fleet et al. (2019);[80] Quartier et al. (2011)[4]

Table 22. Summary of statistical analysis: uncontrolled studies (sJIA)

Trial	Hypothesis objective	Statistical analysis	Sample size, power calculation	Patient withdrawals
Gattorno, 2008	To assess the clinical response to interleukin-1 blockade and in vitro IL-1 β and IL-18 secretion in patients with sJIA.	Comparisons of clinical and laboratory parameters before and after treatment were performed using Wilcoxon's matched pairs test and McNemar's chi-square test for continuous and categorical variables, respectively. Differences in serum cytokine levels and in vitro cytokine secretion between patients with sJIA and healthy controls or between disease subgroups (responders versus nonresponders) were analysed by Mann-Whitney U test.	NR	NR
Irigoyen, 2006	To describe the result of the use of anakinra in 14 patients with sJIA	No statistical analysis performed, other than plots of variables with confidence intervals	NR	NR
Lequerre, 2008[b]	To assess the efficacy and the safety of anakinra treatment in sJIA and AOSD	Data are expressed as mean (SD). Intention-to-treat analyses were used: percentages of improvement of each clinical and biological marker were analysed at 3 months, 6 months and at the latest follow-up under anakinra treatment. Differences between marker values before and after treatment were analysed using either a two-sided t test or the Wilcoxon matched-pairs test for nonparametric data at a significance level of 0.05.	NR	NR
Marvillet, 2011a	To examine the safety and the efficacy of anakinra treatment in a regional cohort of sJIA patients.	NR	NR	NR
Nigrovic, 2011	To examine the safety and efficacy of the anakinra as first-line therapy for sJIA.	Continuous variables were compared using the Mann-Whitney U test and are expressed as the median and interquartile range. Proportions were compared using Fisher's exact test. In this exploratory analysis, P values less than 0.05 were considered significant, without correction for multiple comparisons. Significant univariate predictors of complete response were entered into multivariate logistic regression (SPSS software, version 18.0) to identify independent predictors of complete response.	NR	NR
Ohlsson, 2008	NR	Retrospective chart review with median values and range presented. No further analyses.	NR	NA
Pardeo, 2015	To assess anakinra as a therapy for sJIA in a single-centre series	Continuous variables were expressed as medians and interquartile ranges, and were compared using the Mann Whitney U test. Proportions were compared using Fisher's exact test. In this analysis, p values less than 0.05 were considered significant. Variables significantly associated with clinically inactive disease at 6 months in univariate analysis were entered into a multivariate logistic regression analysis.	NR	NR
Pascual, 2005	To show data which indicate that IL-1 is a major mediator of the inflammatory cascade that	NR	NR	NR

Trial	Hypothesis objective	Statistical analysis	Sample size, power calculation	Patient withdrawals
	underlies sJIA, and that IL-1Ra is an effective treatment for this disease.			
Vastert, 2014	To conduct a prospective cohort study using anakinra, a recombinant IL-1 receptor antagonist (IL-1Ra), as first-line therapy in patients with new onset sJIA	Results are expressed as the median (IQR), when appropriate. All statistical analyses were performed using SPSS software version 12.0.1. P values less than 0.05 were considered significant.	NR	NR
Ter Haar, 2019[d]	To evaluate long-term efficacy of treat-to-target approach with IL-1 receptor antagonist (IL-1Ra), as first-line therapy in patients with new onset sJIA	Continuous variables presented as the median (IQR), when appropriate. Differences between 2 groups were analysed using Mann-Whitney U and correlations determined by Spearman's rho. Differences in categorical variables were analysed using Pearson's chi square test or Fisher's exact test as appropriate. Time to inactive disease or flare was assessed using the Kaplan-Meier method. To determine factors associated with the achievement of inactive disease at 1 year, clinical and biochemical markers with a p value <0.05 for the comparison between patients with active disease and those with inactive disease at 1 year in univariate analysis were entered into a multivariable binomial logistic regression model. If variables correlated strongly (Spearman's rho >0.6), the variable with the lowest p value was chosen. Furthermore, principal components regression was used to achieve dimension reduction. Goodness-of-fit of the models was assessed by the area under the curve (AUC) of the receiver operating characteristic curve. For significant continuous variables, an optimal cut-off was determined by choosing the highest sum of specificity and sensitivity. Internal validation of the models was performed by leave-one-out cross-validation.	NR	NR
Zeft, 2009	To examine the efficacy and safety of anakinra in a regional cohort of systemic juvenile arthritis patients.	The effect of anakinra on corticosteroid dose, sedimentation rate, platelet count, albumin, haemoglobin, arthritis joint counts, and height Z score was determined using the paired t test.	NR	NR

Key: AOSD, adult onset Still's disease; IQR, interquartile range; NR, not reported; SD, standard deviation; sJIA, systemic onset juvenile idiopathic arthritis;

Notes: [a] Poster abstract, therefore detail limited; [b] The study included 15 AOSD patients; [c] Total population (n=475) is mixed indication including 72 sJIA and 78 AOSD patients; safety data reported for total population; [d] Long-term follow-up of prospective study Vastert 2014. (In addition, to the 20 patients included in Vastert et al. [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: Gattorno et al. 2008[81]; Irigoyen et al., 2006[82]; Lequerre et al., 2008;[83] Marvillet et al., 2011;[84]; Nigrovic et al., 2011 [85]; Ohlsson et al, 2008[86]; Pardeo et al., 2015;[87] Pascual et al., 2005;[88] Ter Haar et al., 2019;[89] Vastert et al., 2014;[90]; Zeft et al., 2009[91]

B.2.5.2. AOSD

Table 23 describe the primary objectives, statistical methodology and data handling techniques used in the identified AOSD population (Nordstrom et al. [2016]).[92] Where available participant flow data for the included studies are shown in Appendix D.

Table 23. Summary of statistical analysis for AOSD trials

Trial	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Nordström (2012) (NORDIC AOSD05)	The objective was to follow 3 clinical variables describing remission for 24 weeks in patients receiving anakinra or a DMARD plus corticosteroids.	Statistical comparisons between groups were made by permutation-type tests.	Originally, the number of patients needed for statistical power was calculated to be 30 in each group.	NR

Key: DMARD, disease modifying antirheumatic drug; NR, not reported

Source: Nordstrom et al. (2012)[92]

B.2.5.2.1. Supporting studies: uncontrolled evidence

The statistical analysis methods of the uncontrolled studies for anakinra in AOSD are provided in Table 24.

Table 24. Summary of statistical analysis: uncontrolled studies (AOSD)

Trial	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Cavalli, 2015	To describe the efficacy and safety of different biological agents in large cohort of 20 patients with AOSD.	Collected data were analysed using Fisher's two-tailed exact test and Wilcoxon's matched-pairs rank test.	NR	NR
Colafrancesco, 2017	To evaluate the efficacy and safety of anakinra and canakinumab in a large group of AOSD patients.	D'Agostino–Pearson's test for normality was used. The normally distributed variables were described by the mean ± (SD), and the non-normally distributed variables using the median and range. Wilcoxon's matched-pairs test and paired t-tests were performed. Pearson's and Spearman's tests were carried out to analyse the correlations where appropriate. Univariate analysis of nominal variables was carried out using the chi-square test or Fisher's exact-test where appropriate. The p-values of two-tailed tests were calculated; p-values less than or equal to 0.05 were considered significant.	NR	NR
Dall'Ara, 2016	To evaluate the presence, at disease onset, of clinical or serological markers able to predict the use of biologic treatments during the follow-up, because of severe and refractory disease to traditional therapy.	Continuous variables were reported as median value and IQR. Frequencies and percentages of categorical variables were compared using chi-square test with Pearson correction or Fisher's exact test, and continuous variables were compared using Student's t test, Mann-Whitney U test, or Wilcoxon rank-sum test, as appropriate. When appropriate, ORs with 95% 95% CI were indicated.	NR	NR
Gerfaud-Valentin, 2014	To identify the prognostic factors in AOSD	Variables were first displayed per type of clinical course. Differences between the three subgroups were tested overall. In order to limit the inflation of the alpha level with such a small sample size, a few relevant variables were tested using the Fisher exact test for categorial variables. Then continuous variables were standardised before regression analyses.	NR	NR
Giampietro, 2013	To assess the long-term efficacy and safety of anakinra in AOSD	The effect of anakinra treatment was analysed globally or separately for systemic, articular, and biologic manifestations at 3 months, 6 months, and the last follow-up, with baseline. No further details provided	NR	NR

Trial	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Giampietro, 2010	To assess the long-term efficacy and safety of anakinra in AOSD	The effect of anakinra treatment was analysed globally or separately for systemic, articular, and biologic manifestations at 3 months, 6 months, and the last follow-up, with baseline. No further details provided	NR	NR
Iliou, 2013	To describe the clinical manifestations, laboratory abnormalities and treatment of AOSD in Greek patients	NR	NR	NR
Laskari, 2011	To assess the efficacy and safety of the IL-1R inhibitor anakinra in adult patients with refractory Still's disease	Scaled and/or ordinal patient characteristics were compared during follow up using the Wilcoxon test for paired observations and nominal parameters using the McNemar test. Time to event analyses were performed according to the Kaplan-Meier method. Disease outcome was compared between patients receiving and those not receiving concomitant medication using both the chi squared test and survival analysis in means of the log-rank test. Results were considered significant when P value of 0.05 or less. All P values are two-tailed.	NR	NR
Lequerre, 2008[a]	To assess the efficacy and the safety of anakinra treatment in AOSD	Data are expressed as mean (SD). Intention-to-treat analyses were used: percentages of improvement of each clinical and biological marker were analysed at 3 months, 6 months and at the latest follow-up under anakinra treatment. Differences between marker values before and after treatment were analysed using either a two-sided t test or the Wilcoxon matched-pairs test for nonparametric data at a significance level of 0.05	NR	Rheumatologists filled in a standardised questionnaire sent online with the support of the ''Club Rhumatisme et Inflammation'' (http://www.cri-net. com).
Naumann, 2010	To assess the long-term efficacy and safety of anakinra in AOSD	NR	NR	NR
Ortiz-Sanjuan, 2015	To evaluate the efficacy of anakinra in a large series of Spanish patients with AOSD refractory to other therapies	Results were expressed as mean±SD for variables with a normal distribution or as median and 25th -75th IQR when not normally distributed. The comparison of continuous variables was performed using the Wilcoxon test.	NR	Extracted information was stored in a computerised file according to a protocol established beforehand. To minimise entry error, all data were double-checked.

Key: AOSD, adult-onset Still's disease; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; CI, confidence interval; DDR, drug retention rate: IQR, interquartile range; IL-1R, interleukin-1 receptor; OR, odds ratio: SD, standard deviation

Notes: [a] The study included 20 sJIA patients; [b] The study also described 15 patients with AOSD treated with anakinra; [h] Patients enrolled in the present study are almost overlapping with those included in Colafrancesco et al., 2017

Source: Cavalli et al. 2015[93]; Colafrancesco et al. 2017[94]; Dall'Ara et al. 2016;[95] Gerfaud-Valentin et al. 2014[23]; Giampietro et al. 2013;[97] Giampietro et al. 2010;[96] Iliou et al. 2013;[98] Laskari et al. 2011;[99]; Lequerre et al. 2008;[83] Naumann et al., 2010;[100] Ortiz-Sanjuan et al. 2015[101]

B.2.6. Quality assessment of the relevant clinical effectiveness evidence

Quality assessment was performed in line with guidance for undertaking reviews in healthcare issued by the Centre for Reviews and Dissemination (University of York).

B.2.6.1. sJIA

The quality assessment of the identified RCTs is summarised in Table 25, quality assessment of the non-randomised UK registry study is summarised in Table 26, and quality assessment of the supporting studies is provided in Section B.2.6.1.1 and in Appendix D.

Table 25. Quality assessment of eligible randomised, controlled trials (sJIA)

Trial	Quartier (2011)	Ilowite (2008)
Was randomisation carried out appropriately?	Yes	NR
Was the concealment of treatment allocation adequate?	Yes	NR
Were the groups similar at the outset of the study in terms of prognostic factors?	Unclear[a]	Unclear[c]
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Unclear[b,c]
Were there any unexpected imbalances in drop-outs between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
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[c]

Key: JIA, juvenile idiopathic arthritis; sJIA, systemic juvenile idiopathic arthritis

Notes: [a] Analysis was not performed to assess whether differences between groups was statistically significant. Low samples size means small differences have a larger impact; [b] Unclear if only patients are blinded; [c] Note that population in scope of this submission was the sJIA subgroup of the JIA population

Source: Ilowite et al. (2009);[3] Quartier et al. (2011)[4]

Table 26. Quality assessment of eligible non-randomised (UK registry) study (sJIA)

Quality criterion	Assessment
Confounding bias	Serious risk of bias
Selection of participants bias	Serious risk of bias
Classification of interventions bias	Low risk of bias
Deviations from intended interventions bias	Serious risk of bias
Missing data bias	Moderate risk of bias
Measurement of outcomes bias	Low risk of bias
Selection of reported results bias	No information

Source: Kearsley-Fleet et al. (2019)[80]

Overall the study quality for Kearsley-Fleet et al. (2019)[80] was moderate. There were serious concerns with confounding bias: the study did not mention how patients were assigned to each drug; selection of participant bias: there was staggered entry into the study along with minimal inclusion or exclusion criteria; deviation from intended interventions bias: 20% of the participants stopped taking their assigned medication by one-year follow-up combined with treatment switching. There were moderate concerns with missing data bias as it was unclear how the 20% of patients who were not on the study medication at 1-year follow-up were accounted for in the analysis. However, there were low concerns with the classification of intervention bias and measurements of outcomes bias, as these were all clearly predefined, consistent between groups and adequately described. Finally, there was no mention of a pre-registered protocol or statistical analysis plan to assess the selection of reported results bias.

B.2.6.1.1. Quality assessment of eligible uncontrolled studies (sJIA)

The quality assessment of the identified uncontrolled studies is summarised below and also in Appendix D.

Given that Gattorno et al. (2008)[81]; Irigoyen et al., (2006)[82]; Lequerre et al., (2008)[83]; Marvillet et al., (2011)[84]; Nigrovic et al., (2011)[85]; Ohlsson et al, (2008)[86]; Pardeo et al., (2015)[87]; Pascual et al., (2005)[88] Vastert et al., (2014);[90] and Ter Haar et al., (2019) were all single arm trials, the ratings for confounding bias, classification of intervention bias and deviation from intended interventions bias were not applicable for this study design.

The selection of participants bias was rated moderate for studies where some details on how the participants were recruited along with some basic inclusion criteria (Irigoyen et al.,

(2006)[82]; Lequerre et al., (2008)[83]; Nigrovic et al., (2011)[85]; Pardeo et al., (2015)[87]; and Vastert et al., (2014),[90] and Ter Haar et al. (2019)). Studies with critical concerns were those where no details were given on how participants were recruited (Gattorno et al. (2008)[81]; Marvillet et al., (2011)[84]; Ohlsson et al, (2008)[86] and Pascual et al., (2005)[88]). Of note, the Ter Haar et al. (2019) study included the 20 patients from the Vastert et al. [2014] study, in addition to 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.[89]

Generally, there were low concerns with missing data as either they were accounted for or all participants completed the study (typically in the case of the retrospective studies). Two studies had moderate concerns for missing data where a small proportion of the included participants did not have follow-up results for all outcomes (Nigrovic et al., (2011)[85] and Ohlsson et al, (2008)[86]). One study had serious concerns for missing data where not all the data were accounted for and no reasons were given as to why the data was missing (Pascual et al., (2005)[88]).

The measurement of outcome bias rated from low to serious concerns. Studies with low concerns were the prospective studies, where there were adequate descriptions of the measurements of outcomes (Gattorno et al. (2008)[81]; Pascual et al., (2005)[88] Vastert et al., (2014),[90] and Ter Haar et al., (2019)). Studies with moderate concerns were retrospective in design, gave simple details on how measures were carried out and recruited all their participants same centre (Pardeo et al., (2015)[87] and Marvillet et al., (2011)[84]). Studies with serious concerns were retrospective in design, gave basic details on how measures were carried out and recruited from multiple centres where there was no control for the different clinicians carrying out the measurements (Irigoyen et al., (2006)[82]; Lequerre et al., (2008)[83]; Nigrovic et al., (2011)[85] and Ohlsson et al, (2008)[86]).

Finally, there was no mention of a pre-registered protocol or statistical analysis plan to assess the selection of reported results bias in any of the studies (Gattorno et al. (2008)[81]; Irigoyen et al., (2006)[82]; Lequerre et al., (2008)[83]; Marvillet et al., (2011)[84]; Nigrovic et al., (2011)[85]; Ohlsson et al, (2008)[86]; Pardeo et al., (2015)[87]; Pascual et al., (2005)[88] Vastert et al., (2014).[90] and Ter Haar et al., (2019)[89]).

B.2.6.2. AOSD

The quality assessment of the identified RCT is summarised in Table 27 and assessment of the uncontrolled studies in Section B.2.6.2.1 and Appendix D.

Table 27. Quality assessment of eligible randomised, controlled trials (AOSD)

Trial	Nordström (2012)
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Unclear
Were the groups similar at the outset of the study in terms of prognostic factors?	Unclear
Were the care providers, participants and outcome assessors blind to treatment allocation?	No
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Unclear

Key: JIA, juvenile idiopathic arthritis; sJIA, systemic juvenile idiopathic arthritis

Notes: [a] Analysis was not performed to assess whether differences between groups was statistically significant. Low samples size means small differences have a larger impact; [b] Unclear if only patients are blinded; [c] Note that population in scope of this submission was the sJIA subgroup of the JIA population

Source: Nordstrom et al. (2012)[92]

B.2.6.2.1. Quality assessment of eligible uncontrolled studies

The quality assessment of the identified uncontrolled studies is summarised below and also in Appendix D.

Given that Cavalli et al. 2015[93]; Colafrancesco et al. 2017[94]; Gerfaud-Valentin et al. 2014[23]; Giampietro et al., 2010;[96] Giampietro et al. 2013[97]; Iliou et al. 2013[98]; Laskari et al. 2011[99]; Lequerre et al. 2008[83]; Ortiz-Sanjuan et al. 2015[101] were all single arm trials, the ratings for confounding bias, classification of intervention bias and deviation from intended interventions bias were not applicable for this study design. Lequerre et al. 2008[83] was a 2-arm trial, where data was reported for sJIA or AOSD separately, therefore ratings for classification of intervention bias and deviation from intended interventions bias were not applicable for this study design.

The selection of participants bias was rated moderate for studies where some details on how the participants were recruited along with some basic inclusion criteria were given (Cavalli et al. 2015[93]; Colafrancesco et al. 2017[94]; Dall'Ara et al. 2016[95]; Gerfaud-Valentin et al. 2014[23]; Giampietro et al. 2013;[97] Giampietro et al. 2010;[96] Laskari et al. 2011;[99] Lequerre et al. 2008;[83] Naumann et al. 2010;[100]; Ortiz-Sanjuan et al. 2015[101]). One study was rated with serious concerns (Iliou et al. 2013[98]) where the only inclusion criteria was for participants to meet the definition for AOSD from one of three definitions.

There were low concerns with missing data for all studies as either they were accounted for or all participants completed the study, typically in the case of the retrospective studies (Cavalli et al. 2015[93]; Colafrancesco et al. 2017[94]; Dall'Ara et al. 2016[95]; Gerfaud-Valentin et al. 2014[23]; Giampietro et al., 2010;[96] Giampietro et al. 2013[97]; Iliou et al. 2013[98]; Laskari et al. 2011[99]; Lequerre et al. 2008[83]; Ortiz-Sanjuan et al. 2015[101]).

The measurement of outcome bias rated from low to serious concerns. Studies with low concerns either described that standardisation was taken into consideration when collecting data from multiple centres (Gerfaud-Valentin et al. 2014[23]) or where all the data was collected from the same centre with a clear description on the methods used (Laskari et al. 2011[99]). Studies with moderate concerns were retrospective in design, gave simple details on how measures were carried out and recruited all their participants same centre or recruited from different centres with clear description on the methods used, but no details on standardisation between centres (Cavalli et al. 2015[93]; Colafrancesco et al. 2017[94]; Dall'Ara et al. 2016[95]; Lequerre et al. 2008[83]; Ortiz-Sanjuan et al. 2015[101]). Studies with serious concerns were retrospective in design, gave either basic details on how measures were carried out and/or recruited from multiple centres where there was no control for the different clinicians carrying out the measurements (Giampietro et al., 2010;[96] Giampietro et al. 2013;[97] Naumann et al., 2010;[100]) or were retrospective in design, but recruited over a large time period (1985 to 2011) with no description for how changes over time were accounted for (Iliou et al. 2013[98]).

Finally, there was no mention of a pre-registered protocol or statistical analysis plan to assess the selection of reported results bias in any of the studies (Cavalli et al. 2015[93]; Colafrancesco et al. 2017[94]; Dall'Ara et al. 2016[95]; Gerfaud-Valentin et al. 2014[23]; Giampietro et al., 2010;[96] Giampietro et al. 2013;[97]; Iliou et al. 2013[98]; Laskari et al. 2011;[99]; Lequerre et al. 2008;[83] Naumann et al., 2010;[100] Ortiz-Sanjuan et al. 2015[101]).

B.2.7. Clinical effectiveness results of the relevant trials

B.2.7.1. sJIA

An overview of outcomes assessed in the identified comparative studies in the sJIA population is provided in Table 28

Table 28. sJIA: Summary of outcomes (comparative studies)

	Ilowite, 2009	Quartier, 2011	Kearsley-Fleet, 2019
Study design	RCT	RCT	PrC
Comparison	AKA vs PBO	AKA vs PBO	AKA vs TOC
Disease activity: Response/remission		X[b,c,e]	X[f,h,i]
Disease activity: Other[l]	X[a]	X[d]	X[g]
Recurrence			
Glucocorticoid-sparing effect		X	
Discontinuation			
Drug survival			X[j]
AE	X[k]	X[k]	
HRQL			

Key: ACRPedi, American College of Rheumatology paediatric; AEs, adverse events; AKA, anakinra; CHAQ; childhood health assessment questionnaire; CID, clinical inactive disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; HRQL, health-related quality of life; ISR, injection site reaction; JADAS-71, juvenile arthritis disease activity score; MAS, macrophage activation syndrome; MDA, minimal disease activity; PGA, physician's global assessment of disease activity; PGE, patient's or the parents' global assessment of overall wellbeing; PrC, prospective controlled; RCT, randomised controlled trial; SF-36, short form 36; TOC, tocilizumab; vs, versus

Notes: [a] Changes in JRA core components at Week 28; ESR and CRP; [b] Modified ACRPedi 30, 50, 70 and 100 responses, included an improvement of 30%, 50%, 70% or more and 100% respectively, in at least three of the six core criteria for juvenile rheumatoid arthritis and a worsening of 30% or more in no more than one of the following criteria: PGA, PGE, number of joints with active arthritis; number of joints with limited range of motion; Childhood Health Assessment Questionnaire; ESR; [c] Modified ACRPedi 30 response defined as absence of disease-related fever (body temperature <38°C over the previous 8 days) and 50% decrease compared with Day 1 or normalisation of both CRP and ESR values. Note that ACRPedi 30 was also measured (refer to footnote b for how this was defined); [d], Defined as active joint count, limited joint count, PGA, PGE, childhood HAQ (CHAQ) for functional ability, and ESR; [e], Proportion of patients at Month 6 with inactive disease as defined by Wallace et al. (2004) under a daily dose of prednisone <0.3 mg/kg or 10 mg, whichever is lower; [f], Defined as 3 of the 6 JIA core outcome variables: active joint count, limited joint count, PGA, PGE, childhood HAQ (CHAQ) for functional ability, and ESR) improved by at least 90%, with a maximum of one variable worsening by >30%; [g] Change from baseline for the following measures: active joint count; limited joint count; PGA; PGE; CHAQ; ESR; JADAS-71; [h] Assessed disease activity at a single timepoint. Patients with sJIA were defined as achieving MDA if the PGA was ≤3.4 cm, PGE was ≤2.1 cm, & maximum of 1 active joint; [i] Assessed disease activity at a single timepoint and no active joints, no systemic features, no active uveitis, PGA of zero and ESR ≤20 mg/mm (referenced to Wallace et al. 2004); [j] Patients who stopped biologic therapy by 1 year. The stop reasons of therapy were categorised as inefficacy, remission, adverse event; [k] Incidence of MAS was not reported in the included studies; [l] Systemic or inflammatory features/arthritic features

Source: Ilowite et al. (2009);[3] Kearsley-Fleet et al. (2018);[80] Quartier et al. (2011)[4]

B.2.7.1.1. Ilowite et al. (2008)

Disease activity: ACRPedi 30

A total of 11 of 15 sJIA patients (73%) were ACRPedi 30 responders in the 12-week open-label run-in phase. During the 16-week double-blind, placebo-controlled phase, 2 of 9 patients randomised to anakinra had disease flares at Week 28 compared with 1 of 2 patients randomised to placebo.

Disease activity: Other measures

Post hoc analyses showed that CRP and ESR decreased over time during the open-label run-in phase when all patients receive anakinra, with a median CRP level of 114.0 mg/L at baseline vs 1.5 mg/L at Week 12, and a median ESR level of 45.5 mm/hour at baseline vs. 7.5 mm/hour at Week 12 (Table 29).

The decreased CRP and ESR levels during anakinra treatment seen during the open-label run-in phase were sustained during the blinded-phase (Table 30). Out of two placebo patients, one patient had CRP and ESR data.

Table 29. CRP and ESR over time (study 990758, sJIA ITT Population, Open-label run-in phase)

Inflammatory marker	Baseline (n=13)	Week 2 (n=13)	Week 4 (n=13)	Week 8 (n=12)	Week 12 (n=12)
Median CRP, mg/l (Q1, Q3)	114.0 (41.0 to 40.0)	3.0 (1.0, 26.0)	1.0 (1.0, 22.0)	1.0 (1.0, 37.0)	1.5 (1.0, 96.5)
Median ESR, mm/hour (Q1, Q3)	50.0 (20.0, 70.0)	14.0 (10.0, 0.0)	7.0 (6.0, 20.0)	6.0 (4.5, 25.0)	7.5 (4.5, 32.0)

Key: CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; ITT, Intent to treat; sJIA, systemic juvenile idiopathic arthritis.

Source: Statistical report 990758

Table 30. CRP and ESR over time (Study 990758, sJIA ITT Population, anakinra patients during blinded phase)

Inflammatory marker	Week 12 (Baseline) (n=8)	Week 20 (n=8)	Week 24 (n=8)	Week 28 (n=8)
Median CRP, mg/l (Q1, Q3)	1.5 (1.0, 12.0)	1.0 (1.0, 14.5)	1.0 (1.0, 24.5)	1.0 (1.0, 5.0)

Inflammatory marker	Week 12 (Baseline) (n=8)	Week 20 (n=8)	Week 24 (n=8)	Week 28 (n=8)
Median ESR, mm/hour (Q1, Q3)	7.5 (3.5, 19.5)	9.0 (5.0, 12.0)	5.5 (2.0, 8.5)	5.5 (2.0, 8.5)

Key: CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; ITT, Intent to treat; sJIA, systemic juvenile idiopathic arthritis.

Source: Statistical report 990758

Glucocorticoid-sparing effect

Glucocorticoid-sparing effect was not reported in this study.

Health-related quality of life

Health-related quality of life was not reported in this study.

B.2.7.1.2. Quartier et al. (2011)

Disease activity: modified ACRPedi 30, 50, 70, 100

Eight of 12 patients (67%) receiving anakinra, and 1 of 12 (8%) patients receiving placebo were responders (modified ACRPedi 30, absence of disease-related fever, and a decrease of at least 50% of both CRP and ESR compared with baseline) (Table 31).[4]

Table 31. Number (%) of modified ACRPedi 30, 50, 70 and 100 responders at Month 1

Response	Anakinra (n=12)	Placebo (n-=12)	P value[d]
Modified ACRPedi 30[a] (primary objective)	8 (67)	1 (8)	0.003
Systemic symptoms responders[a]	8 (67)	1 (8)	0.003
Primary objectives used in other trials:			
ACRPedi 30 responders	11 (92)	7 (58)	0.059
ACRPedi 30 and no fever[b]	11 (92)	6 (50)	0.025
ACRPedi 30, no fever and CRP <15 mg/l[c]	10 (83)	3 (25)	0.004
Modified ACRPedi 50 responders[a]	7 (58)	0	0.005
Modified ACRPedi 70 responders[a]	5 (42)	0	0.038
Modified ACRPedi 100 responders[a]	0	0	1

Key: ACRPedi, American College of Rheumatology Paediatric; CRP, C-reactive protein

Notes: [a] Body temperature <38°C for more than 7 days, CRP and ESR normalised or decreased by at least 50% (=systemic symptoms responders) and also, in responders to the trial primary objective, ACRPedi 30, 50, 70 or 100 (whichever level is indicated) response compared with Day 1; [b] Body temperature <38°C for more than 7 days and ACRPedi 30 response compared with Day 1; [c] Body temperature <38°C for more than 7 days, CRP <15 mg/l and ACRPedi 30 response compared with Day 1 as in a recent trial with the anti-interleukin 6 receptor antibody tocilizumab; [d] Chi^2 test

Source: Quartier et al. (2011)[4]

Disease activity: clinically inactive disease

Of the 24 patients in the randomised phase of the study (Day 1 to Month 1), 22 patients entered the second open-label phase of the study.

Nine out of 10 patients from the placebo group who switched to anakinra at Month 1 responded at Month 2.

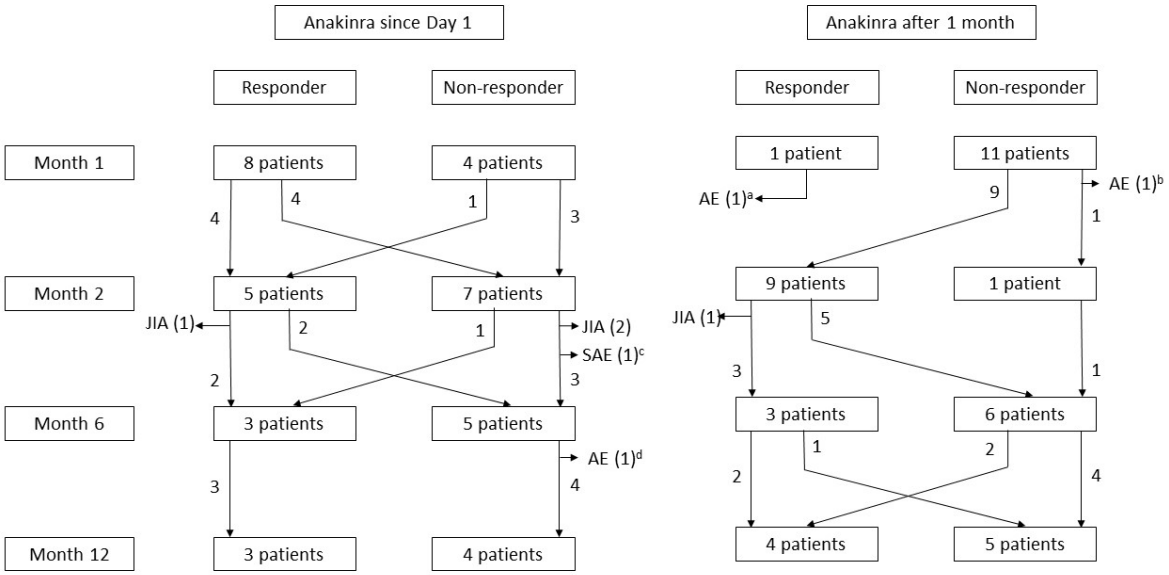
The dose of prednisone was reduced after the Month 1 visit in accordance with the protocol recommendations in all the responders who continued the trial (eight patients, all from the group who had received anakinra since Day 1) and in 7 other patients (4 who had received anakinra since Day 1, and 3 who had received anakinra since Month 1) who showed some improvement (investigator's decision). Three responders who had received anakinra from Day 1 in whom the dose of corticosteroids had been reduced were no longer classed as responders at Month 2.

Seventeen patients continued the trial until Month 6 (Figure 5). Their mean daily dose of prednisone was 0.18 mg/kg (median 0.16, range 0–0.58); the 6 responders at Month 6 had a daily prednisone dose of <10 mg or 0.3 mg/kg. These 6 patients, in whom mean prednisone

dose at enrolment was 0.51 mg/kg (SD 0.32), were all responders to 1 month of anakinra treatment and had already achieved ACRPedi 50 or 70 improvement at this stage.

Sixteen patients reached Month 12; among 7 responders, 6 had stopped corticosteroid treatment and 5 of them had inactive disease.

Figure 5. Response assessment Month 1 to Month 12[a]



Key: AE, adverse event; JIA, juvenile idiopathic arthritis; SAE, serious adverse event

Notes: [a] Open-label phase Month 1 to Month 12; [b] Two patients from the control group stopped treatment after 5 and 11 days, respectively, owing to pain from injections and were withdrawn from the trial after the Month1 visit; [c] Cutaneous and digestive symptoms leading to the diagnosis of Crohn's disease shortly after Month 2; [d] Increase of serum transaminases over five times the upper limit of normal at Month 6

Source: Quartier et al. (2011)[4]

Disease activity: Other measures

There was a significant difference in favour of the anakinra group in the number of joints with active disease, physician general assessment of disease activity, CRP, ESR and SAA values at Month 1 compared with Day 1 (Table 32). However, loss of response in respect of number of joints with active or limited disease, childhood HAQ (CHAQ), PGA, PGE, PGE pain, CRP, ESR and SAA was observed in most patients over the longer term.[4]

Table 32. Response to individual variables, mean variation (%) from Day 1 to Month 1

Response	Anakinra (n=12)	Placebo (n-=12)	P value [a]
CRP	-71	-16	0.001
ESR	-64	-18	0.002
SAA	-70	-2	<0.001
Number of active joints	-46	-18	0.040
Number of joints with LOM	-36	-20	0.148
CHAQ	-37	-9	0.236
Physician's global disease activity assessment	-63	-20	0.005
Parent/patient's global assessment	-36	-23	0.544
Parent/patient's global assessment of pain	-29	-21	0.219

Key: CHAQ, childhood health assessment questionnaire; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LOM=joints with limitation of passive motion; SAA, serum amyloid A

Notes: [a] Mann-Whitney test; [b] Using a visual analogue scale (0 to 100 mm);

Source: Quartier et al. (2011)[4]

Glucocorticoid-sparing effect

All patients received glucocorticoids at treatment start. The glucocorticoid dose was reduced at study end in 12 of 12 anakinra-treated patients compared to 3 of 12 patients in the placebo group.[4]

Health-related quality of life

Health-related quality of life was not reported in this study.

B.2.7.1.3. Kearsley-Fleet et al. (2019)

Disease activity: ACRPedi 90

Overall, at 1 year, 42% achieved ACRPedi 90 with no statistical difference between groups: 31% in the anakinra group versus 46% in the tocilizumab group (adjusted odds ratio [OR] 1.9 [95% CI 04, 7.8]; p=0.4) (Table 33).[80]

Disease activity: Minimal disease activity

Overall, at 1 year, 51% MDA with no statistical difference between groups: 49% in the anakinra group versus 52% in the tocilizumab group (adjusted OR 1.9 (95% CI 0.4, 3.5); p=0.9) (Table 33).[80]

Disease activity: Clinically inactive disease

Overall at 1 year, 39% CID with no statistical difference between groups: 25% in the anakinra group versus 45% in the tocilizumab group (adjusted OR 2.7 [95% CI 0.6, 11.2]; p=0.2) (Table 33) [80]

Table 33. Outcomes in all patients with sJIA starting either tocilizumab or anakinra

	Anakinra N=22	Tocilizumab N=54	P value
Timepoint: 1 year			
ACRPedi 90, %	31	46	
Unadjusted OR (95% CI)	Reference	2.0 (0.6, 6.6)	0.3
Propensity adjusted[a] OR (95% CI)	Reference	1.9 (0.4, 7.8)	0.4
Minimal disease activity, %	49	52	-
Unadjusted OR (95% CI)	Reference	1.1 (0.4, 3.5)	0.8
Propensity adjusted[a] OR (95% CI)	Reference	1.1 (0.3, 4.3)	0.9
Clinically inactive disease, %	25	45	-
Unadjusted OR (95% CI)	Reference	2.5 (0.8, 8.2)	0.1
Propensity adjusted[a] OR (95% CI)	Reference	2.7 (0.6, 11.2)	0.2
Systemic features, %	17	27	0.3
Change from baseline to 1 year, mean (SE)			
Active joint count	-6.4 (2.0)	-6.2 (1.2)	0.6
Limited joint count	-5.2 (2.1)	-4.1 (1.1)	0.9
PGA	-2.1 (0.9)	-2.9 (0.6)	0.9
PGE	-2.1 (1.0)	-2.5 (0.6)	0.8
CHAQ	-0.4 (0.2)	-0.5 (0.2)	0.6
ESR	-32 (5)	-43 (11)	0.02
JADAS-71	-14 (3.1)	-14 (1.8)	0.8

Key: ACRPedi, American College of Rheumatology Paediatric; CHAQ, Childhood HAQ; CI, confidence interval; ESR, erythrocyte sedimentation rate; IQR, interquartile range; JADAS-71, 71-joint juvenile arthritis disease activity score; MAS, macrophage activation syndrome; MTX, methotrexate; OR, odds ratio; PGA, physician global assessment of disease; PGE, patient (or parent) global evaluation of wellbeing; SE, standard error; VAS, visual analogue scale

Source: Kearsley-Fleet et al. (2019)[80]

Disease activity: Other measures

Mean change in JADAS-71 from baseline to 1 year was −14 units (p<0.001), mean change in CHAQ was −0.5 units (p<0.001), and mean change in ESR −35 (p<0.001) (Table 33). Twenty percent of the patients reported systemic features at 1 year (Table 33).[80]

Glucocorticoid-sparing effect

Glucocorticoid-sparing effect was not reported in this study.

Health-related quality of life

Health-related quality of life was not reported in this study.

B.2.7.1.4. Supporting studies: uncontrolled studies (sJIA)

A summary of the outcomes of interest reported in the identified uncontrolled (supporting) studies for anakinra in sJIA is provided in Table 40. Summary results from the reported studies are summarised by outcome in the subsections below.

Table 34. sJIA: summary of reported outcomes in identified studies

Study	Disease activity: Responder rate/remission	Disease activity: Other measures[a]	Glucocorticoid-sparing effect	HRQoL
Gattorno, 2008	X	X		
Irigoyen, 2006	X	X		
Lequerre, 2008	X	X	X	
Marvillet, 2011	X	X		
Nigrovic, 2011	X	X	X	
Ohlsson, 2008	X	X	X	
Pardeo, 2015	X	X	X	
Pascual, 2005	X	X	X	
Ter Haar, 2019	X			
Vastert, 2014	X	X		
Zeft, 2009		X	X	

Abbreviations: HRQoL, health-related quality of life; sJIA, systemic juvenile idiopathic arthritis

Notes: X indicates data for a given outcome were reported in a study; [a] Systemic or inflammatory features/arthritic features

Source: Gattorno et al. 2008;[81] Irigoyen et al., 2006;[82] Lequerre et al., 2008;[83] Marvillet et al., 2011;[84] Nigrovic et al., 2011 [85]; Ohlsson et al, 2008;[86] Pardeo et al., 2015;[87] Pascual et al., 2005;[88] Ter Haar et al., 2019;[89] Vastert et al., 2014;[90] Zeft et al., 2009[91]

Disease activity: responder rate

In 9 of the supporting studies (reported in 10 publications), the patients were defined as responders, complete responders, partial responders or non-responders. The definition of a responder was study-specific. The percentage of responders ranged between 55% and 100%, with a responder rate above 75% in most studies (Table 35). In 3 studies where only the percentage of complete responders was reported, this ranged between 56% and 73% (Table 35).

Table 35. Responders and non-responders during treatment in patients with sJIA

Study	N	Time	Responders % (n)	Complete responders % (n)	Partial responders % (n)	Non-responders % (n)
Gattorno, 2008	22[a]	1 mth	77% (17)[b]	45% (10)	32% (7)	18% (4)
Irigoyen, 2006	14	1.5 mths	Not reported	71% (10)	Not reported	Not reported
Lequerre, 2008	20	3 mths	85% (17)[d]	30% (6)[d]	55% (11)[d]	15% (3)[d]
	20	6 mths	85% (17)[d]	35% (7)[d]	50% (10)[d]	15% (3)[d]
	20	14.7 mths[e]	75% (15)[d]	30% (6)[d]	45% (9)[d]	25% (5)[d]
Marvillet, 2011	22	3 mths	Not reported	73% (16)	Not reported	Not reported
Nigrovic, 2011	46	1 mth	98% (45)[b]	59% (27)	39% (18)	2% (1)
Ohlsson, 2008	7	1 mth	86% (6)	86% (6)	0	14% (1)
Pardeo, 2015	25	6 mths	Not reported	56% (14)	Not reported	Not reported
Pascual, 2005	9	2 mths	100% (9)[b]	78% (7)	22% (2)	0% (0)
Ter Haar, 2019	42[c]	1 yr	76% (32)	Not reported	Not reported	Not reported
	25	5 yrs	96% (24)	Not reported	Not reported	Not reported
Vastert, 2014	20	1 mth	80% (16)[f]	Not reported	Not reported	Not reported
	20	1 yr	85% (17)[f]	Not reported	Not reported	Not reported
	14	2 yrs	86% (12)[f]	Not reported	Not reported	Not reported
	11	3 yrs	91% (10)[f]	Not reported	Not reported	Not reported

Abbreviations: N, number of patients; n, number of responders or non-responders; sJIA, systemic juvenile idiopathic arthritis

Notes: Studies report response or remission. Remission is interpreted as complete response; [a] One patient could not be classified in terms of response; [b] Responders were further divided into complete and partial responders; [c] Ter Haar et al., 2019 reports the long-term follow-up data for the 20 patients included in Vastert et al., 2014 and included patients who presented since January 2012; [d] Complete response defined as ACRPedi ≥50%, partial response defined as ACRPedi <50%. Responders equals n complete response plus n partial response and non-responders equals total population minus non-responders; [e] Latest follow-up was mean 14.7 (range 2, 27) months; [f] Adapted ACRPedi 90 response

Source: Gattorno et al. 2008;[81] Irigoyen et al., 2006;[82] Lequerre et al., 2008;[83] Marvillet et al., 2011;[84] Nigrovic et al., 2011;[85]; Ohlsson et al, 2008;[86]; Pardeo et al., 2015;[87]; Pascual et al., 2005;[88]; Ter Haar et al., 2019;[89] Vastert et al., 2014[90]

Disease activity: Other measures

In all supporting studies, except Gattorno et al. (2008),[81] fever and rash normalized in more than half of patients (56% to 100%) of patients, and inflammatory markers in 56% to 90% of patients (Table 36). Normalization of fever and rash was seen within days, and of inflammatory markers within weeks of therapy.

Table 36. Normalization of systemic signs and symptoms during treatment in patients with sJIA

Study	N	Fever % (n)	Rash % (n)	Inflammatory markers % (n)
Gattorno, 2008	22[a]	45% (10)	45% (10)	45% (10) CRP, ESR, ferritin
Irigoyen, 2006	14	100% (3 of 3)	100% (9 of 9)	Not reported
Lequerre, 2008	20	70% (14)	70% (14)	Not reported
Marvillet, 2011	22	82% (18)	82% (18)	Not reported
Nigrovic, 2011	46	97% (35 of 36)	97% (35 of 36)	84% of 31 patients (CRP) 63% of 30 patients (ESR) 83% of 26 patients (ferritin)
Ohlsson, 2008	7	Not specified	Not specified	86% (6) ESR
Pardeo, 2015	25	56% (14)	56% (14)	56% (14) CRP, ESR, ferritin, neutrophils
Pascual, 2005	9	100% (7 of 7)	Not reported	89% (8) ESR
Vastert, 2014	20	90% (18)	Not reported	90% (18) CRP, ESR, ferritin
Zeft, 2009	33	100% (7 of 7)	100% (7 of 7)	Significant decrease in mean ESR at 1 to 2 months, and 3 to 4 months

Abbreviations: CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; N, number of patients; n, Number of patients with specified systemic feature

Notes: [a] One patient could not be classified in terms of response.

Source: Gattorno et al. 2008;[81] Irigoyen et al., 2006;[82]; Lequerre et al., 2008;[83] Marvillet et al., 2011;[84] Nigrovic et al., 2011;[85] Ohlsson et al, 2008;[86]; Pardeo et al., 2015;[87] Pascual et al., 2005;[88] Vastert et al., 2014;[90]; Zeft et al., 2009[91]

Glucocorticoid-sparing effect

In supporting studies reporting discontinuation of glucocorticoids (Lequerre et al. 2008, Pascual et al. 2005, Pardeo et al. 2015), a total number of 12 of 43 patients (28 %) stopped

glucocorticoid treatment completely (Table 37). In studies reporting reduction in dosage of glucocorticoids, the majority of patients had tapered their dose of glucocorticoids at study end (Table 37).

Table 37. Glucocorticoid-sparing effect in patients with sJIA

Study	Number of patients	Glucocorticoid use at anakinra start % (n)	Glucocorticoid use during study
Lequerre 2008	20	100% (20)	• Glucocorticoid treatment stopped in 1 patient • Glucocorticoid dose reduced in 10 patients (by 15% to 78%)
Nigrovic 2011	46	67% (31)	• Glucocorticoid treatment stopped in the majority of patients at Month 2
Ohlsson 2008	7	100% (7)	• Glucocorticoid dose reduced to a median value of 0 mg/kg/day at 6 months (range 0 to 0.25 mg/kg/day)
Pardeo 2015	25	56% (14)	• Glucocorticoid treatment stopped in 10 patients • Glucocorticoid dose reduced in 4 patients
Pascual 2005	9	100% (9)	• Glucocorticoid treatment stopped in 1 patient • Glucocorticoid dose reduced in 6 patients
Zeft 2009	33	82% (27)	• Glucocorticoid dose significantly reduced (mean 0.4 mg/kg at baseline to mean 0.13 mg/kg at 3 to 4 months; p=0.009)

Abbreviations: n=Number of patients receiving glucocorticoids

Source: Lequerre et al., 2008[83]; Nigrovic et al., 2011 [85]; Ohlsson et al, 2008[86]; Pardeo et al., 2015[87]; Pascual et al., 2005[88]; Zeft et al., 2009[91]

B.2.7.2. AOSD

An overview of outcomes assessed in the identified studies in the AOSD population is provided in Table 38.

Table 38. AOSD: Summary of outcomes (comparative studies)

	Nordstrom 2012
Study design	RCT (open-label)
Comparison	AKA vs PBO
Disease activity: Response/remission	X[a]
Disease activity: Other measures[d]	

	Nordstrom 2012
Study design	RCT (open-label)
Comparison	AKA vs PBO
Recurrence	
Glucocorticoid-sparing effect	X
Discontinuation	
Drug survival	
AE	X[b]
HRQL	X[c]

Key: ACR American College of Rheumatology (30%, 50%, 70%, 90%, 100% improvement); AEs, adverse events; AKA, anakinra; CID, clinical inactive disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; HRQL, health-related quality of life; MAS, macrophage activation syndrome; MDA, minimal disease activity; PGA, physician's global assessment of disease activity; PGE, patient's or the parents' global assessment of overall wellbeing; PBO, placebo; RCT, randomised controlled trial; SF-36, short form 36; vs, versus

Notes: [a] Defined as: afebrile, with normal CRP and ferritin and normal SC and TJC; [b] Incidence of MAS was not reported in the included study; [c] Nordstrom et al. 2012 report data for SF-36 (the publication notes that HAQ and global and disease-related assessments of health were assessed but data not reported for these measures); [d] Systemic or inflammatory features/arthritic features

Source: Nordstrom et al. (2012)[92]

B.2.7.2.1. Nordstrom et al. (2012)

Disease activity: Remission/clinically inactive disease

The primary endpoint was remission according to specific criteria at 8 weeks: afebrile (≤37ºC body temperature) in the absence of NSAIDs 24 hours prior to measurement; and, decrease of CRP and ferritin to reference limits and normal swollen and tender joint counts.

More patients receiving anakinra than those on csDMARD achieved remission at Week 8. At Week 24, 6/12 on anakinra were in remission versus 2/10 on csDMARD. These differences did not reach statistical significance. In both treatment groups, CRP had normalized by Week 8, and the mean corticosteroid doses had been reduced by Week 24 (Table 39).

Table 39. AOSD (Nordstrom et al. [2012]): Achievement of remission

Outcome	Timepoint (Weeks)	AKA (n=12)	csDMARD (n=10)
Proportion of patients in remission (%)	4	50	30
	8	58	50
	24	50	20

Key: AKA, anakinra; AOSD, adult onset Still's disease; csDMARD, conventional synthetic disease modifying anti-rheumatic drugs

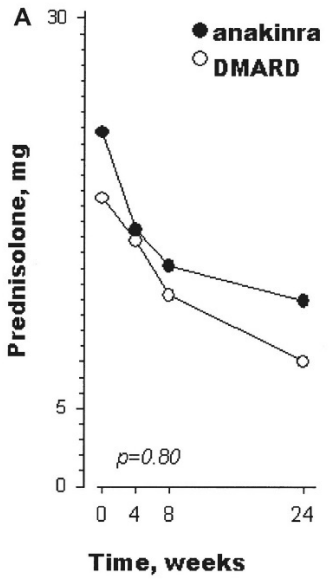
Source: Nordstrom et al. (2012)[92]

A 28-week open-label extension (OLE), with switching or add-on treatment with the comparator drug, was possible if improvement did not occur within 24 weeks. A total of 17 patients completed the OLE phase (Week 52), of which 7 of 14 anakinra-treated patients, and 2 of 3 patients on csDMARD, were in remission.

Glucocorticoid-sparing effect

In both the anakinra and the csDMARDs group by Week 24 mean, prednisone equivalent doses could be significantly reduced by mean 10.8 and 10.5 mg, respectively (Figure 6).

Figure 6. Prednisolone (mg) reduction



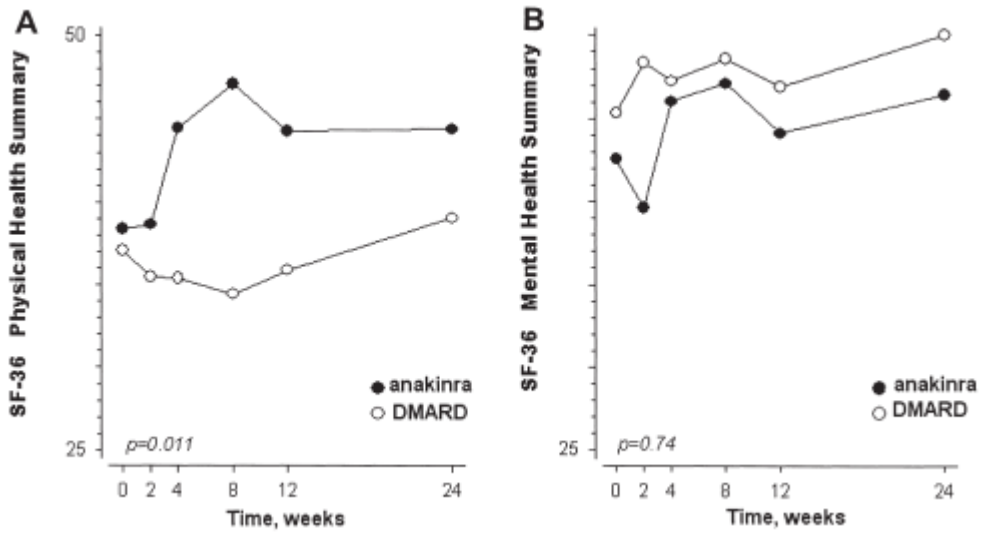
Key: (cs)DMARD, (conventional synthetic) disease modifying antirheumatic drug

Three patients on anakinra but none on csDMARD were able to discontinue oral corticosteroids (p=0.22). Two patients on csDMARD needed 1 intraarticular (corticosteroid) injection each. CRP normalised by Week 8, but with no difference between the groups.

Health-related quality of life

More patients on anakinra than on csDMARD achieved improvements in the Short Form-36 (SF-36) physical health summary (Figure 7; p=0.011). SF-36 mental health summary showed no differences between groups (B).[92]

Figure 7. Short-Form 36 (SF-36) physical health summary of patients receiving anakinra compared to placebo



Source: Nordström et al. (2012)[92]

B.2.7.2.2. Supporting studies: uncontrolled studies (AOSD)

A summary of the outcomes of interest reported in the identified uncontrolled (supporting) studies for anakinra in AOSD is provided in Table 40. Summary results from the reported studies are summarised by outcome in the subsections below.

Table 40. AOSD: summary of reported outcomes in identified studies

Study	Disease activity: Responder rate/remission	Disease activity: Other measures[a]	Glucocorticoid-sparing effect	HRQoL
Cavalli, 2015	X	X	X	

Study	Disease activity: Responder rate/remission	Disease activity: Other measures[a]	Glucocorticoid-sparing effect	HRQoL
Colafrancesco, 2017		X	X	
Dall'Ara, 2016	X	X	X	
Gerfaud-Valentin, 2014[b]	X			
Giampietro, 2010	X		X	
Giampietro, 2013	X	X	X	
Iliou, 2013	X	X	X	
Laskari, 2011	X	X	X	
Lequerre et al. 2008	X	X	X	
Naumann, 2010	X	X	X	
Ortiz-Sanjuan, 2015		X	X	

Abbreviations: AOSD, adult-onset Still's disease; HRQoL, health-related quality of life

Notes: X indicates data for a given outcome were reported in a study; [a] Systemic or inflammatory features/arthritic features; [b] On-label and off-label use of anakinra and canakinumab but some anakinra safety data reported (reports data for the same cohort as Colafrancesco et al., 2017)

Source: Cavalli et al. 2015;[93] Colafrancesco et al., 2017;[94] Dall'Ara et al. 2016 ;[95] Gerfaud-Valentin et al. 2014;[23] Giampietro et al. 2013;[97] Giampietro et al. 2010[96]; Iliou et al. 2013[98]; Laskari et al. 2011[99]; Lequerre et al. 2008;[83] ; Naumann et al., 2010;[100] Ortiz-Sanjuan et al., 2015;[101]

Disease activity: responder rate

In 9 supporting studies, the patients were defined as responders, complete responders, partial responders or non-responders. The definition of a responder was study-specific. The other studies, the percentage of responders ranged between 73% and 100%, with a responder rate above 80% in most studies (Table 41). In 2 studies where only the percentage of complete responders was reported, this was 83% and 92%.

Table 41. Responders and non-responders during treatment in patients with AOSD

Study	N	Time	Responders % (n)	Complete responders % (n)	Partial responders % (n)	Non-responders % (n)
Cavalli, 2015	20		80 % (16)a	70 % (14)	10 % (2)	20 % (4)
Dall'Ara, 2016	13		Not reported	92 % (12)	Not reported	Not reported
Gerfaud-Valentin, 2014[b]	6		Not reported	83 % (5)	Not reported	Not reported
Giampietro, 2010	19		89.5 % (17)a	68.4 % (13)	21.1 % (4)	10.5 % (2)

Study	N	Time	Responders % (n)	Complete responders % (n)	Partial responders % (n)	Non-responders % (n)
Giampietro, 2013	28		86 % (24)a	54 % (15)	32 % (9)	14 % (4)
Iliou, 2013	10		100 % (10)a	100 % (10)	0	0
Laskari, 2011	25		96 % (24)a	84 % (21)	12 % (3)	4 % (1)
Lequerre et al. 2008	15		73 % (11)a	60 % (9)	13 % (2)	27 % (4)
Naumann, 2010	8		100 % (8)	100 % (8)	0	0

Abbreviations: csDMARD, conventional synthetic disease modifying anti rheumatic drug; N, number of patients; n, Number of responders or non-responders.

Notes: Studies report response or remission. Remission is interpreted as complete response; [a] Responders were further divided into complete and partial responders.

Source: Cavalli et al. 2015[93] Dall'Ara et al. 2016;[95] Gerfaud-Valentin et al. 2014;[23] Giampietro et al. 2013;[97] Giampietro et al. 2010[96]; Iliou et al. 2013[98]; Laskari et al. 2011[99]; Lequerre et al. 2008;[83] ; Naumann et al., 2010;[100]

Disease activity: other measures

Across 9 of the supporting studies, fever, rash and inflammatory markers normalized in 54% to 100% of patients. Normalization of fever and rash was seen within days, and of inflammatory markers within weeks of therapy (Table 42).

Table 42. Normalization of systemic signs and symptoms during treatment in patients with AOSD

Study	N	Fever % (n)	Rash % (n)	Inflammatory markers % (n)
Cavalli, 2015	20	70% (14)	70% (14)	70% (14) CRP, ESR
Colafrancesco, 2017	118 109 97	13% (15)[b] 10% (11)[c] 1% (1)[d]	9% (11)[b] 4% (5)[c] 3% (3)[d]	32.1% (38) ESR; 30.5% (36) CRP[b] 9.1% (10) ESR; 12.8% (14) CRP[c] 8.2% (8) ESR; 8.2% (8) CRP[d]
Dall'Ara, 2016	13	92% (12)	92% (12)	92% (12) Systemic AOSD: 100% (8 of 8) Rheumatic AOSD: 80% (4 of 5)
Giampietro, 2013	28	54% (15)	54% (15)	54% (15)
Iliou, 2013	10	100% (10)	100% (10)	100% (10) CRP, ESR
Laskari, 2011	25	84% (21)	84% (21)	84% (21) CRP, ESR, ferritin
Lequerre, 2008	15	81.8% (9 of 11)	81.8% (9 of 11)	81.8% (9 of 11) CRP, ESR
Naumann, 2010	8	Not reported	100% (7 of 7)	87.5% (7) CRP, ESR, ferritin, neutrophils
Ortiz-Sanjuan, 2015	41	78% (32) at	Not reported	90.2% (37) at baseline to 46.3%

Study	N	Fever % (n)	Rash % (n)	Inflammatory markers % (n)
		baseline to 14.6% (6) at Year 1[a]		(19) at Year 1 (CRP)[a] 78% (32) at baseline to 22% (9) at Year 1 (ESR)[a]

Abbreviations: AOSD, adult-onset Still´s disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; n, number of patients treated with anakinra.

Notes: [a] The percentages and patient numbers refer to the proportion with elevated inflammatory markers at baseline and Year 1, and not to % (n) of patients with normalized systemic parameters; [b] Percentage of patients with improved levels after 3 months; [c] Percentage of patients with improved levels after 6 months; [d] Percentage of patients with improved levels after 12 months

Source: Cavalli et al. 2015;[93] Colafrancesco et al., 2017;[94] Dall'Ara et al. 2016 ;[95] Giampietro et al. 2013;[97] Iliou et al. 2013[98]; Laskari et al. 2011[99]; Lequerre et al. 2008;[83] ; Naumann et al., 2010;[100] Ortiz-Sanjuan et al., 2015;[101]

In studies where the actual levels of CRP and ESR were measured at start and end of anakinra treatment, both CRP and ESR levels were decreased at last follow-up (Table 43).

Table 43. CRP and ESR levels at anakinra onset and at last follow-up (AOSD)

Study	At start of anakinra	At last follow-up
CRP		
Lequerre, 2008	91.9 (71.8) mg/L[a]	16.6 (20.6) mg/L[a]
Giampietro, 2013	82.9 (95.7) mg/dL[a]	15.19 (15.9) mg/dL[a]
Laskari, 2011	111 (19 to 318) mg/dL[c]	3.5 (0.4–9) mg/dL[c]
ESR		
Lequerre, 2008	74 (33.5) mm/hour[a]	22.1 (24.6) mm/hour[a]
Giampietro, 2013	57.9 (25.3) mm/hour[a]	14.6 (13.1) mm/hour[a]
Laskari, 2011	75 (26 to 120) mm/hour[c]	4 (1–15) mm/hour[c]

Abbreviations: AOSD, adult onset Still's disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SD, standard deviation.

Notes: [a] Values depict mean (SD); [b] Values depict mean; [c] Values depict mean (range)

Source: Giampietro et al. 2013[97]; Laskari et al. 2011[99]; Lequerre et al. 2008[83] (adapted from Hong et al., 2014[104])

A marked improvement in TJC and SJC was seen in 3 studies when comparing the values at anakinra onset and at last follow-up (Table 44).

Table 44. Tender joint count and swollen joint count at anakinra onset and at last follow-up (AOSD)

Study	At start of anakinra	At last follow-up
Tender joint count		
Lequerre, 2008	8.5 (5.9)[a]	1.5 (2.7)[a]
Giampietro, 2013	3.6 (3.2)[a]	1.4 (2.9)[a]
Laskari, 2011	12 (0 to 38)[b]	Not applicable

Study	At start of anakinra	At last follow-up
Swollen joint count		
Lequerre, 2008	5.9 (5.8)[a]	0.9 (1.5)[a]
Giampietro, 2013	4.2 (4.5)[a]	1.53 (4.1)[a]
Laskari, 2011	1 (0 to 15)[b]	Not applicable

Abbreviations: AOSD, adult onset Still's disease; SD, standard deviation.

Notes: [a] Values depict mean (SD); [b] Values depict mean (range)

Source: Giampietro et al. 2013[97]; Laskari et al. 2011[99]; Lequerre et al. 2008[83] (adapted from Hong et al., 2014[104])

Glucocorticoid-sparing effect

In supporting studies reporting discontinuation of glucocorticoids (Laskari et al. 2011, Lequerre et al. 2008, Cavalli et al. 2015), a total number of 21 of 53 patients (40%) stopped glucocorticoid treatment completely (Table 45). In supporting studies reporting reduction in dosage of glucocorticoids, many patients had tapered their dose of glucocorticoids at study end (Table 45).

Table 45. Glucocorticoid-sparing effect in patients with AOSD

Study	N	Glucocorticoid use at anakinra start % (n)	Glucocorticoid use during study
Cavalli, 2015	20	95% (19)	• Glucocorticoid treatment stopped in 7 patients • Glucocorticoid dose reduced in 8 patients
Colafrancesco, 2017	140	97.8% (137)	• Glucocorticoid use: 3 months 102 of 118 patients (86%); 6 months 75 of 109 patients (69%); and 54 of 97 patients (56%) • Glucocorticoid dose reduced: baseline 77.6 (SD ±186.3) mg; 3 months 8.8 (SD ±11.2) mg; 6 months 5.2 (SD ±6.9) mg; 12 months 3.4 (SD ±4.8) mg
Dall'Ara, 2016	13	100% (13)	• Glucocorticoid dose reduced
Giampietro, 2010	19	100% (19)	• Glucocorticoid dose reduced
Giampietro, 2013	28	100% (28)	• Glucocorticoid dose reduced in 15 patients
Iliou, 2013	10	100% (10)	• Glucocorticoid dose reduced in 10 patients
Laskari, 2011	25	88% (22)	• Glucocorticoid treatment stopped in 12 patients • Median glucocorticoid dose significantly reduced at each visit
Lequerre, 2008	15	80% (12)	• Glucocorticoid treatment stopped in 2 patients • Glucocorticoid dose reduced in 8 patients

Study	N	Glucocorticoid use at anakinra start % (n)	Glucocorticoid use during study
			(by 45% to 95%)
Naumann, 2010	8	100% (8)	• Glucocorticoid dose reduced in all patients
Ortiz-Sanjuan, 2015	41	97.6% (40)	• Median glucocorticoid dose significantly reduced

Abbreviations: AOSD, adult onset Still's disease; csDMARD, conventional synthetic disease modifying anti rheumatic drug; N, number of patients; n, number of patients receiving glucocorticoids

Notes: [a] Mean glucocorticoid dose reduced by 10.8 prednisolone equivalents; [b] Mean glucocorticoid dose reduced by 10.5 prednisolone equivalents

Source: Cavalli et al. 2015;[93] Colafrancesco et al., 2017;[94] Dall'Ara et al. 2016 ;[95] Giampietro et al. 2013;[97] Giampietro et al. 2010[96]; Iliou et al. 2013[98]; Laskari et al. 2011[99]; Lequerre et al. 2008;[83] Naumann et al., 2010;[100] Ortiz-Sanjuan et al., 2015;[101]

B.2.8. Subgroup analysis

This appraisal considers the sJIA and AOSD populations separately. Therefore, while these constitute subgroups of the overall Still's disease population, their results are presented separately within this section.

The effect of major demographic factors, including sex or ethnicity, and other factors, such as disease severity, prior treatment, concomitant illness or drugs, alcohol, tobacco and body weight, has not systematically been reported in the published studies.

No data were reported for the proportion of patients with MAS in the identified trials.

B.2.9. Meta-analysis

B.2.9.1. sJIA

Evidence of efficacy and safety in sJIA has been demonstrated in 2 randomised, controlled studies (Ilowite et al. [2009]; and Quartier et al. [2011]).[3;4] No new RCTs were identified and these studies were the primary source of evidence for anakinra in the submission. One registry study (Kearsley-Fleet et al. [2019]) was identified.

No new meta-analysis was conducted; however, a meta-analysis was conducted in support of the marketing authorisation application (full details – methods and results - are reported in the European Public Assessment Report [EPAR] documentation).

B.2.9.2. AOSD

Evidence of efficacy and safety in AOSD has been demonstrated in 1 randomised, open-label study evaluated the efficacy and safety of anakinra in patients with AOSD. This study was the primary source of evidence for anakinra in the submission and the economic model.

No new meta-analysis was conducted; however, a meta-analysis was conducted in support of the marketing authorisation application (full details – methods and results - are reported in the EPAR documentation [and published in Hong et al. [2014][104]).[103;105-107]

In addition, 1 systematic review including meta-analyses was identified in the literature searches that evaluated the efficacy of biologic treatments in AOSD (Ruscitti et al. [2017]).[108] In Ruscitti et al. (2017), a total of 417 patients with AOSD in 19 studies (18 observational studies/case series and the anakinra open-label RCT) (Ruscitti et al. [2017]).[108] Included studies for anakinra have been accounted for in the literature searches conducted for this submission. The pooled analysis under a random-effects model showed an overall rate of clinical response of 0.85 (95% CI: 0.77–0.91, $p < 0.0001$) (all bDMARDs) and an overall rate of complete remission of 0.66 (95% CI: 0.54–0.77, $p = 0.01$) (all bDMARDs). The heterogeneity across studies was high ($Q = 59.82$ with $df = 19.0$, $p<0.0001$, $I^2 = 68.23\%$).

B.2.10. Indirect and mixed treatment comparisons

No indirect or mixed treatment comparisons were conducted.

B.2.10.1. Network meta-analysis (Tarp et al. 2016)

One network meta-analysis (NMA) was identified in the searches assessing the efficacy and safety of biological agents for sJIA (Tarp et al. [2016]).[109] This analysis was not used to inform the economic model as the efficacy outcome was modified JIA ACR 30 rather than established remission but is summarised here as supporting information. Tarp et al. (2016) identified 5 randomised, placebo-controlled trials evaluating biologic agents in sJIA. The primary efficacy outcome was defined as a 30% improvement according to the modified American College of Rheumatology Paediatric 30 response criteria (JIA ACR30). The primary safety outcome was defined as serious adverse events (SAEs). Outcomes were analysed by pairwise and network meta-analyses.[109] Results are reported in Table 46.[109]

Table 46. Results of indirect comparison: anakinra vs canakinumab and tocilizumab (Tarp et al. [2016])

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

Key: ACR 30, American College of Rheumatology 30% improvement; CI, confidence interval; JIA, juvenile idiopathic arthritis; OR, odds ratio; vs, versus

Source: Tarp et al. [2016][109]

B.2.10.2. Uncertainties in the indirect and mixed treatment comparisons

Not applicable.

B.2.11. Adverse reactions

B.2.11.1. sJIA

B.2.11.1.1. Ilowite et al. (2009)

An overview of the adverse events (AEs) in in the Ilowite et al. (2009), occurring in sJIA patients is provided in Table 47.[3] Yearly AE reporting rates in the sJIA population decreased over time. Most treatment-emergent AEs were reported during the open-label phase of the study (66 AEs in 14 patients), giving an AE reporting rate of 21.3 events/patient year.[3]

AE reporting rates were higher for placebo than for anakinra treated sJIA patients during the blinded phase; 23.7 vs 15.9, respectively. However, as there were only 3 patients exposed to placebo no conclusions can be drawn. In the total study population of both sJIA and JIA patients, the AE reporting rates were similar for anakinra and placebo during the blinded phase.

The reporting rate decreased to 7.1 events/patient year (69 AEs in 9 patients) in patients continuing in the open-label phase of the study.[3] There were 2 SAEs in one patient during the open-label phase of the study.[3] One patient discontinued study drug permanently on Day 1 of the open-label phase of the study due to an AE (injection site reaction). There were no discontinuations due to AEs in patients treated with placebo.[3]

Table 47. sJIA: Overview of adverse events (sJIA safety population) (Ilowite et al. [2009])

	Open-label (n=15) (TDUR=3.1)		Open-label (n=15) (TDUR=3.1)		Open-label (n=15) (TDUR=3.1)		Open-label (n=15) (TDUR=3.1)	
	n (%)	F (R)	n (%)	F (R)	n (%)	F (R)	n (%)	F (R)
Any treatment-emergent AE	14 (93.3)	66 (21.3)	6 (60.0)	44 (15.9)	2 (66.7)	12 (23.7)	9 (90.0)	69 (7.1)
Severe treatment-emergent AE	0	0	1 (10.0)	1 (0.4)	0	0	1 (10.0)	3 (0.3)
Death	0	0	0	0	0	0	0	0
Other SAE	0	0	0	0	0	0	1 (10.0)	2 (0.2)
AE leading to permanent discontinuation of study drug	1 (6.7)	1 (0.3)	0	0	0	0	0	0
AE leading to temporary discontinuation of study drug	0	0	0	0	0	0	0	0

Key: AEs, adverse events; F, number of adverse events, n, number of patients; R, number of events divided by total duration of treatment across all patients; TDUR, total duration of follow-up across all patients in years.

Source: Data on File, Summary of clinical safety", Ilowite et al. [2009][3]

B.2.11.1.2. Quartier et al. (2011)

In the first month of the study, during the double-blind phase, 14 AEs were recorded in the anakinra group and 13 in the placebo group, and there were no SAEs or withdrawals due to AEs (Table 48). During the open-label anakinra treatment period from Month 1 to Month 12, a total of 89 AEs were recorded: these AEs mainly consisted of non-severe injection site reactions and common infections (Table 48). Six patients experienced SAEs.[4]

Two patients from the placebo group in the double-blind phase stopped anakinra treatment (after 5 and 11 days, respectively in open-label phase) because of non-serious pain from injections and withdrew from the study. 4 patients were withdrawn for a disease flare-up/lack of response, at Months 2, 3, 4 and 5, respectively.[4]

Table 48. sJIA: adverse events (Quartier et al. [2011])

	Double blind phase (M0-M1)		Open label phase (M1-M12)
	Anakinra	**Placebo**	**Anakinra**
Number of patients (patient-years)[a]	12 (1)	12 (1)	22 (15.7)
Any AE, no. (/patient-year)[b]	14 (14)	13 (13)	89 (5.71)
Serious AE, no. (/patient-year)	0 (0)	0 (0)	5 (0.33)[c]
Post-injection erythema, no.	3	1	6 (0.40)
Infections, no. (/patient-year)	2 (2)	2 (2)	44 (2.90)
ENT infections and laryngitis, no.	1	1	20
Bronchitis, no.	0	0	8
Gastroenteritis, no.	1	1	3
Skin infections, no.	0	0	4
Other infections, no.	0	0	9[d]
Vomiting	0	1	9
Other AE[e], no. (/patient-year)	0 (0)	2 (2)	10 (0.66)

Key: AE, adverse events; ENT, ear, nose and throat; M, month

Notes: [a] patient-years = 12 patients in each group followed up for 1 month during the double-blind phase, 22 patients exposed to study treatment for a total of 182 months during the open-label phase (8 patients were withdrawn from the trial between Month 1 and Month 6); [b] Disease activity/flares was not systematically recorded as an AE; [c] 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; [d] 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; [e] skin lesions (n=5), haematuria (n=2), back pain (n=2), dental fracture, asthenia, vertigo.

Source: Quartier et al. (2011)[4]

B.2.11.1.3. Kearsley-Fleet et al. (2019)

A total of 7 patients were reported to have stopped treatment due to AEs.[80] Of these, 3 patients on tocilizumab treatment (due to rash worse post drug, neutropenia, active MAS [patient switched to anakinra]), and 4 patients on anakinra treatment (due to stomach cramps and diarrhoea, injection site reaction [patient switched to etanercept], difficulty with daily injection [n = 2; both patients switched to tocilizumab]).[80]

B.2.11.1.4. Supporting studies: uncontrolled studies

Summary safety results from the uncontrolled studies for anakinra in sJIA are provided in Table 49.

B.2.11.2.AOSD

B.2.11.2.1. Nordstrom et al. (2012)

Three patients experienced SAEs, that is, worsening of AOSD (lack of efficacy) in 1 on anakinra (Visit 5) and in 2 on csDMARD (methotrexate visit 1; leflunomide Visit 4). The patient on anakinra continued in the open-label extension with combined anakinra and methotrexate, the patient receiving methotrexate withdrew prematurely, and the patient receiving leflunomide started anakinra in the open-label extension and finished the study. Seven patients out of 12 receiving anakinra reported Grade 1 injection-site reaction and 1 patient reported a Grade 2 injection site reaction.[92] Four additional patients in the OLE reported grade 1 ISR. No patient withdrew from the study because of injection site reactions.[92]

B.2.11.2.2. Supporting studies: uncontrolled evidence

Summary safety results from the uncontrolled studies for anakinra in AOSD are provided in Table 50.

Table 49. Summary safety: uncontrolled studies (sJIA)

	Patients N	AEs n	Injection site reactions n	Rash events n	Infections n	Other
Gattorno 2008	22	NR	NR	NR	NR	-
Irigoyen 2006	14	NR	Frequent	NR	NR	-
Lequerre 2008[b]	20	NR	18	NR	5	-
Marvillet 2011	22	NR	0	NR	2	1 patient stopped treatment due to severe skin reaction. Location not reported.
Nigrovic 2011	46[a]	NR	20	NR	6	Eosinophilic hepatitis required discontinuation of therapy in an 8-year-old patient receiving anakinra at 1.5 mg/kg/day Elevation of liver enzymes under anakinra treatment was noted in 2 additional patients, but therapy could be continued. A 9-month-old infant developed mild asymptomatic neutropenia (ANC 500 cells/µl) which resolved with alternate-day dosing.
Ohlsson 2008	7	NR	3	3		-
Pardeo 2015	25	NR	2	NR	NR	-
Pascual 2005	9	NR	9	NR	NR	Two episodes of hypotension and vomiting with negative viral and bacterial cultures in 1 patient who had underlying myocardial dysfunction occurred during treatment. Therapy was restarted after resolution of the symptoms without complications.
Vastert 2014	20	NR	13	NR	NR	No serious side effects were observed during treatment. No serious invasive infection was reported, although mild cutaneous or upper airway infection and reactivation of infection with herpes simplex virus type 1 were reported in several patients, none of whom required hospitalization or intravenous antibiotic treatment.
Ter Haar, 2019[c]	42	NR	NR	NR	0	No patient stopped treatment due to infections or severe adverse events
Zeft 2009	33	NR	18	NR	1	1 neutropenia (neutrophils>0.9x10^3/l). The patient also experienced one episode of MAS Transient hives within weeks of therapy occurred in 2 patients

Key: AEs, adverse events; ANC, absolute neutrophil count; MAS, macrophage activation syndrome; NR, not reported; sJIA, systemic juvenile idiopathic arthritis

Notes: [a] 45 patients with evaluable data; [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 et al. [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: Gattorno et al. 2008[81]; Irigoyen et al., 2006[82]; Lequerre et al., 2008;[83]; Marvillet et al., 2011;[84] Nigrovic et al., 2011;[85] Ohlsson et al, 2008;[86] Pardeo et al., 2015;[87]; Pascual et al., 2005;[88] Ter Haar et al., 2019;[89] Vastert et al., 2014[90]; Zeft et al., 2009;;[91]

Table 50. Summary results: uncontrolled studies (AOSD)

	Patients N	AEs n	Injection site reactions n	Rash events n	Infections n	Other
Cavalli 2015	20	NR	2	NR	2	-
Colafrancesco 2017						
Dall'Ara 2016						
Gerfaud-Valentin 2014	6	NR	1	NR	NR	
Giampietro 2010	19	1	Several	1	NR	-
Giampietro 2013	28	2	Several	2	NR	-
Iliou 2013	10	NR	NR	NR	NR	-
Laskari 2011	25	3	0		7	3 of the 25 patients were withdrawn due to severe urticarial reactions after 1.5 to 3 mths of treatment
Lequerre 2008[c]	15	2	1	2	4	2 withdrawals due to skin rash after 1 mth and 3 months, respectively; 1 osteonecrosis of the femoral hip considered related to long-lasting corticosteroid treatment by the investigator.
Naumann 2010	8	2	2	NR	NR	No severe adverse events due to anakinra were recorded during the follow-up period
Ortiz-Sanjuan 2015	41	NR	6	NR	5	In 2 patients, therapy was permanently discontinued due to cutaneous reactions; in 6 patients, the reactions were mild and only localized to the injection site; 1 patient experienced myopathy with elevation of muscle enzymes and had to stop anakinra treatment; 3 mild leukopenia

Key: AEs, adverse events; AOSD, adult-onset Still's disease; CI, confidence interval; mths, months; NR, not reported

Notes: [a] Total population 245 patients, of whom 35 were treated with anakinra: safety data not reported by treatment type; [b] Safety data not reported by treatment type; [c] The study also described 20 patients with sJIA treated with anakinra; [d] Total population (n=475) is mixed indication including 72 sJIA and 78 AOSD patients; safety data reported for total population; [e] Study is a retrospective study of patients treated with IL-1-INH, study reported data for anakinra and canakinumab but only anakinra data were reported in this submission as canakinumab is not recommended for the treatment of Still's (including sJIA and AOSD) in the UK NHS; [f] The study also described 15 patients with AOSD treated with anakinra; [h] Patients enrolled in the present study are almost overlapping with those included in Colafrancesco et al., 2017

Source: Cavalli et al. 2015[93]; Colafrancesco et al. 2017[94]; Dall'Ara et al. 2016;[95] Gerfaud-Valentin et al. 2014[23]; Giampietro et al. 2013;[97] Giampietro et al. 2010;[96] Iliou et al. 2013;[98] Laskari et al. 2011;[99] Lequerre et al. 2008;[83] Naumann et al., 2010;[100] Ortiz-Sanjuan et al. 2015[101]

B.2.12. Ongoing studies

No relevant additional evidence of ongoing studies is expected to become available in the next 12 months for the indication being appraised.

One ongoing Phase 3 study was identified (anaSTILLs) (NCT03265132).[110] The study is a 12-week, randomised, double-blind, placebo-controlled period with two dose levels of anakinra and a 4-week safety follow-up in patients with AOSD and sJIA. The primary endpoint (proportion of ACR30 responders with absence of fever attributable to the disease during the 7 days preceding Week 2) will be evaluated. Patients meeting specified eligibility criteria will be randomly assigned to anakinra (dose 2 or 4 mg/kg/day, with a maximum dose of 100 or 200 mg once daily) or placebo (corresponding volumes for each of the 2 anakinra dose levels). In June 2019, the anaSTILLs Phase III placebo-controlled RCT of anakinra was terminated, as meeting the enrolment target of 81 patients was no longer considered feasible within reasonable time.[110]

B.2.13. Innovation

Licenced therapeutic options are required for the treatment of active still's disease (both sJIA and AOSD) that does not respond to NSAIDs and corticosteroids.

NSAIDs, the classic first-line treatment of sJIA and AOSD, are rarely sufficient to effectively control the disease, and high corticosteroid doses are frequently required. Although corticosteroids are effective within a few hours, dependence on corticosteroids is frequently observed, with a relapse of symptoms at dose tapering or discontinuation. Refractory still's disease is associated with high levels of remission failure after treatment with NSAIDs (80% remission failure) and corticosteroids (40% remission failure).[111-113] In addition, standard treatments have the potential to cause adverse events (AEs) in Still's disease patients, with 20% of NSAID users experiencing AEs and steroid dependency occurring in more than 40% of NSAID users.[23] If NSAID and/or steroid treatment are insufficient, csDMARDs (typically methotrexate) are frequently added.[24;78] Following methotrexate, AOSD patients are required to be treated with a second csDMARD (likely CyA), before biologic treatment may be considered. However, csDMARDs may cause rash, stomach disturbances, and may be toxic to the liver or bone marrow.[53]

Biologic treatments that specifically inhibit IL-1 have improved the clinical outcomes for many patients with Still´s disease and 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 licensed for the treatment of adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg 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 NSAIDs or glucocorticoids. It 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.[87] 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.[89;90;114] Early treatment with an IL-1 inhibitor may also reduce the risk for the later development of arthritis.[85] 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.[49]

B.2.14. Interpretation of clinical effectiveness and safety evidence

B.2.14.1.1. Principal findings from the clinical evidence for anakinra

Anakinra improves the clinical and laboratory manifestations of sJIA and AOSD:

Many patients achieve clinical remission and response, with rapid and sustained improvements in refractory AOSD- and sJIA-induced symptoms and normalization of laboratory values.[3;4;92 23;81-88;90;91;93-101] The clinical effect of anakinra is most evident in the resolution of systemic signs and symptoms, usually appearing early during disease progression. Fever and rash usually resolved within a few days of treatment.[3;4;92 23;81-88;90;91;93-101]

Normalization of inflammatory markers was observed within weeks of therapy.[3;4;92 23;81-88;90;91;93-101] In studies that measured CRP and ESR at the start and end of anakinra treatment indicated both CRP and ESR levels were decreased at last follow-up.[83;92;97;99]

Treatment with anakinra in patients with Still´s disease in randomized controlled trials provide short-term efficacy data.[3;4;92]

Supporting uncontrolled evidence provides estimates of efficacy over the longer term (up to nearly 6 years in the sJIA and AOSD population).[23;81-91;93-101]

Anakinra is corticosteroid-sparing:

Improvements in the signs and symptoms of refractory AOSD and sJIA allows concomitant exposure to corticosteroids to be avoided, reduced or discontinued.[3;4;92 23;81-88;90;91;93-101] Thus, anakinra provides a potential glucocorticoid-sparing effect in patients with Still´s disease (avoiding the adverse effects associated with glucocorticoids).

Anakinra use in patients with insufficient response to NSAIDs is associated with positive outcomes:

Four non-randomised (supporting) studies (reported in 5 publications) evaluating the use of anakinra after NSAIDs in patients with sJIA were identified in the review.[84;87;89;90;114]

The available evidence suggested that the use of anakinra early in the disease course demonstrated an improvement in systemic signs and symptoms and inflammatory parameters.[84;85;87;90] Response was achieved in the majority of patients (>50% of patients over 6, 12, 24, and 36 months),[84;85;87;90] and sustained over the long-term (median follow-up 5.8 years [IQR 2.9, 5.6]: 96% of the patients included had inactive disease, and 75% had inactive disease while not receiving medication).[89] The evidence also demonstrated a reduction in the use of glucocorticoids (and therefore of the AEs associated with glucocorticoids).[85;87]

Evidence demonstrates that a “treat-to-target” approach in sJIA, using first-line monotherapy with rIL-1Ra, resulted in early and sustained inactive disease in the majority of sJIA patients, reduced glucocorticoid use, and prevented the development of long-term disease and therapy-related damage.

Anakinra has an acceptable safety profile that is well established:

The safety profile of anakinra has been well established since its approval for treatment of RA in 2002.[106] The published studies included more than 600 patients treated with anakinra,[3;4;23;80-101] together with extensive safety data from studies in RA and CAPS, as well

as more than 15 years of post-marketing experience in various indications, provide safety data for the use of anakinra in Still's disease.

No dose-limiting toxicities were observed during the clinical studies. The most common AEs were non-serious, mostly mild injection site reactions; typically reported within the first 4 weeks of therapy, and resolved during continued treatment.[3;4;92] injection site reactions were reported more frequently in the sJIA population compared with the AOSD population but there were no other important differences in the safety profile between paediatric and adult patients.[3;4;92] In longer term studies there were no indications of increasing rates of AEs over time. The ability to adopt flexible dosing can minimise the duration of potential treatment-related adverse reactions particularly early in the course of treatment.

No relevant differences in the safety profile of anakinra in patients with Still's disease were identified compared to patients with other indications for anakinra treatment.[106]

B.2.14.1.2. Strengths and limitations of the clinical evidence for anakinra

Internal validity:

Efficacy of anakinra in paediatric patients with Still´s disease was described in 1 company-sponsored prospective, randomized, double-blind, placebo-controlled study of JIA and sJIA patients.[3] Furthermore, published data in the paediatric population demonstrated efficacy of anakinra in 1 prospective, randomized, double-blind, placebo-controlled study[4] and 1 registry study.[80] The efficacy of anakinra in adult patients with Still's disease was shown in 1 published prospective, randomized, active-controlled, open-label study.[92]

Efficacy in sJIA and AOSD populations has also been shown in uncontrolled (prospective and retrospective) single-arm studies.[81-92] Uncontrolled, non-randomised study designs are associated with an inherent risk of bias; e.g. selection bias, reporting bias, variation in the definition of outcomes, incomplete follow-up data. However, the benefit of anakinra has been demonstrated consistently across the studies. In addition, the consistency of results across age groups in real-world clinical settings in a representative patient population, as well as the well-known progressive disease course of untreated Still´s disease, supports the validity of the treatment effect reported in the studies. Consideration of all levels of evidence is perhaps more appropriate given that Still's disease is a rare autoinflammatory disease for which several effective treatment options have been previously studied and are now available (i.e., anakinra, tocilizumab, and canakinumab). As such, there is little incentive for patients to

enrol within placebo- or DMARD-controlled RCTs, as biologic therapies are now considered the mainstay of treatment for refractory Still's disease. As such, it is unlikely that there will be any further large-scale randomised studies conducted regarding the efficacy of anakinra versus no anakinra in Still's disease.

External validity:

Clinical outcomes:

The most common parameter for measuring response in the studies in the sJIA population, was ACRpedi30, and in the AOSD population, was ACR response. In both populations, study-specific response comprised a complete or partial response to anakinra treatment for which the definition varied between the studies but typically included a combination of assessment of disease activity as well as pain assessed by physician, patient/carer, laboratory tests and the requirement for medication to maintain remission. In addition, responder rate, systemic signs and symptoms of inflammation and arthritis, and glucocorticoid-sparing effect. Outcomes assessed in the clinical studies are reflective of the clinical measures of response used in clinical practice in the UK. Disease remission is typically assessed over a long period of time, and given the study duration in the clinical studies this outcome was not assessed.[23;81-88;90;91;93-101]

Study population:

The baseline population of patients in the identified studies were considered representative of the population likely to receive anakinra in routine clinical practice in the UK. The study populations included both males and females (63% and 50%, in sJIA and AOSD respectively). The studies in the sJIA population reported mean or median ages between 6 and 12.4 years (range of 0.75 to 17 years) and mean or median disease duration from 0.2 to 7 years (range from 1 month to 21 years).[3;4;80-88;90;91] In studies in the AOSD population the reported mean or median age varied between 32 and 42 years with an age range of 17 to 73 years and mean or median disease duration varying from 7 months to 9.4 years (range 1 month to 22 years).[23;83;92-101] Active symptoms were present at baseline in most patients. Severity varied at treatment initiation.

Treatment pathway and comparison:

Anakinra use in the included controlled studies was in the refractory population who had not responded to prior treatment including glucocorticoids, methotrexate (or other csDMARDs),

or would require high dose glucocorticoid over the longer term. Per current NHS policy, after failing to achieve remission with NSAIDs + corticosteroids patients are progressed to csDMARD treatment (policy requires adults to be treated with a second csDMARD [likely CyA], before biologic treatment may be considered). In sJIA, patients are only required to be treated with 1 csDMARD (methotrexate) prior to progression to bDMARDs (per the NHS policy for sJIA).

The available evidence in sJIA, considered a refractory sJIA population.[3;4;80] The RCT conducted by Quartier (2011) included patients who had received prior treatment with corticosteroids and/or csDMARDs which was discontinued 1 month before study onset though treatment with stable dosage of NSAIDs and oral corticosteroid (mean 0.59 mg/kg) was allowed.[4] Patients were randomised to anakinra or placebo.[4] In the UK Registry study, the majority of patients had prior exposure to methotrexate: 98% of tocilizumab and 86% of anakinra.[80] In uncontrolled, retrospective studies, anakinra was used with a variety of concomitant agents, including corticosteroids, NSAIDs and csDMARDs, with anakinra allowing corticosteroid treatment to be reduced or discontinued.[81-83;86-88;91]

Uncontrolled evidence was also available for anakinra use in patients with sJIA with continued disease after treatment with NSAIDs but prior to treatment with corticosteroids or csDMARDs or other bDMARDs;[84;85;89;90] one study reported data after median follow-up of 5.8 years.[89]

In AOSD, available comparative evidence was in a refractory AOSD population who had received prior glucocorticoid treatment (≥10 mg/day prednisone) ± 1 concomitant csDMARD and compared treatment with anakinra with a DMARD.[92] In uncontrolled, retrospective studies, anakinra was used with a variety of concomitant agents, including corticosteroids, NSAIDs and csDMARDs, with anakinra allowing corticosteroid treatment to be reduced or discontinued.[23;83;93-101]

Anakinra dose:

The starting dose in most sJIA studies was 1 to 2 mg/kg/day. In patients with inadequate response the dose was increased up to 4 or 5 mg/kg/day.[3;4;80-88;90;91] AOSD patients described in the studies received anakinra 100 mg/day as a starting dose, and often also as the maintenance dose. The dose was not adjusted for body weight.[23;83;92-101] The doses used in the studies were the same as the licensed dose. The majority of paediatric patients were treated for more than 6 months, and the majority of adult patients for more than 12 months.

The anakinra dosing regimen used for the Still´s disease patients was shown to have a positive effect on responder rate, systemic signs and symptoms of inflammation like fever, rash and inflammatory markers and glucocorticoid-sparing effect, in particular when initiated early in the disease course.[23;81-88;90;91;93-101]

B.2.14.1.3. Conclusions

Anakinra specifically inhibits IL-1 and has improved the clinical outcomes for many patients with Still's disease (sJIA and AOSD) and confirmed the pathogenic role of this cytokine in the disease process.

The use of anakinra in patients with continued disease activity (sJIA or AOSD) after treatment with NSAIDs provides the increased possibility for patients to achieve remission earlier than would be otherwise be possible. This leads to a reduced number of patients having unresolved disease (associated with greater costs, poorer quality-of-life, and an increased risk of developing the potentially-fatal complication of MAS).

B.2.14.1.4. End of life

Anakinra is not considered to be a 'life-extending treatment at the end of life'.

B.3. Cost effectiveness

Economic model

- A *de novo* Markov state-transition model was constructed in Microsoft Excel
- The model considers alternative positionings of anakinra within the treatment pathway for Still's disease. The base-case analysis compares two 'states of the world': 1) anakinra is not used for the treatment of Still's ('no anakinra'); and 2) where anakinra is used per its licensed indication (i.e. for patients 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, 'per-label')

Clinical parameters and variables

- Clinical parameters and variables were taken from published studies in sJIA and AOSD, identified via systematic literature review, and supplemented with clinical expert opinion
- The key events that may influence the course of disease and/or the estimation of patient health-related quality of life are: treatment discontinuation, disease remission, disease recurrence, occurrence of injection site reactions (ISRs), and the development of macrophage activation syndrome (MAS) – a potentially fatal complication of Still's disease
- Contemporary NHS practice is centred around the treatment goal of disease remission, which was not the case prior to the introduction of anakinra in the treatment pathway. Therefore, clinical expert validation of key model assumptions was undertaken to ensure the input parameters are reflective of current practice and understanding of the disease

Health-related quality of life

- Utility values were taken from the previous NICE assessment of tocilizumab for sJIA (TA238) to inform the economic model, and used to reflect the key events associated with changes in patient HRQoL (i.e. disease remission and unresolved disease following failure of all recommended treatment options)
- Disutilities were also included to capture the effect of ISRs and MAS on patient HRQoL

Costs and medical resource use

- Costs and medical resource use estimates were taken from a combination of published literature, national reference cost databases, and input from practising UK clinicians with specialisms in both sJIA and AOSD
- Unresolved disease (i.e. following failure to achieve remission with all possible recommended treatment options), is associated with extensive medical resource utilisation, with frequent hospital admissions and diagnostic tests

Results

- Frontline use of anakinra is associated with substantial cost savings (through the reduction in the number of unresolved patients) and improved health outcomes – in other words, earlier use of anakinra provides more quality-adjusted life years (QALYs) with cost savings
- Sensitivity analyses further demonstrated the robustness of the results of the economic analysis, with all scenarios showing that per-label use of anakinra leads to more QALYs and reduced costs

Key: AOSD, adult-onset Still's disease; sJIA, systemic juvenile idiopathic arthritis.

B.3.1. Published cost-effectiveness studies

A systematic review was conducted to identify previously published cost-effectiveness studies of anakinra for the treatment of Still's disease, including sJIA and/or AOSD. Search strategies, databases searched, and number of hits are provided in Appendix G.

No relevant published cost-effectiveness studies were identified regarding the use of anakinra for Still's disease, sJIA, or AOSD within its potential positioning in the UK clinical pathway. A total of 7 economic evaluations in populations with sJIA were identified by the review, though none assessed the cost effectiveness of anakinra specifically. No studies were identified in the AOSD population. Six of the sJIA studies were available only as a conference abstract and were excluded. The remaining study was the NICE single technology appraisal (STA) TA238 of tocilizumab for sJIA.[77] A brief summary of this appraisal is provided below:

- **TA238:** considers an sJIA population specifically and considered a comparison of treatment pathways starting with methotrexate, followed by anakinra and anti-TNF drugs such as etanercept, adalimumab, and abatacept. The model structure used to inform this submission does not align with the current NHS commissioning policy for sJIA[78] (which does not recommend the use of anti-TNF drugs for the sJIA population specifically), is not applicable for AOSD patients (AOSD NHS commissioning policy[24] does not recommend use of anti-TNF treatment), and did not capture clinically-important aspects of sJIA (such as development of MAS)

In addition to TA238, it is noted that a multiple technology appraisal (MTA, TA373) considered the use of tocilizumab in a JIA population. sJIA accounts for approximately 10% of JIA cases,[36;115] and outcomes for patients with sJIA and non-sJIA are markedly different. While sJIA is technically classified as a sub-type of JIA, it is increasingly recognised as a distinct disease.[36] As such, this appraisal was not considered relevant to this decision problem

Based on the lack of evidence identified concerning previously published economic evaluations in Still's disease (other than the previous NICE STA of tocilizumab for sJIA only), it was determined that there is no pre-existing cost-effectiveness analysis that would be appropriate to directly inform this appraisal. In addition, some aspects of TA238 are no longer relevant to current clinical practice for patients with sJIA or AOSD – for example, the use of anti-TNF drugs and extended use of methotrexate. However, elements of NICE TA238 may be relevant, and so are referenced accordingly throughout this submission.

B.3.2. Economic analysis

No pre-existing cost-effectiveness analyses of anakinra for the treatment of active Still's disease were identified by the systematic literature review that would be considered appropriate to address the decision problem relating to this submission (Section B.1). Therefore, a *de novo* cost-effectiveness model was constructed to inform this submission.

B.3.2.1. Patient population

Still's disease can affect both adult and paediatric patients and is generally categorised as either adult-onset Still's disease (AOSD) or systemic-onset juvenile idiopathic arthritis (sJIA). Patients diagnosed with sJIA usually maintain this diagnosis into adulthood (i.e. it is plausible for an adult patient to be categorised as an sJIA case if symptoms were present prior to the age of 16 years).

Patients previously diagnosed with Still's disease can be categorised as 'monocyclic', where a patient will experience one disease flare followed by life-long remission, or 'chronic', where the patient has polycyclic or persistent disease. Patients with polycyclic disease achieve remission and may discontinue treatment for long periods of time before an episode of recurrence, whereas patients with persistent disease may require life-long management; in both instances however, patients are considered to have 'chronic' disease.

The course of the disease (i.e. 'monocyclic' or 'chronic') cannot be determined upon presentation, and so these diagnoses are attributed to patients retrospectively.[6;32;36] Nevertheless, the distinction between the costs and outcomes associated with each disease course is an important consideration when interpreting the evidence available regarding the outcomes associated with anakinra treatment, as well as determining its likely cost effectiveness (see Section B.2 for further information regarding disease course).

The economic evaluation conducted to determine the cost-effectiveness of anakinra in patients with Still's disease therefore considers patients within four distinct groups: (1) AOSD with monocyclic disease; (2) sJIA with monocyclic disease; (3) AOSD with chronic disease; and (4) sJIA with chronic disease.

The base-case analysis presented in this submission refers to the Still's disease population as a whole, including sJIA and AOSD patients with monocyclic or chronic disease course. However, the economic model can assess the cost-effectiveness of anakinra for sJIA or AOSD patients separately. It should be noted however that in practice, it is impossible to determine whether a patient has chronic or monocyclic disease *a priori*, hence the model does not allow for a comparison of patients with monocyclic or chronic disease only.

B.3.2.2. Positioning of anakinra

The licensed indication for anakinra is provided within the box below:

Licensed indication for anakinra
Anakinra is indicated in adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg 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 NSAIDs or glucocorticoids. Anakinra can be given as monotherapy or in combination with other anti-inflammatory drugs and DMARDs.

The positioning of anakinra within the treatment pathway for Still's disease is expected to influence the estimated total costs incurred and benefits accrued by patients. Therefore, the economic model was constructed based on alternative 'states of the world'. The term 'state of the world' is used instead of the conventional terminology referring to the intervention (anakinra) and its comparators, as the context in which treatments are used is an important consideration when interpreting the likely cost-effectiveness of anakinra.

The economic evaluation compares three states of the world in total, which are described in further detail below. The base-case analysis considers a comparison of the 'per-label' positioning of anakinra, versus 'no anakinra'. Comparisons of the 'post-csDMARD' state of the world to the 'no anakinra' and 'per-label' states of the world are considered as sensitivity analysis.

'Per-label'

Summary: *Anakinra used following treatment with NSAIDs and/or corticosteroids (per label)*

Description: *The majority of patients are first treated with NSAIDs +/- corticosteroids. For those who fail to achieve remission, treatment is progressed to the use of anakinra. The use of anakinra in this setting is not based on current policy documents, and the choice of first-line biologic is assumed to be 100% anakinra in the model base case. Failure to achieve response with anakinra would lead to initiation of tocilizumab for both sJIA and AOSD patients. Use of tocilizumab for AOSD patients is 'off-label', though is recommended in the NHS policy for AOSD, and therefore is assumed to be used following anakinra where necessary.[24] Subsequent failure to achieve responses results in complete exhaustion of all available systemic treatment options, and so patients would be categorised as 'unresolved' and require further treatment (see Section B.3.2.3).*

'Post-csDMARD'

Summary: *Anakinra used following NSAIDs, corticosteroids and csDMARDs*

Description: *After failing to achieve remission with NSAIDs +/- corticosteroids, patients progress to csDMARDs and are expected to first receive methotrexate. Following methotrexate, AOSD patients are required to be treated with a second csDMARD (likely CyA), before biologic treatment may be considered.[24] sJIA patients are assumed to only require treatment with methotrexate prior to the use of biologic DMARDs.[78] AOSD patients may receive anakinra or tocilizumab first, based on clinician preference. sJIA patients currently receive tocilizumab first, based on current NICE guidance (TA238).[36] The remainder of the treatment pathway is identical to that described for the 'per-label' state of the world.*

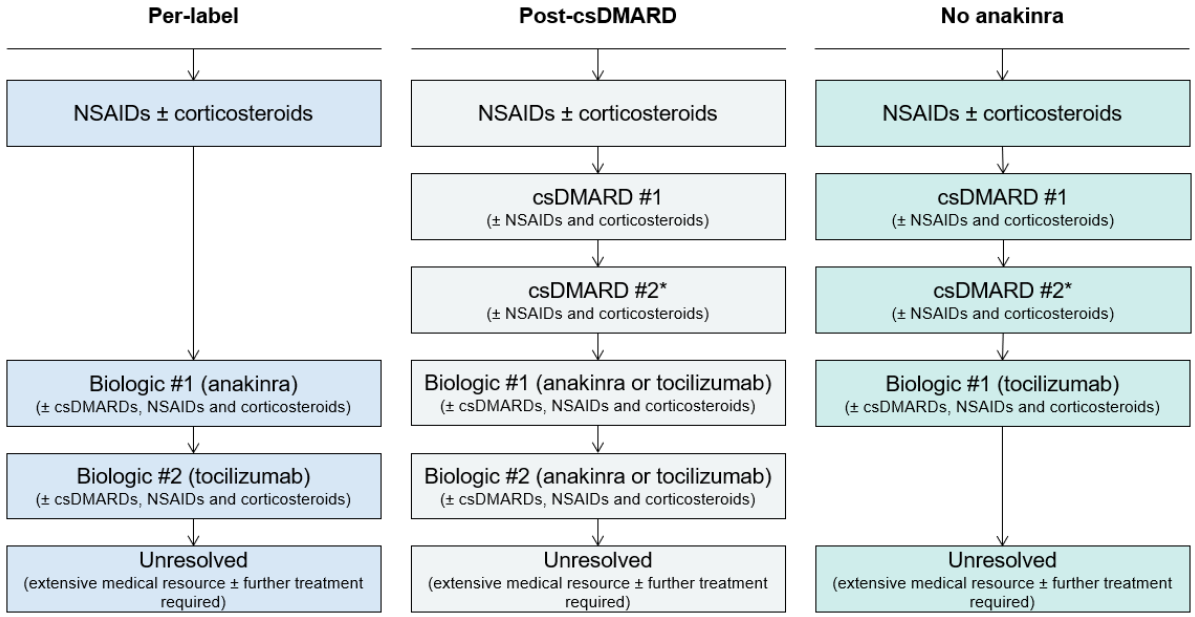
'No anakinra'

Summary: *Anakinra not used in practice for sJIA or AOSD*

Description: *Patients follow the same pathway as detailed in the 'post-csDMARD'; however, the only biologic DMARD assumed to be available is tocilizumab. Following an insufficient response to csDMARDs, both sJIA and AOSD patients will receive tocilizumab. Should tocilizumab fail to lead to remission, patients would be categorised as 'unresolved' and require further treatment (see Section B.3.2.3).*

The difference in the patient pathways is summarised Figure 8.

Figure 8. Comparison of treatment pathways for each state of the world



Key: AOSD, adult-onset Still's disease; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; NSAID, nonsteroidal anti-inflammatory drug; sJIA, systemic-juvenile idiopathic arthritis.

Note: *Use of second csDMARD only applies within the AOSD population. This diagram covers both the sJIA and AOSD populations, noting that in the 'post-csDMARD' state of the world, sJIA patients may proceed to be treated with biologic treatments (such as anakinra) after only one csDMARD (i.e. methotrexate).

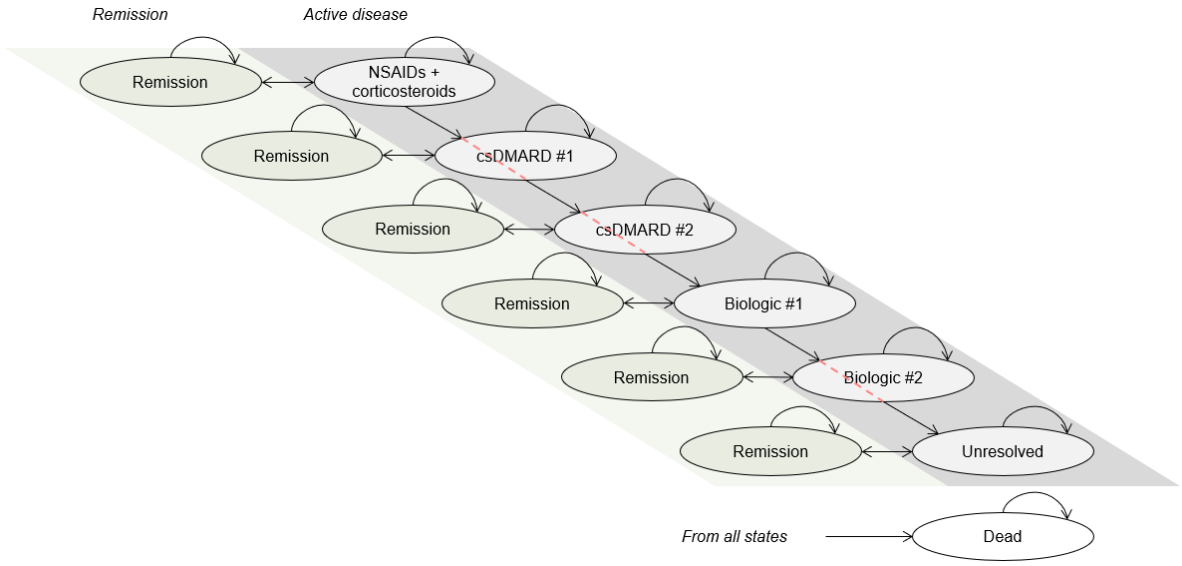
Further to the three possible clinical positionings of anakinra within the treatment pathway for Still's disease, the model input parameters may vary between patients with AOSD or sJIA, and patients with monocyclic or chronic disease. Examples of these parameters include age at baseline (differs between sJIA and AOSD patients), and the probability of experiencing disease recurrence following remission (set to 0% for monocyclic patients). These parameters are discussed in further detail throughout this submission.

In the model base-case, NSAIDs + corticosteroids are used in the first line in each state of the world. This allows for comparisons to be made across each state of the world starting from a comparable point in the treatment pathway. As discussed in Section B.1.3.2, NSAIDs are almost always used to ease symptoms during the differential diagnostic process to reach a final diagnosis, after which glucocorticoids are commonly used as first-line treatment once a diagnosis is made.

B.3.2.3. Model structure

A Markov state-transition model was constructed in Microsoft Excel® comprising the treatment pathway for patients with Still's disease. An economic model schematic is presented in Figure 9.

Figure 9. Model schematic



Key: csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; NSAID, nonsteroidal anti-inflammatory drug.
Notes: Red dashed lines (- - - - - -) denote states that are omitted for some states of the world.

The modelling approach considers states of the world for comparison in which anakinra is either used per its license ('per-label', base-case analysis), following csDMARDs ('post-csDMARD', sensitivity analysis), or is unavailable ('no anakinra'). As discussed in Section B.3.2.2, the model comparison considers the treatment pathway as a whole as opposed to comparing directly to other treatments available at each stage of the treatment pathway, as dependent on where anakinra is used costs and outcomes are expected to differ.

All states of the world revolve around the same core model structure. In the model base-case, all patients enter the model in the 'NSAIDs and corticosteroids' state and progress through the treatment-related health states until death. At a given health state, it is possible for patients to transition based on treatment discontinuation, achieving remission, failure to maintain remission, or death. It is possible within the model to choose whether patients start at different stages of the treatment pathway. However, this option should be used with caution so as to allow for a fair comparison across the different states of the world (i.e. all

patients should enter the model at a comparable time point, and some parts of the treatment pathway may not exist in all states of the world [e.g. use of csDMARDs as monotherapy]).

The model schematic (Figure 9) includes red dashed lines denoting differences between the modelled states of the world:

- In the 'per-label' state of the world (base-case analysis), it is assumed that patients are not treated with csDMARDs (such as methotrexate), and so after discontinuing NSAIDs +/- corticosteroids will bypass 'csDMARD #1' and 'csDMARD #2' states

- In the 'post-csDMARD' state of the world (sensitivity analysis), it is assumed that sJIA patients are not treated with a second csDMARD (per current NHS practice), and therefore bypass the 'csDMARD #2' state after discontinuing 'csDMARD #1'

- In the 'no anakinra' state of the world, the same assumption concerning use of csDMARDs as per the 'post-csDMARD' state of the world is assumed to apply for sJIA patients. In addition, following discontinuation of tocilizumab ('Biologic #1'), patients are assumed to bypass the use of anakinra ('Biologic #2') and progress to the 'unresolved' state

Given that the primary aim of treatment is to achieve clinical disease remission (Section B.1.3.2), patients are assumed to cascade down the treatment pathway until remission is achieved. If recurrence of disease should occur following remission, patients will return to the health state occupied prior to remission (i.e. revert to the treatment used to achieve remission). For simplicity, 6 states relating to remission are captured within the model, such that treatment history may be recorded (but are otherwise identical). The model also incorporates the option for patients to 're-enter' the model (i.e. return to treatment with NSAIDs +/- corticosteroids) or progress to the next line of treatment. These alternative pathways are discussed further in Sections B.3.3 and B.3.4.

Following an insufficient response on all currently-available treatment options (including anakinra), patients progress to the 'unresolved' health state. The inclusion of this health state is aligned with NICE TA238, which adopted a model structure wherein after failing all options patients were assumed to have 'uncontrolled disease'.[36] For patients in this health state in current NHS practice, a basket of non-recommended (e.g. canakinumab), experimental (e.g. Janus kinase [JAK] inhibitors), or surgical (e.g. bone marrow transplantation [BMT]) interventions may be considered. Some patients may not be treated with any active intervention (e.g. if no clinical trials available, exhausted all other options,

and opted out of BMT). These patients reside within a permanently 'unresolved' state, and are managed through extensive medical resource use and symptomatic medication.

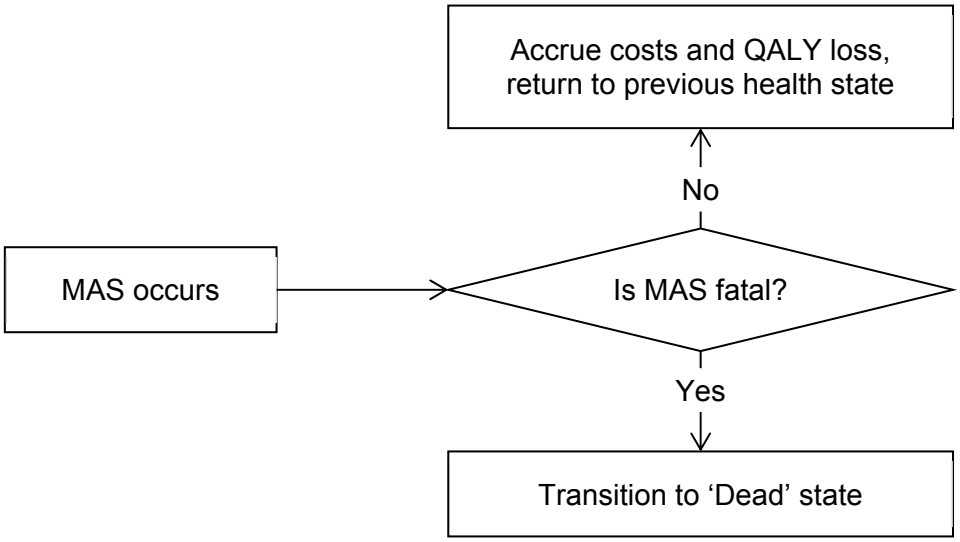
Following the introduction of biologic DMARDs (including anakinra) within the treatment pathway for Still's disease, there was a substantial reduction in the number of patients with unresolved disease. Consequently, there is a great deal of uncertainty with respect to the types of treatments offered to patients who fail all recommended treatment options, as experimental treatments may only be offered to patients on a case-by-case basis (e.g. an individual funding request), or as part of a clinical trial. Furthermore, the use of BMT in practice is subject to practical constraints concerning the scheduling of surgeries, and the availability of donor cells (should an allogeneic BMT be undertaken); as well as the known risks of the surgery. The model therefore relies upon assumed medical resource use as well as assumptions regarding the efficacy of any 'further treatments' (see Section B.3.3 for further information).

B.3.2.3.1. Macrophage activation syndrome (MAS) sub-model

For patients with unresolved disease, a lack of disease control is expected to lead to poorer health-related quality of life (HRQL) and an increased probability of developing MAS. Poor disease control is also expected to lead to progression to hip replacement and other long-term detrimental health effects; however, these are not captured within the economic model – the inclusion of all possible long-term health impacts of poorly-controlled disease would be difficult to robustly capture with available evidence, though it should be noted that these health effects are real and have an extremely detrimental effect on patient HRQL. The exclusion of such long-term health effects is considered conservative, as the use of anakinra is expected to reduce the occurrence of these negative health effects.

Given that MAS is an uncommon but potentially fatal complication of Still's disease (Section B.1.3.1.6), a 'sub-model' concerning the occurrence of MAS is implicitly included within the economic evaluation (Figure 10). MAS is considered as an event within the model structure, and patients are exposed to a risk of developing MAS at any point in the treatment pathway (though for patients in remission, this probability is expected to be 0% - see Section B.3.3 for further details). Following the occurrence of MAS, patients are exposed to a probability of death, a cost associated with medical resource use, and a loss of quality-adjusted life years (QALYs) for patients who do not die as a result of MAS. The incorporation of MAS is discussed further in Sections B.3.3 and B.3.4.

Figure 10. Macrophage activation syndrome 'sub-model' structure



Key: MAS, macrophage activation syndrome; QALY, quality-adjusted life year.

B.3.2.4. Analysis features

Table 51 summarises the key features of the economic analysis.

Table 51. Key features of the economic analysis

Factor	Previous appraisal (TA238)	Current appraisal	
		Chosen values	Justification
Time horizon	16 years	30 years	Time horizon long enough to reflect all important differences across treatment arms. In the base-case analysis a 30-year horizon was selected as a suitable balance between computational burden and reflecting differences in costs and outcomes. Varying the time horizon from 1 to 30 years exhibited little impact on the overall conclusion of the economic model. 16 years was rejected as the diagnosis of sJIA is maintained in adulthood.[116]
Model structure	Markov state-transition	Markov state-transition	Aligned with treatment pathway, allows for transparent and simplified use of a broad range of data sources.
Treatment waning effect?	Not described explicitly	Treatment effect assumed to be maintained for as long as patients are either receiving treatment or are in remission	Treatment effect is based on health state occupancy, and so the waning of treatment effect is explicitly captured within the model structure and possible transition probabilities.
Source of utilities	Use of a non-linear model to map CHAQ to utility	Use of same equation from TA238	Limited data for sJIA and AOSD. Used same equation from TA238 to obtain a suitable utility value for each health state

Factor	Previous appraisal (TA238)	Current appraisal	
		Chosen values	Justification
	value. Equation derived by submitting company	supplemented with age adjustment, disutilities for MAS and ISRs	but adjusted for age (as lifetime horizon was not considered within TA238). In TA238, it was stated within the FAD that *"because of the lack of data in the trial and the literature, the ERG considered the approach used by the manufacturer to be reasonable and acceptable."*[36] Disutilities for MAS and ISR included as relevant to decision problem.
Source of costs	BNF, PSSRU, NHS reference costs, previous NICE appraisals (not in sJIA), KOL input, published literature	BNF, eMIT, PSSRU, NHS reference costs, NICE TA238, KOL input, published literature	Costs used within the model were obtained from a range of sources. Some evidence from NICE TA238 should be interpreted with caution, due to the date it was published and its relevance to the decision problem – where applicable, this has been stated throughout the current submission.
Discount of 3.5% for utilities & costs	✓	✓	NICE reference case
Perspective (NHS/PSS)	✓	✓	NICE reference case

Key: BNF, British National Formulary; eMit, electronic Marketing information tool; KOL, key opinion leader; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSSRU, Personal Social Services Research Unit; TA, technology appraisal.

B.3.2.5. Baseline patient characteristics

Age at baseline is calculated according to the population under consideration – that is, either AOSD or sJIA. Nordström et al. (2012) reported an average age of patients enrolled within the RCT of anakinra versus placebo for AOSD of 39 years and Quartier et al. (2011) reported an average sJIA age of 8.5 years (also a placebo-controlled RCT of anakinra).[4;92]

Females are affected by AOSD slightly more than males (70:30), and so the base-case analysis assumed 70% of patients are female. Alternatively, the Quartier et al. (2011) or Nordström et al. (2012) studies may be used to inform the model (63% and 50%, respectively). It is also possible within the model to specify the use of the general population (50.7% female).

Grevich et al. (2017) reported 11%–40% of sJIA patients present with monocyclic disease.[32] The economic model assumes (in the base-case analysis), that the average of this range (25.5%) constitutes the proportion of patients with monocyclic disease, and the remaining 74.5% of patients are assumed to have chronic disease. The same proportions are assumed

to apply for AOSD patients, though these settings are amendable within the model and explored within sensitivity analysis.

Cost-effectiveness results are produced within the model for the sJIA and AOSD populations separately. However, a weighted average is obtained via the 'Results' sheet in the model based on the specification of how many patients are diagnosed as children versus adults. Subgroup analyses are presented for the sJIA and AOSD populations separately (see Section B.3.9). The model does not allow for comparisons between monocyclic and chronic patients separately, as these groups cannot be determined at baseline and would not constitute an appropriate basis for decision making. In the base-case analysis, 37.5% of patients are assumed to have been diagnosed with AOSD (based on an estimate 400-800 AOSD and 1,000 sJIA cases in the UK).[117]

A summary of the baseline patient characteristics assumed to apply within the economic model is provided in Table 52.

Table 52: Modelled baseline patient characteristics

Parameter	Value	Source or Justification
Age (years)	8.5 (sJIA), 39 (AOSD)	Nordström et al. (2012),[92] Quartier et al. (2011)[4]
Female	70%	Efthmiou et al. (2006),[26] Gerfaud-Valentin (2014),[10] Lebrun,[28] Ruscitti (2016),[27]
Male	30%	
Monocyclic disease	25.5%	Estimated based on range provided by Grevich et al. (2017)[32]
Chronic disease	74.5%	
AOSD	37.5%	Derived from estimates provided in the NICE final scope (2019)[117]
sJIA	62.5%	

Key: AOSD, adult-onset Still's disease; sJIA, systemic juvenile idiopathic arthritis

B.3.2.6. Intervention technology and comparators

Anakinra (Kineret®, Sobi) is the intervention considered in this appraisal. Anakinra is indicated in adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg 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 NSAIDs or glucocorticoids. Anakinra can be given as monotherapy or in combination with other anti-inflammatory drugs and csDMARDs.[1]

The recommended dose of anakinra for patients weighing 50 kg or more is 100 mg per day by SC injection. Patients weighing less than 50 kg should be dosed by body weight with a starting dose of 1-2 mg/kg per day. Response to treatment should be evaluated after 1

month: In case of persistent systemic manifestations, the dose may be adjusted in children or continued treatment with anakinra should be reconsidered by the treating physician.[1]

Due to the use of each treatment option in different positions within the clinical pathway for Still's disease, the economic evaluation considers possible states of the world, as described in Sections B.3.2.2 and B.3.2.3. Consequently, the relevant comparator to anakinra is dependent on its position within the treatment pathway. If used following NSAIDs +/- corticosteroids (per the base-case analysis), the relevant comparators are csDMARDs (methotrexate, cyclosporin, etc.) and/or tocilizumab (RoActemra®, Roche). If intended for use following csDMARDs (per the sensitivity analysis), the only relevant comparator is tocilizumab. The input parameters for each 'state of the world' are described in turn in Sections B.3.3, B.3.4, and B.3.5.

B.3.3. Clinical parameters and variables

The economic model requires a number of clinical parameters and variables in order to ascertain the cost-effectiveness of anakinra for the treatment of Still's disease (i.e. sJIA and AOSD). To inform model transitions, the following probabilities are required:

- Treatment discontinuation and remission
- Disease recurrence following remission
- Development of MAS
- Experiencing of an adverse event
- Death

The incorporation of these parameters within the economic model is discussed in the remainder of this section. However, it is important to acknowledge the following limitations of the evidence base to inform the model:

- **Short duration of follow-up in RCTs:** Measurement of disease remission is usually based on an extended period of time, and so remission may not be possible to determine if a study is conducted over a short time period. For example, in the Ilowite et al. (2009) study the double-blind period was 16 weeks; whereas the Nordström et al. (2012) study was conducted over a 24-week period.[3;92] This means that the

relevant data to inform the economic model is not available from some studies in sJIA or AOSD

- **Lack of data available for both sJIA and AOSD populations:** There have been a limited number of studies conducted to date in the sJIA and AOSD populations, and so cross-comparing outcomes should be interpreted with respect to the study designs adopted. There is increasing acceptance that sJIA and AOSD are broadly considered to be the same disease which presents at different ages. The model assumes the majority of parameters for sJIA patients over the age of 18 years and AOSD patients are the same (excluding those relating to specific recommendations for sJIA that differ from AOSD such as the use of tocilizumab prior to anakinra, and the requirement of only one csDMARD pre-biologic use)

- **Difficulties in conducting contemporary RCTs in Still's disease:** Still's disease is a rare autoinflammatory disease for which several effective treatment options have been previously studied and are now available (i.e., anakinra, tocilizumab, and canakinumab). As such, there is little incentive for patients to enrol within placebo- or DMARD-controlled RCTs, as biologic therapies are now considered the mainstay of treatment for refractory Still's disease. As such, it is unlikely that there may be any further studies conducted regarding the efficacy of anakinra versus no anakinra in Still's disease. In June 2019, the anaSTILLs Phase III placebo-controlled RCT of anakinra was terminated, as meeting the enrolment target of 81 patients was no longer considered feasible within reasonable time.[110]

To ensure the parameterisation of the model has been performed using a transparent and methodical approach, a tabulated summary of the potential sources is provided in Section B.3.3.1.5 (Table 53) to illustrate the base-case choice(s) of parameter sources, alongside reasons other sources identified via literature reviewing were not selected.

B.3.3.1. Treatment discontinuation and disease remission

Patients are expected to be treated with a given regimen with the intention of achieving remission until treatment either: (a) the patient achieves remission (after which treatment may be continued), or (b) the patient fails to achieve remission. The model attempts to account for these competing risks for discontinuing a given treatment regimen specifically to achieve remission (i.e. patients may transition within the model through achieving remission or failing to achieve remission).

The probability of discontinuation and/or achieving remission is expected to be influenced by the treatment assigned and its positioning (i.e. where anakinra is used). Due to a lack of data, the model assumes no difference in discontinuation or remission between the sJIA and AOSD populations. However, the model assumes different probabilities of remission and discontinuation based on treatment and anakinra's positioning.

In addition, the model accounts for the possibility that the probabilities of remission may be affected by the course of disease (i.e. monocyclic or chronic). Given that it is not possible for these probabilities to be studied within a prospective trial (due to the retrospective classification of disease course), the probabilities applied in the base-case are informed by clinical expert opinion and are discussed by regimen in the sections below.

B.3.3.1.1. NSAIDs +/- corticosteroids

For NSAIDs + corticosteroids, patients are expected to be treated for a maximum of 4-6 weeks before patients may be switched to an alternative regimen (or have an alternative treatment added).[24;78] Weekly probabilities for monocyclic patients were estimated using the Excel Solver plug-in, where the input probabilities for remission and discontinuation were varied until 5% of patients were on treatment (i.e. most patients [95%] had discontinued or achieved remission] and approximately 30% of patients were in remission after 6 weeks (TA238 assumes 68% of patients would be non-responders to NSAIDs + corticosteroids).[36] A weekly discontinuation probability of 27.31% was estimated, along with a weekly remission probability of 12.56%.

For patients with chronic disease course, clinical expert opinion provided to Sobi indicated that it is highly unlikely that these patients would achieve remission through use of NSAIDs and/or corticosteroids alone. As such, the model assumes the probability for chronic patients of achieving remission with NSAIDs and corticosteroids is zero. A weekly discontinuation probability of 39.30% was estimated using the same methodology as per the monocyclic group (with an estimated 0% of chronic patients in remission at 6 weeks).

B.3.3.1.2. Non-biologic DMARDs

In the study by Nordström et al. (2012) 20% of AOSD patients treated with csDMARDs achieve remission by 24 weeks.[92] A weekly remission probability of 0.93% was therefore estimated for monocyclic patients. This probability was assumed to apply for both sJIA and AOSD patients in the absence of RCT evidence concerning remission achieved with DMARDs for sJIA patients.

In NICE TA238, treatment discontinuation rates for csDMARDs were based on the pre-biologic era wherein csDMARDs were used for extended periods of time (as no other treatment options were available).[36] Solver was again used to inform the discontinuation for csDMARDs. Patients are expected to be treated with csDMARDs for 12-16 weeks,[24;78] and so the model was calibrated such that after 16 weeks, 5% of patients were still on treatment (approach taken similar to that for NSAIDs + corticosteroids). This yielded a weekly probability for discontinuation of 16.23%.

Per the clinical input relating to the use of NSAIDs +/- corticosteroids in patients with chronic disease course, treatment with csDMARDs is also not expected to result in remission for patients with chronic disease course. As such, a weekly discontinuation probability was calibrated assuming 0% of patients would be in remission at 16 weeks, and 5% would still be on treatment (yielding an estimate of 17.07%).

B.3.3.1.3. Anakinra and tocilizumab

Estimated remission probabilities for anakinra and tocilizumab are not reported within all the available RCTs conducted in sJIA and AOSD. This is because at the time earlier studies were conducted, remission was not considered a relevant endpoint (given that remission had not been achieved for patients prior to study entry, and the studies were planned to be conducted for only a limited time horizon). Instead, outcomes relating to improvement measured via the ACR are indicative of the potential for remission (with continued treatment over a longer time period). These outcomes are presented and discussed within Section B.2.

There is limited information regarding the expected probabilities of discontinuation or remission for post-NSAIDs + corticosteroids use of biologics. In a study by Horneff et al. (2018), daily SC injections of anakinra for 3 months resulted in complete remission in 4 of 9 sJIA patients (44.4%) in the first-line setting.[118] This yields a weekly probability of 4.41%. Due to a lack of equivalent data for AOSD patients, this value was applied for both cohorts.

Following the use of csDMARDs, the efficacy of anakinra was studied by Nordström et al. (2012) wherein 50% of AOSD patients treated with anakinra achieved remission by 24 weeks.[92] A weekly remission probability of 2.85% was therefore estimated. Like with the csDMARDs, this probability was assumed to apply for the sJIA population in the absence of RCT evidence concerning remission achieved with either anakinra or tocilizumab. An alternative study by Pardeo et al. (2015) reported the experience of a single-centre where anakinra was used in sJIA patients.[87] 56% of patients treated with anakinra met the criteria

for inactive disease by 6 months. Using these data, a weekly remission probability of 3.10% was estimated. This probability is considered as a sensitivity analysis.

A weekly discontinuation probability of 1.14% may be estimated using NICE TA238 where 12.6% of patients were estimated to discontinue treatment every 12 weeks. Discontinuation and remission probabilities were assumed to be equal for the sJIA and AOSD populations. For simplicity, the discontinuation rate is set to be the same for all states of the world (1.14% per model cycle). A recent study reported cumulative survival of anakinra for a cohort 137 sJIA and AOSD patients. In this study, after 12 months approximately 23% of patients had discontinued treatment with anakinra for all reasons (including achieving clinical remission).[119] Therefore, this data source was not considered appropriate to inform the economic model.

In the model base-case, the probability of achieving remission with anakinra or tocilizumab is considered equal. The model includes the option to specify a relative risk (RR) for the probability of achieving remission for tocilizumab versus anakinra (e.g. RR of 1.1 would suggest a 10% improvement in the probability of remission for tocilizumab compared to anakinra, and a RR of 0.9 would assume a 10% reduction in the probability of remission for tocilizumab compared to anakinra). Sensitivity analyses were explored wherein the RR of achieving remission with anakinra versus tocilizumab was varied between 0.9 and 1.1.

Discontinuation and remission probabilities are assumed to be equal for monocyclic and chronic patients.

B.3.3.1.4. Unresolved

The only treatments considered possible to achieve remission following NSAIDs +/- corticosteroids, csDMARDs, anakinra and tocilizumab are (if used): (1) canakinumab, and (2) BMT. There are no other licensed or recommended interventions for use in Still's disease, per the available NHS Clinical Commissioning policies for both sJIA and AOSD.[24;78]

The probability of achieving remission with canakinumab is set to the maximum of achieving remission with anakinra or tocilizumab in the 'post-csDMARDs' positioning, which may be deemed an over-estimate of the likely remission probability for patients who have previously failed to achieve remission on anakinra and tocilizumab. This is considered highly conservative, as the true probability of achieving remission is expected to be lower (given that anakinra and canakinumab both block the activity of IL-1), and the use of a higher

remission probability will thus yield more QALYs in the states of the world where additional further treatment is required.

For patients who survive the surgery, the probability of achieving remission with BMT is set to 100%. Per the assumption used for canakinumab, this is also considered highly conservative (higher remission probability leads to more QALYs for the states of the world wherein excess further treatment is necessary).

It is assumed that it is not possible to achieve remission with any other treatment used in this setting, as there are no other licensed or recommended options remaining in the pathway. Use of other interventions is not aligned with the NHS clinical commissioning policies for sJIA or AOSD, and so assigning the possibility of achieving remission with these treatments would contradict the available clinical guidance regarding the management of Still's disease in UK practice.

Discontinuation is not included as a model parameter for the 'unresolved' state, as this health state is assumed to be occupied until either remission or death.

B.3.3.1.5. Summary

A summary of the remission and discontinuation probabilities is provided in Table 53.

Table 53. Summary of modelled remission and discontinuation probabilities (per model cycle)

Parameter	Value	State(s) of the world used in			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 *et al.* (2012): 20% remission after 24w. C: 0% in remission.
Anakinra	4.41%	✓	×	×	Horneff *et al.* (2018): 44.4% remission after 3mth.
	2.85%	×	✓	×	Base-case: Nordström *et al.* (2012): 50% remission after 24w. SA: Pardeo et al. (2015): 56% inactive disease after 6mth.
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).
Discontinuation					
NSAIDs+C	27.31%[MC]; 39.30%[C]	✓*	✓*	✓*	Calibrated. MC: 5% on treatment after 6w, 30% in remission. C: 5% on treatment after 6w.
csDMARDs	16.23%[MC]; 17.07%[C]	×	✓*	✓*	Calibrated. MC and C: assume 5% on treatment after 16w.
Anakinra	1.14%[First]; 2.03%[Second]	✓	✓	×	NICE TA238 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 *et al.* (2019).
Tocilizumab	1.14%[First]; 2.03%[Second]	✓	✓	✓	

Key: AOSD, adult-onset Still's disease; C, chronic; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; MC, monocyclic; mth, month(s), NICE, National Institute for Health and Care Excellence; NSAIDs+C, nonsteroidal anti-inflammatory drug + corticosteroids; SA, sensitivity analysis; sJIA, systemic-juvenile idiopathic arthritis; TA, technology appraisal; w, week(s).

Notes: Model cycle length is 7 days; * Only included if patients are assumed to start at this or an earlier stage within the pathway; [C] Chronic disease course; [MC] Monocyclic disease course; [First] Discontinuation probability applied for first biologic used; [Second] Discontinuation probability applied for second biologic used.

It is noted that the use of an average discontinuation probability per cycle is imperfect, as a small proportion of patients are estimated to remain on treatment beyond what may be considered a plausible maximum treatment duration (e.g. 5% of patients still receiving NSAIDs + corticosteroids beyond 6 weeks). This is noted as a limitation of the model structure adopted, but as there is little difference expected between the modelled states of the world (given the maximum treatment duration of approximately 6 weeks for NSAIDs + corticosteroids), this was not considered a major limitation in the interpretation of the model results. The specification of a constant discontinuation probability was also considered appropriate for those treatments for which long-term treatment is possible (e.g. anakinra and tocilizumab).

B.3.3.2. Disease recurrence following remission

By definition of the disease course, it is impossible for a monocyclic patient to experience disease recurrence following remission and so this feature of the disease is explicitly incorporated within the model (i.e., the probability of experiencing disease recurrence for monocyclic patients is fixed at 0%).

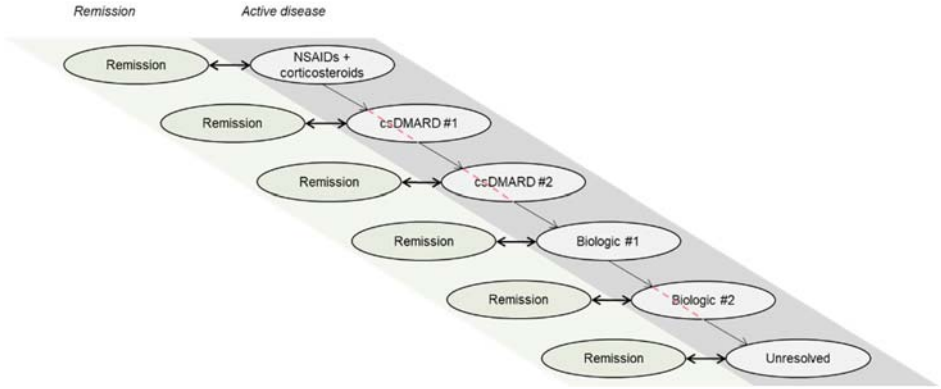
Due to a lack of data regarding the probability of maintaining disease remission for chronic patients, it is assumed there is an equal probability of experiencing disease recurrence irrespective of previous treatment. A study by Yamada et al. (2018) recently reported the findings of a study regarding relapse in patients with AOSD treated with tocilizumab.[120] In this study, 48 patients with AOSD were enrolled, and a total of 30 relapses during the observation period of 3.5 years were identified. Using this information, a probability of relapse per week was calculated using Equation 1 (assuming one relapse per patient).

Equation 1. Calculation of relapse probability

$$\mathbb{P}(relapse) = 1 - e^{\frac{\ln\left(1-\frac{30}{48}\right)}{3.5 \times Weeks\ per\ year}} = 0.5356\%\ (per\ week)$$

In the base case, following loss of remission it is assumed that patients receive the last treatment they previously were given. This application is shown in Figure 11.

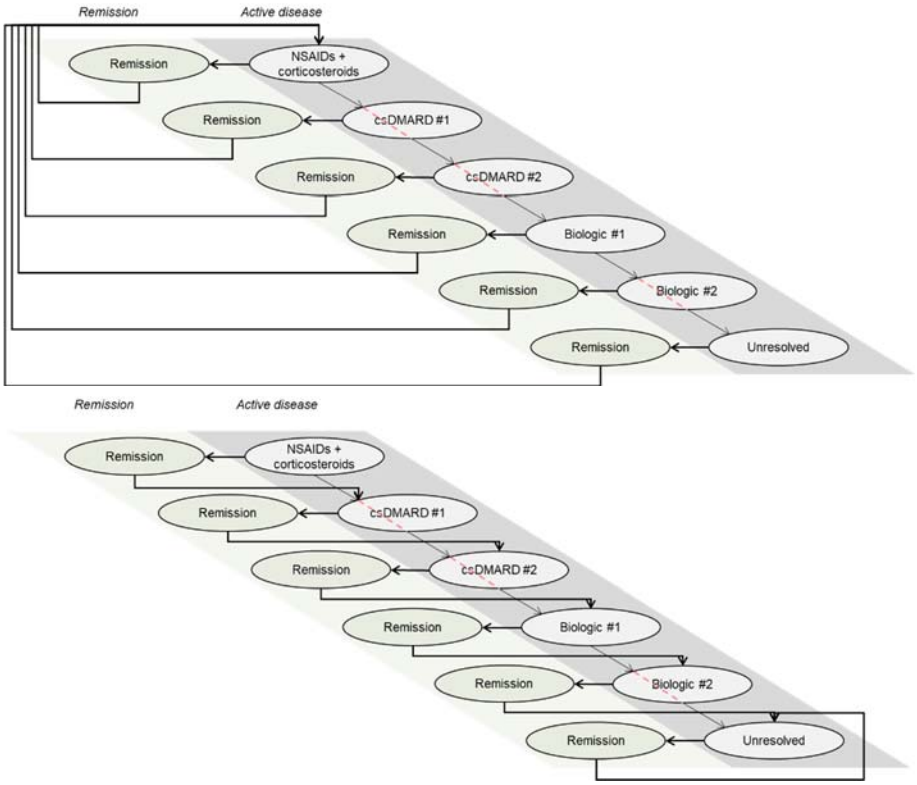
Figure 11. Base-case transitions following loss of remission



Key: csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; NSAIDs + C, nonsteroidal anti-inflammatory drug + corticosteroid.

The model includes two other options following loss of remission: (1) patients return to first treatment (Figure 12 [left], patients 'restart' the pathway beginning with NSAIDs + corticosteroids) or (2) patients progress to the next line (Figure 12 [right], if a patient achieves remission with the second biologic and subsequently experiences loss of remission, they would be progressed to the 'unresolved' state).

Figure 12. Transitions following loss of remission in return to first treatment scenario (top) and progress to the next line scenario (bottom)



Key: csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; NSAIDs + C, nonsteroidal anti-inflammatory drug + corticosteroid.

Expert clinical opinion sought by Sobi indicated that in practice, the next treatment following loss of remission is considered on a case-by-case basis – for patients who previously achieved response on a biologic therapy, the expert advisers noted that provided the response was maintained for a reasonable timeframe (typically for at least six months), they would treat patients with the same biologic again.[116] However, were the response short-lived, they may look at other options. For patients who relapse several years after being discharged from routine monitoring after achieving remission, there may be some cases where treatment with NSAIDs +/- corticosteroids would be initiated (e.g. due to a lack of information regarding a patient's treatment history). The model assumption that patients return to the treatment they received prior to achieving remission was considered the most likely scenario given the lack of data, and because the other two scenarios are associated with the following caveats:

- **Patients return to first treatment:** If patients are assumed to return to the first treatment they received (NSAIDs +/- corticosteroids), some may achieve remission ahead of progressing to the last treatment they received (e.g. a patient may have experienced loss of remission previously achieved through biologic treatment but may subsequently achieve disease remission through NSAIDs +/- corticosteroids). This is considered clinically implausible, as treatments that previously did not lead to disease remission in the first instance would be highly unlikely to lead to remission if given subsequently (but could theoretically still be used if there has been a long period of time since treatment was last required)

- **Patients progress to next treatment:** If patients are assumed to progress to the next line of treatment, there may be some patients who could have achieved remission if re-treated with the same treatment they previously achieved remission with. This scenario is inherently biased against the use of biologic treatments (anakinra and tocilizumab) as this scenario does not allow the possibility of achieving remission with a previously-successful biologic. Furthermore, it was considered implausible to progress from the last recommended option (i.e. first- or second-line biologic) if previously successful, as there are no other options available thereafter

Therefore, while these scenarios are considered within sensitivity analysis, they should be interpreted with caution.

B.3.3.3. Macrophage activation syndrome (MAS)

MAS is captured in the model as an event, as it is an uncommon but potentially fatal complication associated with Still's disease. Patients who develop MAS are not considered a 'subgroup' of the disease *per se;* rather, MAS is defined as condition that may develop for patients with poorly-controlled disease symptoms or if patients have an infection.[1] If treated successfully, the majority of the costs of treatment and determinate health effects are only incurred within a restricted timeframe. However, there may be some long-term health effects for patients who recover from their development of MAS.

The model omits the long-term consequences of recovering from MAS, such as post-traumatic stress disorder (PTSD) as a result of having a 'near-death' experience.[116] These long-term effects would be extremely difficult to capture robustly within the model owing to the rarity of MAS, and a lack of data to quantify specific health effects in the long term. However, through omitting the long-run costs and outcomes attributed to MAS, the model potentially underestimates the cost-effectiveness of a given state of the world which leads to lower occurrence of MAS (i.e. through increased use of anakinra).

Current clinical opinion is that the probability of developing MAS is dependent primarily upon the management of disease-related symptoms and/or presence of infection.[59;116;121] There is some emergent evidence which suggests that use of anakinra specifically may reduce the probability of patients developing MAS, as in sJIA MAS episodes are often triggered by disease flare, and so it may be reasonable to expect some response to IL-1 inhibition (through anakinra use) due to better control of the underlying disease.[122]

Historical estimates of MAS occurrence suggest that an estimated 7–10% of patients with sJIA may develop overt MAS, though these estimates were reported in the pre-biologic era of care (which as described above is expected to have reduced the number of cases) and many estimates have been derived for a non-sJIA specific cohort. There is very limited evidence of the development of MAS for AOSD patients – Giacomelli et al. (2018) suggested that MAS has been reported in up to 15% of AOSD patients.[64] Clinical expert advice provided to Sobi suggested that approximately 8-10% of patients would be expected to develop MAS (excluding the potential reduction in risk attributable to anakinra use), which is broadly aligned with previously published estimates in sJIA and AOSD.[32;60-62]

To inform the economic model, the probability of developing MAS was based on a study by Grom et al. (2016).[123] This study was undertaken to assess the impact of canakinumab (versus placebo) on the incidence of MAS in sJIA patients, and found that the rates of

'probable MAS' events (using criteria developed by the Medical and Scientific Advisory Council) expressed per 100 patient-years were 2.8 (canakinumab) versus 7.7 (placebo). The difference was numerically advantageous towards canakinumab, though not statistically significant (-4.9 [95% CI: -15.6, 5.9]), and the analysis was based on a relatively small sample (for a rare event) of 324 patients across a number of trials.

For patients not treated with anakinra, the probability of developing MAS was assumed to be the mid-point of this estimate range – that is, a weekly probability was calculated assuming a rate of 5.25 per 100 patient-years.[123] This results in a weekly probability of 0.1006%. For patients treated with anakinra, this probability is expected to be lower (based on clinical expert opinion and the findings of the IL-1β-targeting canakinumab study by Grom et al. [2016]).[123] The model incorporates an RR to allow an adjustment to the probability of developing MAS, though this is assumed to be 1.00 in the model base case (and is varied within sensitivity analysis) due to a lack of clear evidence in support of a more definitive RR.

For patients who have achieved disease remission, the model assumes it is not possible to develop MAS. In practice, there may be a very small probability that a patient in clinical remission may develop MAS; however, the model assumes that if a patient develops MAS the patient has also experienced loss of remission. Nevertheless, the model includes an option to specify a probability of developing MAS for those patients in remission (but is disabled in the base-case).

The model assumes the probability of developing MAS is the same between sJIA and AOSD patients, due to a lack of data available for AOSD with the same level of reporting per Grom et al. (2016).[123] However, the model incorporates the option to specify different probabilities for sJIA and AOSD if such data become available.

B.3.3.4. Adverse events

The main AE associated with anakinra is injection site reaction (ISR), based on clinical studies in sJIA and AOSD.[3;4;92] Clinical experience with anakinra across a range of indications suggests that up to 70% of patients experience an ISR, and of those 95% are mild to moderate in severity.[124]

ISRs with anakinra tend to occur within the first weeks of initiating treatment, and patients who do not experience an ISR within 4 weeks are unlikely to experience any ISR for the remainder of their treatment.[124] In the Quartier et al. (2010) RCT of anakinra versus placebo, the AE *"pain at injection site"* was observed at a rate of 8.00 per patient-year in the first

month of administration, followed by a rate of 0.99 per patient-year thereafter (follow-up until one year, including 50% of patients who crossed over from placebo).[4]

ISRs are also known to occur in patients treated with tocilizumab, though given that tocilizumab is administered once per week these events are expected to occur at a lower frequency versus anakinra. In the Yokota et al. (2008) RCT of tocilizumab versus placebo, 18% of patients experienced mild ISRs within the open-label lead in phase (tocilizumab administered once every 2 weeks for a period of 6 weeks).[125] No further ISRs were reported in the double-blind and extension periods of the study (which covered a follow-up period of at least 60 weeks).

The model considers a probability of patients treated with anakinra experiencing ISRs per model cycle (week); and captures separate probabilities for sJIA and AOSD patients. For tocilizumab, a probability of 0% is assumed to apply (based on the relatively low proportion of ISRs observed in the study by Yokota et al. [2008] after the first 6 weeks).

For sJIA patients treated with anakinra, the probability of ISR was calculated by assuming a weighted average rate of $\frac{8.00 \times 1 + 0.99 \times 11}{12} = 1.574$ per patient-year, based on the study by Quartier *et al.*[4] By dividing this value by 365.25 (days per year), a per-administration probability of 0.43% was calculated.

For AOSD patients treated with anakinra, data from the Nordström et al. (2012) study were considered.[92] In this study, seven patients out of 12 receiving anakinra reported a Grade 1 ISR, one patient reported a Grade 2 ISR, and four additional patients in the open-label extension (OLE) study reported a Grade 1 ISR. Based on a total of n=12 anakinra patients and n=10 csDMARD patients (8 of whom switched to anakinra and completed the OLE study), and assuming a 1-year follow-up for all patients, $\frac{7+1+4}{12+8} = 0.60$ per patient-year. By dividing this value by 365.25 (days per year), a per-administration probability of 0.16% was calculated.

A summary of the input values is reported in Table 54.

Table 54. Injection site reaction adverse event included in economic model

Treatment	Group	Dosing frequency (per week)	Probability (per administration)	Source / Rationale
Tocilizumab	sJIA	0.50	0.00%	Assumption
	AOSD	0.25	0.00%	Assumption

Treatment	Group	Dosing frequency (per week)	Probability (per administration)	Source / Rationale
Anakinra	sJIA	7.00	0.42%	Quartier (2011)
	AOSD	7.00	0.16%	Nordström (2012)

Key: AOSD, adult-onset Still's disease; sJIA, systemic juvenile idiopathic arthritis

All other AEs were not considered in the economic analysis. This omits some known AEs associated with other treatments (particularly those associated with corticosteroids such as weight gain, diabetes, and osteoporosis). These AEs were not considered necessary to capture within the model as all states of the world incorporate the same NSAID + corticosteroid treatment duration, costs and utilities. Consequently, the omission of other AEs is a relatively-conservative assumption (in relation to assessing the likely cost-effectiveness of anakinra in either treatment setting).

B.3.3.5. Mortality

The model captures two potential causes of disease-related mortality; MAS and BMT:

- **MAS:** MAS may occur at any point in the treatment pathway and is expected to be fatal in approximately 10-41% of cases.[64] Evidence suggests mortality may be higher for sJIA versus AOSD patients, however this has not been studied in depth. The base-case analysis assumes a 12.9% mortality risk associated with MAS based on a published study by Kumakura *et al.*[62]

- **BMT:** BMT is anticipated to only be used as a 'last resort' for patients with uncontrolled disease in the 'further treatment' health state who are unresponsive to other treatments, therefore is only applied in this health state. Clinical expert opinion estimated BMT to be fatal in 25% of cases, which is similar to mortality rates observed at the Great Ormond Street Hospital for Children (acknowledging that mortality at 1-year may not be directly-linked to the transplant procedure itself).[126] However, a recent study by Silva et al. (2018) identified a transplant-related mortality risk of 12.5% which is used within the model base case[127]

Mortality from all other causes are assumed to be captured within background mortality estimates, derived using the Office for National Statistics (ONS) life tables (based on data from 2015 to 2017, published in September 2018).[128]

The application of mortality in the model used to inform this submission differs from the assumptions used in the previous NICE submission of tocilizumab in sJIA (TA238). In TA238, a constant mortality risk was estimated and applied for the 16-year time horizon. Within the context of a time horizon of 30 years and acknowledging the importance of capturing differences in mortality estimates owing to the probability of MAS in particular, the application of mortality in the model used to inform this submission was considered more appropriate for the decision problem. Similar to TA238 however, the model used to inform this submission assumes no difference in mortality according to treatment received (except due to MAS or use of BMT, both of which were not captured in TA238).[77]

The application of mortality in this submission omits some known mortality effects, such as long-term issues associated with prolonged steroid use (e.g. renal and/or cardiovascular problems). Due to the complexity of attempting to capture such mortality effects, these were omitted from the analysis, which is noted as a limitation of the submitted model. However, the omission of other mortality effects is considered conservative, since increased/earlier use of anakinra is expected to lead to reduced need for prolonged steroid use (e.g. use of steroids for patients who develop MAS due to uncontrolled disease).

B.3.3.6. Summary of sources to inform economic model

There are several important limitations with the evidence base for Still's disease required to inform the model. Nevertheless, some studies were not considered appropriate to inform the economic model, and so a summary of the sources used, alongside reasons why alternative studies were or were not used to inform the economic model is provided in Table 55.

Table 55: Summary of selected sources to inform economic model parameters

	Approach and justification
Discontinuation	Estimated constant discontinuation* rates for NSAIDs + corticosteroids and csDMARDs were used such that 95% of patients discontinued after 6 weeks (NSAIDs + corticosteroids) or 16 weeks (csDMARDs). For anakinra and tocilizumab, the same rate of discontinuation was assumed per NICE TA238 (tocilizumab for sJIA), with an adjustment applied to account for increased discontinuation for patients with a history of prior treatment with biologics. Limited evidence is available to quantify discontinuation rates for NSAIDs, corticosteroids and csDMARDs (such as methotrexate) in current UK clinical practice. Published NHS clinical commissioning policies for sJIA and AOSD note maximum treatment times of 6 and 16 weeks. 95% was chosen as an arbitrary estimate of the majority of patients having discontinued within this time period. For anakinra and tocilizumab, data from NICE TA 238 were considered appropriate to inform this appraisal.

	Approach and justification
Remission	For NSAIDs + corticosteroids, 30% of patients were assumed to achieve remission (noting that these are expected to be monocyclic patients). If anakinra or tocilizumab are used after NSAIDs + corticosteroids, it is assumed that data from a study by Horneff (2018) apply. For csDMARDs, anakinra and tocilizumab (when used after csDMARDs**), the Nordström (2012) study was used. For csDMARDs, it was assumed that remission is only possible for monocyclic patients. In a sensitivity analysis, data from a study by Pardeo (2015) were also considered should anakinra or tocilizumab be used after csDMARDs. For 'unresolved' patients, bone marrow transplantation was assumed to be 100% effective at achieving remission in those patients who survive the procedure. Should canakinumab be included within this state, the same rate of remission was assumed as per anakinra and tocilizumab. The probability of remission is expected to be dependent on the treatment used and the positioning of anakinra, as well as the baseline severity of disease. A real-world evidence study by Kearsley-Fleet (2018) was not considered appropriate to inform the economic model. This study considered a non-randomised population, of which the difference in patient characteristics may lead to biased estimates of treatment effect (e.g. the anakinra arm had far greater history of MAS, which is directly linked to poor disease control).
Loss of remission	Data from a study by Yamada (2018) were used to inform the probability of (chronic) loss of remission. Following loss of remission, it was assumed that patients would return to the point in the treatment pathway where remission was achieved based on clinical expert opinion. For completeness, a sensitivity analysis was undertaken to explore the impact on results should loss of remission be omitted from the economic model structure. In an open-label extension to the Nordström (2012) study, 7/14 patients receiving anakinra were still in remission at week 52 (an additional 28 weeks) versus 2/3 still receiving csDMARD. This study was not considered appropriate for informing loss of remission as follow-up was still relatively short (28 weeks), and some patients crossed over from csDMARD to anakinra (n=5).
MAS	The probability of developing MAS was taken from Grom (2016). While this study considered patients treated with canakinumab versus placebo, the study provides a recent estimate of likely development rates across a biologic treatment that acts upon IL-1 and placebo. IL-1 is understood to play an important role in MAS, and so these two treatment arms provide a useful range of development rates for consideration within the economic model. The majority of other studies did not provide a timeframe over which MAS is expected to develop – for example, in a study by Giacomelli (2018) it was noted that MAS "has been reported in up to 15% of AOSD patients". To avoid the need to estimate the duration of follow up, the Grom (2016) study was preferred for use within the model.
AEs	The only AE captured within the economic model was ISR, as these events were considered the most impactful on patients and occur with the greatest frequency. Through consultation with clinical experts, this was noted as a key adverse event associated with anakinra, and so while other AEs are known to exist, these were not captured within the model for simplicity. Also, in the previous TA238 of tocilizumab in sJIA, AEs were excluded from the economic model, and so the same approach was carried forward in this appraisal.

Key: AE, adverse event; AOSD, adult-onset Still's disease; csDMARDs, conventional synthetic disease-modifying antirheumatic drug; ISR, injection site reaction; MAS, macrophage activation syndrome; NICE, National Institute for Health and Care Excellence; NSAIDs, non-steroidal anti-inflammatory drugs; sJIA, systemic juvenile idiopathic arthritis.

Notes: * Discontinuation within this context refers to ceasing to continue treatment without adding and/or switching to achieve remission. ** In the Nordström (2012) study, patients were excluded if considered refractory to corticosteroids and DMARD. Refractory state was defined as need for prednisolone ≥ 10 mg/day (or equivalent) with or without concomitant use of DMARD, and unacceptable disease activity as determined by the investigator.

B.3.4. Measurement and valuation of health effects

B.3.4.1. Summary of approach to capturing health effects within the model

As discussed in Section B.3.2, the primary aim of treatment for patients with Still's disease (sJIA or AOSD) is to achieve clinical disease remission. Consequently, the model adopts a relatively simplistic approach to capture differences in HRQL over time. Upon entering the model, the key events that are expected to affect utility are:

- Achieving disease remission
- Exhausting all available treatment options (NSAIDs, corticosteroids, csDMARDs, anakinra, and tocilizumab), and thus having 'unresolved' disease
- Developing macrophage activation syndrome (MAS)
- Experiencing an injection site reaction (ISR)

The previous NICE assessment of tocilizumab for sJIA (TA238) considered the relationship between ACR response and utility while patients received multiple lines of treatment.[77] This resulted in the use of a model which included 22 Markov states based on a combination of the line of therapy and response category (plus death). The model considered the possibility of achieving an ACR response of 30, 50, 70, or 90; as well as the potential for patients to not achieve a response to treatment and therefore have 'uncontrolled' disease.

Since publication of TA238, clinical practice has shifted towards achieving remission (i.e. complete disappearance of clinical symptoms such as fever, and normalisation of laboratory test results) versus only managing clinical symptoms. Therefore, while patients may experience improvements in HRQL attributable to treatment response, the use of an economic model centred around disease remission was considered to be more reflective of current practice and would capture the majority of the health benefits associated with treatment.

B.3.4.2. Health-related quality-of-life data from clinical trials

In the previously mentioned clinical trials of anakinra, the EQ-5D questionnaire was not administered to patients. However, were the EQ-5D questionnaire administered it is unlikely that the estimates obtained would be directly relevant to inform the economic model

presented within this submission. This is due to the treatment pathway structure of the economic model, which would be impossible to collect data for within a single trial.

For the two sJIA studies, the CHAQ was administered to patients. In the Ilowite et al. (2009) study, anakinra was associated with an improvement in the mean change in CHAQ (versus placebo) at week 28 of −0.25 vs 0.13.[3] In the Quartier et al. (2011) study (ANAJIS), patients treated with anakinra reported a non-statistically significant reduction in the CHAQ of approximately 37% at 1 month, versus 9% for placebo (p=0.236).[4]

The Nordström et al. (2012) study in AOSD collected information using the HAQ, SF-36, as well as global and disease-related assessments of health.[92] A significantly greater number of patients using anakinra achieved improvements according to the SF-36 physical health summary compared to patients using DMARDs (Figure 7A; p=0.011). SF-36 mental health summary showed no differences between groups (Figure 7B, p=0.74). Findings relating to the HAQ and other assessments of health were not reported within this study.

While these studies provided outcomes relating to HRQL, they were not considered appropriate for informing the economic model as:

- The studies were conducted in a relatively low number of patients (n=22 for Quartier et al. [2011] and Nordström et al. [2012], n=50 for Ilowite et al. [2009]) for a limited follow-up period (1 month for Quartier et al. [2011], 28 weeks for Ilowite et al. [2009], 24 weeks for Nordström et al. [2012])[3;4;92]

- No patients were recorded as achieving disease remission within the three studies, given that the maximum duration of follow-up was only 24 weeks

- The reporting of information concerning the HRQL for patients was not reported to a high level of detail that may be necessary to inform the economic model (for example, it is unclear how changes in CHAQ occurred over time with respect to the 12-week run-in phase of the Ilowite et al. [2009] study) [3]

Therefore, external information was sought to inform the cost-effectiveness analysis.

B.3.4.3. Health-related quality-of-life studies

A systematic review was conducted to identify HRQL studies undertaken in sJIA and/or AOSD. Details of the search strategies employed, databases searched, and number of hits are provided in Appendix H. Only one study was identified that provides utility values that

may be appropriate for use within this submission – the previous NICE assessment of tocilizumab for sJIA (TA238).[77] Further information regarding this study is provided in Section B.3.4.

B.3.4.4. Mapping

Within TA238, utility values were derived according to a relationship between the CHAQ and utility, and each response category measured according to ACR score was associated with a correspoding CHAQ value.[77] Four possible equations were presented, and the TA238 base-case assumes a quadratic relationship between utility and CHAQ (shown in Equation 2).

Equation 2. Utility estimation (base-case from NICE TA238)

$$Utility = 0.82 - 0.11 \times CHAQ - 0.07 \times CHAQ^2$$

Key: CHAQ, Childhood Health Assessment Questionnaire.

It should be noted that the relationship used in TA238 was derived using data from two tocilizumab trials of adult rheumatoid arthritis patients (OPTION and LITHE, N=1800). Further details of the derivation of Equation 2 may be found in the TA238 company submission.

The assumed CHAQ values per ACR category are presented within Table 56. Provided alongside these are the assumptions imposed within the model used to inform this submission. These are:

- For patients in remission, the highest ACR score of 90 reported within TA238 is assumed to be representative of average utility
- For patients with active disease, an ACR score of 30 is assumed to apply

Table 56. Assumed CHAQ scores according to ACR achieved

ACR category	CHAQ	Health state(s)
No response or uncontrolled disease	1.7442	Not used in base-case analysis
ACR 30	1.2699	All patients not in remission
ACR 50	1.1351	Not used
ACR 70	0.8601	Not used
ACR 90	0.6692	All patients in remission

Key: ACR, American College of Rheumatology; CHAQ, Childhood Health Assessment Questionnaire.

Note: Baseline CHAQ in the Quartier *et al.* study was 1.67 for patients randomised to anakinra, and 1.44 for patients randomised to placebo.

In practice, patients residing within the 'unresolved' state are expected to be treated with various experimental treatments (e.g. Janus kinase inhibitors [JAK] inhibitors), unlicensed and/or non-recommended therapies (e.g. canakinumab), or invasive interventions (e.g. bone marrow transplantation). It is unknown how successful each of these therapies may be, or how accessible these options may be. In the absence of data to inform this model parameter, it is assumed that patients have the same utility as those receiving recommended treatment options. However, for patients that are truly uncontrolled, utility is expected to be lower.

A summary of the health-state utility values used to inform the economic model is provided in Table 57.

Table 57. Health-state utility values used in economic model

Health state(s)	Utility	Description
Remission	0.7150	Patients assigned higher utility value through achieving remission.
Not in remission	0.5674	Patients assumed to maintain an ACR score of 30.

Key: ACR, American College of Rheumatology; DMARD, disease-modifying anti-rheumatic drug; NSAID, non-steroidal anti-inflammatory drug.

Note: Within the model, utility values are age adjusted.

To ensure these values exhibit face validity in the longer-term, age-adjustment was applied to take into account the expected decline in utility as patients age. A general population study by Ara and Brazier (2011) was used to estimate utility multipliers (Table 58).[129] This study provides average utility scores for the general population within each age category. Baseline age within the model is assigned a multiplier of 1, and all older ages that fall into the categories within the Ara and Brazier study are assigned a corresponding multiplier based on the ratio of utility values. For example, if average age at baseline was 40, utility at age 41 would be based on the ratio of $\frac{0.8824}{0.9069} = 97.30\%$ (based on values in Table 58).

Table 58. General population utility by age group (Ara and Brazier, 2011)

Age range (years)	Number of responders	Utility value
<30	8,083	0.9383
30 to ≤ 35	3,608	0.9145
35 to ≤ 40	4,020	0.9069
40 to ≤ 45	3,746	0.8824
45 to ≤ 50	3,294	0.8639
50 to ≤ 55	3,156	0.8344
55 to ≤ 60	3,285	0.8222
60 to ≤ 65	2,739	0.8072
65 to ≤ 70	2,993	0.8041
70 to ≤ 75	2,501	0.7790
75 to ≤ 80	1,895	0.7533
80 to ≤ 85	1,199	0.6985

B.3.4.5. Injection site reaction (ISR)

ISR disutility has previously been reported as -0.01 in an economic evaluation by Restelli et al. (2017) regarding the treatment of human immunodeficiency virus (HIV).[130] This study cites a disutility for rash from a study by Kauf et al. (2008), also conducted in HIV.[131] The disutility associated with ISR was assumed to apply for one day, and so the calculated QALY loss per occurrence of ISR was estimated as: $\frac{-0.01}{365.25} = -0.0000274$. The impact of ISR-related disutility is explored within sensitivity analysis.

B.3.4.6. Macrophage activation syndrome (MAS)

The utility decrement associated with MAS was assumed to be comparable to the loss in utility experienced as a result of developing sepsis. This assumption was considered appropriate by clinical experts and published literature which noted that in terms of their clinical features, it is difficult to differentiate between sepsis, disease flare-ups, or MAS.[132]

A disutility for sepsis was identified within a cost-utility analysis by Beauchemin et al. (2016) in breast cancer of -0.4684.[133] The disutility associated with MAS was assumed to apply for 14 days, as in practice hospitalisation as a result of developing MAS could vary between several days to several months. Therefore, the calculated QALY loss per occurrence of MAS was estimated as: $-0.4684 \times \frac{14}{365.25} = -0.01795$.

B.3.4.7. Health-related quality-of-life data used in the cost-effectiveness analysis

A summary of the utility values used in the economic analysis is provided in Table 59.

Table 59. Summary of utility values for cost-effectiveness analysis

State	Utility value: mean	95% CI	Reference in submission	Justification
NSAID+C	0.567	(0.537, 0.598)	B.3.4.4, page 141	"Non-remission" utility values assumed to be equivalent.
csDMARD #1				
csDMARD #2				
Biologic #1				
Biologic #2				
Unresolved				
Remission	0.715	(0.987, 0.743)		Patients assigned higher utility value through achieving remission.
ISR	-0.01	(-0.076, 0.000)	B.3.4.5, page 143	Restelli (2017)[130]
MAS	-0.4684	(0.4216, 0.5155)	B.3.4.6, page 143	Beauchemin, (2016)[133]

Key: CI, confidence interval; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; ISR, injection site reaction; MAS, macrophage activation syndrome; NSAID+C, nonsteroidal anti-inflammatory drug + corticosteroids; SE, standard error.

B.3.5. Cost and healthcare resource use identification, measurement and valuation

B.3.5.1. Resource identification, measurement and valuation studies

A systematic review was conducted to identify resource identification, measurement and valuation studies undertaken in sJIA and/or AOSD. Details of the search strategies employed, databases searched, and number of hits are provided in Appendix I. In addition to NICE TA238, one study was identified (Shenoi et al., 2018) but was not considered applicable for use within the economic model. However, data from NICE TA238 were used to inform the economic model, described further in the relevant sections below.

B.3.5.2. Drug costs and market share estimates

Relevant drugs and market share estimates within the treatment pathway for Still's disease were identified using a range of sources, including the previous NICE assessment of tocilizumab for sJIA (TA238), NHS policies for AOSD and sJIA, as well as expert clinical opinion and the British National Formulary (BNF). Table 60 displays the acquisition costs and pack sizes for each drug considered relevant to the submission.

Table 60. Summary of acquisition costs

Drug category	Drug	Cost per pack	Pack size	Reference
NSAIDs	Naproxen (500mg)	£3.58	56	eMIT
	Ibuprofen (200mg)	£0.31	48	eMIT
Corticosteroids	Prednisolone (5mg)	£0.26	28	eMIT
	Methylprednisolone (1,000mg)	£6.42	1	eMIT
csDMARDs	Azathioprine (50mg)	£1.59	56	eMIT
	Cyclosporine (25mg)	£11.14	30	BNF
	Leflunomide (20mg)	£3.57	30	eMIT
	Methotrexate (2.5mg)	£0.86	24	eMIT
Biologics	Anakinra (100mg/0.67ml)	£183.61	7	BNF
	Tocilizumab (80mg/4ml)*	£102.40	1	BNF
	Tocilizumab (162mg/0.9ml)	£913.12	4	BNF
	Canakinumab (150mg/1ml)	£9,927.80	1	BNF

Key: BNF, British National Formulary; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; eMIT, electronic marketing information tool; NSAID, nonsteroidal anti-inflammatory drug.

Note: *Excluding the confidential simple patient access scheme (PAS) discount. In the base-case analysis, an assumed PAS discount of [redacted] is applied for tocilizumab.

It should be noted that there is a confidential, simple patient access scheme (PAS) discount in place for tocilizumab, as of July 2019 (reported on the Patient Access Schemes Liaison Unit website). Due to the confidential nature surrounding the volume of discount offered, it is not possible to include the "true" cost of tocilizumab within this submission, and so sensitivity analysis has been conducted to explore the possible range of prices by considering PAS discounts ranging from 0% to 100%. In the base-case analyses presented, an assumed PAS discount of [redacted] is applied. Results assuming the list price for tocilizumab are also presented in sensitivity analysis.

Naproxen and ibuprofen were the NSAIDs identified as most commonly used in practice. Prednisolone or IV methylprednisolone were the corticosteroids used most frequently. Each of the NSAIDs and corticosteroids were assigned equal market shares (i.e. 50:50 split).

It is assumed that methotrexate is the first choice of csDMARD and cyclosporin the second choice should a patient fail to achieve a sufficient response to methotrexate (and be given a second csDMARD prior to the use of biologics). Azathioprine and leflunomide are included within the model as indicated by the current NHS policy for AOSD[24] but are assigned a market share of 0% in the base case as methotrexate and cyclosporine were identified as the most likely first and second choices by clinical experts.

The use of biologics is dependent on the modelled state of the world:

- In the ‘per-label’ state of the world (base-case analysis), the model assumes all patients would receive anakinra as a first-choice biologic therapy, for both sJIA and AOSD patients

- In the ‘post-csDMARD’ state of the world (sensitivity analysis), the model assumes 50% of AOSD patients would receive anakinra as a first-choice biologic therapy. However, given the pre-existing NICE guidance for tocilizumab in sJIA, the model assumes all sJIA patients would receive tocilizumab as the first-choice biologic therapy

- In the ‘no anakinra’ state of the world, all patients are expected to be treated with tocilizumab as the first (and only) choice of biologic therapy (noting that tocilizumab is not licensed for the treatment of AOSD, but is recommended in the NHS Clinical Commissioning policy for AOSD)

The cost of canakinumab was also included within the model should a proportion of patients be treated with this as part of the ‘unresolved’ state. In the model base-case, it is assumed that 0% of patients receive canakinumab (as it is not recommended in current NHS Clinical Commissioning policies for sJIA or AOSD).

Table 61 provides a brief summary of the market share assumptions for each category of treatment.

Table 61. Summary of market share assumptions

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
	Cyclosporine	**Second-line:** 100% (AOSD only)
	Leflunomide	Not used
	Methotrexate	**First-line:** 100%
Biologics	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’ state of the world, market share is 0% for all patients. **Second-line:** Used in 100% of patients after tocilizumab. In the ‘no anakinra’ state of the world, market share is 0% for all patients.

Drug category	Drug	Market share assumptions
	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' state of the world).

Key: AOSD, adult-onset Still's disease; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; NSAID, nonsteroidal anti-inflammatory drug; sJIA, systemic-juvenile idiopathic arthritis.

Some patients may continue treatment with a previous line in combination with the next line of therapy. While the model assumes no additional efficacy for concomitant NSAIDs, corticosteroids, or csDMARDs, the additional costs are included for completeness. In the base-case analysis, all patients are assumed to incur the costs for NSAIDs indefinitely (given that these are relatively very low costs). A recent study by Vitale *et al.* (2019) highlighted that of patients receiving biologics, 41.1% were still receiving concomitant corticosteroids at the latest follow-up, and 51.1% were still receiving concomitant csDMARDs.[134] For simplicity, it was assumed that all patients receiving csDMARDs continued to receive corticosteroids.

B.3.5.3. Dosing

For AOSD, all patients are administered a fixed dose for drugs excluding prednisolone, azathioprine, cyclosporine and tocilizumab which are dosed according to patient weight (kg). sJIA patients are dosed according to weight (kg) with the exceptions of leflunomide (fixed) and methotrexate which is dosed according to body surface area (BSA, m^2). The doses per administration and total dose per model cycle length (7 days) are displayed in Table 62.

Table 62. Summary of dosing application

Drug	Group	Dosing			Reference	Dosing notes
		mg/admin	Freq	mg/cycle		
Naproxen	sJIA	3.125/kg	2 /d	1,093.75	BNFc	5–7.5 mg/kg twice daily; max 1 g per day
	AOSD	375.0	2 /d	5,250.00	BNF	500-1,000mg daily in 1-2 divided doses
Ibuprofen	sJIA	9.0/kg	5 /d	7,875.00	BNFc	Up to 60mg/kg daily (sJIA), 30-40mg/kg (JIA) in 4-6 doses, max 2.4g per day
	AOSD	300.0	3 /d	6,300.00	BNF	300-400mg 2-4 times a day initially, can be increased to 600mg 4 times a day, 200-400mg 3 times a day may be adequate for long-term use
Prednisolone	sJIA	1.5/kg	1 /d	262.50	BNFc	1-2mg/kg per day initially, to be reduced after a few days, max 60mg per day
	AOSD	0.9/kg	1 /d	472.50	AOSD policy, NHS ref: 170056P	0.8-1mg/kg per day for 4-6 weeks
Methyl-prednisolone	sJIA	20.0/kg	0.75 /d	1,125.00	BNFc	10–30 mg/kg once daily or on alternate days (max. per dose 1 g) for up to 3 doses.
	AOSD	1000.0	1 /d	3,000.00	Fujii T. et al. (1997)	1,000 mg, 3 administrations
Azathioprine	sJIA	2.0/kg	1 /d	350.00	Frosch M. et al. (2008)	2 mg/kg/day
	AOSD	2.0/kg	1 /d	1,050.00	AOSD policy, NHS ref: 170056P	2-2.25mg/kg for patients with normal TPMT levels, 1-1.25mg/kg for patients with heterozygote TPMT levels
Cyclosporine	sJIA	2.0/kg	2 /d	700.00	BNF, AOSD policy, NHS ref: 170056P	Assume per AOSD
	AOSD	2.0/kg	2 /d	2,100.00		1.5mg/kg twice daily initially, up to 2.5mg/kg twice daily after 6 weeks, max 5mg/kg per day
Leflunomide	sJIA	12.5	1 /d	87.50	Hayward K. et al. (2009)	5-20mg a day (based on weight). Loading dose of 100mg/day for 3 days can be given to adult sized patients to facilitate rapid attainment of steady-state levels
	AOSD	15.0	1 /d	105.00	AOSD policy, NHS ref: 170056P	10-20mg daily
Methotrexate	sJIA	12.5/m²	1 /w	11.66	BNFc	10-15mg/m² once weekly initially, increase up to 25mg/m² once weekly if necessary
	AOSD	16.25	1 /w	16.25	AOSD policy, NHS ref: 170056P	7.5-25mg/week
Anakinra	sJIA	1.5/kg	1 /d	262.50	BNFc	1-2mg/kg per day for <50kg, max 100mg
	AOSD	100.0	1 /d	700.00	AOSD policy, NHS ref: 170056P	100mg/day. Can be increased to 200mg/day, can be reduced to 50mg/day (administered as 100mg on alternate days)

Drug	Group	Dosing			Reference	Dosing notes
		mg/admin	Freq	mg/cycle		
Tocilizumab (intravenous)	sJIA	12.0/kg	0.50 /w	150.00	BNFc	For sJIA <30kg, 12mg/kg every 2 weeks, else 8mg/kg per 2 weeks
	AOSD	8.0/kg	0.25 /w	150.00	BNF	8mg/kg every 4 weeks, max 800mg
Tocilizumab (syringe)	sJIA	162.0	1/ w	162.0	BNFc	Assumed one syringe per week
	AOSD	162.0	0.50 /w	81.0	BNF	Assumed one syringe every 2 weeks (for weight ≥30kg)
Canakinumab	sJIA	4.0/kg	0.25 /w	25.00	BNFc	4mg/kg every 4 weeks, max 300mg. Must be >7.5kg
	AOSD	300.0	0.25 /w	75.00	BNF	4mg/kg every 4 weeks, max 300mg

Key: AOSD, adult-onset Still's disease; BNF, British national formulary; BNFc, British national formulary for children; d, day; kg, kilogram; m² metres squared; mg, milligram; NHS, National health service; sJIA, systemic-juvenile idiopathic arthritis; TPMT, thiopurine methyltransferase; w, week

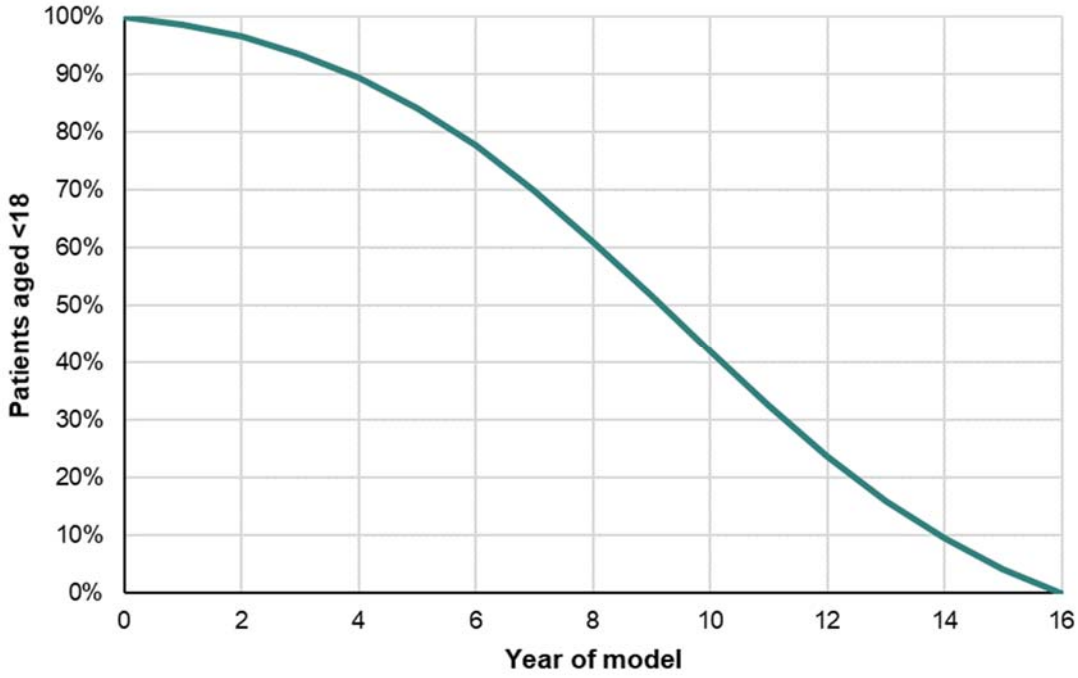
Source: BNF, 2019;[5] NHS England Commissioning Policy AOSD NHS Ref 170056P[24] Fujii et al. 1997;[135] Frosch et al. (2008);[136] Hayward et al. (2009)[137]

To incorporate the costs of treatment, it is necessary to establish the average doses of medications administered to patients. For simplicity, the average weight and BSA for the AOSD and sJIA populations were used to obtain an average dose per treatment per patient group. Weight data were taken from NICE TA238, and BSA was calculated using a combination of the aforementioned weight data and UK demographic data concerning general population height.

In the base case, sJIA patients are given a weight of 25kg and BSA of 0.95m² until they reach the age of 18, at which point they are assumed to be the same as an average AOSD patient at 75kg (and a BSA of 1.87m², though no AOSD doses are based on BSA). The average weight and BSA for each sub-population were varied within sensitivity analysis.

As the costs of treatment vary between the AOSD and sJIA patients, it is necessary to determine the proportion of the sJIA cohort who become adults in the longer term. In the Quartier et al. study, the age range at baseline was 2 to 20 years. Using the mean and standard deviation of the age of the cohort, the proportion of patients over 18 for each model year was obtained, with all patients classed as adults after 16 years (i.e. the minimum age of patients is 2 years, and so after 16 years all sJIA patients would be considered adults). The proportion of sJIA patients moving to adulthood over time is shown in Figure 13.

Figure 13. Proportion of sJIA patients younger than 18 years of age



B.3.5.4. Administration costs

The majority of drugs are administered orally and so no costs are assumed to apply. Methylprednisolone and tocilizumab may be administered via IV infusion which is costed at £154.46 per administration (eMIT – code 410 [assumed to be consultant led outpatient rheumatology]). Anakinra and canakinumab are self-administered SC injections and therefore are assumed to have zero administration costs (however, based on limited experience with canakinumab, it could be administered within a hospital setting).

In September 2019, a subcutaneous formulation of tocilizumab was licensed. Based on clinical opinion provided to Sobi, it is expected that approximately 50% of patients are currently receiving SC tocilizumab, with the remaining 50% still receiving IV tocilizumab. Over time, practice is expected to shift to a larger proportion of patients receiving SC tocilizumab, and so this assumption may be varied within the model. For patients receiving SC tocilizumab, zero administration costs are assumed to apply.

In practice, sJIA patients may require an additional appointment with a consultant to demonstrate how they may self-administer anakinra or tocilizumab. To explore the potential impact of adding this cost within the model, an additional cost of one consultant-led outpatient rheumatology appointment is applied for all patients in the 'per-label' and 'post-csDMARD' states of the world in a scenario analysis. This cost is separate to general medical resource use, which is discussed in further detail within Sections B.3.5.5 and B.3.5.6.

B.3.5.5. Medical resource use costs

Routine tests and medical resource use costs were taken from published sources, primarily NHS reference costs (2017/18) and are displayed in Table 63.

Table 63. Medical resource use unit costs

Category	Resource	Cost	
		sJIA	**AOSD***
Tests	Full blood count	£2.51	
	Liver function test	£1.11	
	Erythrocyte sedimentation rate	£2.51	
	C-reactive protein	£2.51	
	Urea, electrolytes and creatinine	£1.11	
	Lipid test	£2.51	
	GP appointment	£31.00	
	Haematology	£288.00	£160.00

Category	Resource	Cost	
		sJIA	AOSD*
Contact with Health Care Professional and Admissions	Radiology	£192.00	£145.00
	Ophthalmology	£102.00	£98.00
	Rheumatology	£245.00	£146.00
	Psychology	£243.00	£170.00
	Immunology	£219.00	£269.00
	Occupational therapy	£73.00	
	Physiotherapy	£55.00	
	Inpatient stay (per day)	£339.00	

Key: AOSD, adult-onset Still's disease; GP, General Practitioner; sJIA, systemic juvenile idiopathic arthritis.
Note: *AOSD costs assumed to apply for sJIA cohort after age 18.

B.3.5.6. Medical resource use frequencies

Medical resource use frequencies separated by sub-population (AOSD or sJIA) and medication type were estimated based on the previous NICE submission in sJIA (TA238), and consultation with clinical experts. A summary of these frequencies is provided in Table 64. The same medical resource use frequencies were assumed to apply for sJIA and AOSD patients, though some cost items were identified as specific to adult and paediatric patients (marked with an asterisk in Table 64).

Table 64. Medical resource use frequencies per year (for each treatment)

Resource	NSAID+C	DM #1	DM #2	Ana	Toc	Can
Full blood count	18.0	18.0	18.0	18.0	18.0	18.0
Liver function test	18.0	18.0	18.0	18.0	18.0	18.0
Erythrocyte sedimentation rate	18.0	18.0	18.0	18.0	18.0	18.0
C-reactive protein	18.0	18.0	18.0	18.0	18.0	18.0
Urea, electrolytes and creatinine	18.0	18.0	18.0	18.0	18.0	18.0
Lipid test	-	-	-	-	18.0	-
GP appointment	3.5	3.5	3.5	3.5	3.5	3.5
Haematology*	2.0	2.0	2.0	2.0	2.0	2.0
Radiology*	0.4	0.4	0.4	0.4	0.4	0.4
Ophthalmology*	2.0	2.0	2.0	2.0	2.0	2.0
Rheumatology*	1.5	1.5	1.5	1.5	1.5	1.5
Psychology*	0.4	0.4	0.4	0.4	0.4	0.4
Clinical Immunology*	1.5	1.5	1.5	1.5	1.5	1.5
Occupational therapy	3.5	3.5	3.5	3.5	3.5	3.5
Physiotherapy	3.5	3.5	3.5	3.5	3.5	3.5
Inpatient stay (days)	1.7	1.7	1.7	1.7	1.7	1.7

Key: A&E, accident and emergency; Ana, anakinra; AOSD, adult-onset Still's disease; Can, canakinumab; DM, conventional systemic disease-modifying anti-rheumatic drug; GP, General Practitioner; NSAID+C, nonsteroidal anti-inflammatory drug + corticosteroids; sJIA, systemic juvenile idiopathic arthritis; Toc, tocilizumab.

Note: *Different costs available for adult and paediatric patients incurring this medical resource use item.

B.3.5.7. Adverse event costs

ISRs were the only adverse event considered in the model. The cost associated with the resolution of ISRs is assumed to be zero as treatment is primarily hot or cold compresses, and the majority of ISRs experienced are usually mild and transient in nature. No other AEs are considered within the submission (please see Section B.3.3 for further information).

B.3.5.8. Macrophage activation syndrome (MAS) costs

There is no clearly established guidance for the treatment of MAS in UK clinical practice. The NHS Clinical Commissioning Policy for sJIA (NHS England E03X04) recommends where MAS is severe or steroid resistant, treatment with anakinra may be life-saving and should not be delayed.[78] However, patients may also be treated with a combination of high-dose IV corticosteroids with cyclosporin or IV immunoglobulin.[138]

Within the model base-case analysis, it is assumed that patients will require an average hospital stay of 14 days, comprising of 7 days within an intensive care unit (ICU) and 7 days in a high dependency unit (HDU). For drug costs, all patients are assumed to require treatment with corticosteroids (IV methylprednisolone, 30mg/kg for 3 days), cyclosporin (4mg/kg for 3 days), and anakinra (100mg/day for the duration over which utility impacts are expected to apply [14 days in the base-case analysis]). In addition, approximately 50% of patients are expected to require IV immunoglobulin (IVIG, 1.5g/kg for 2 days).

A summary of the costs applied in the model following the development of MAS is presented in Table 65.

Table 65. 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). 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). 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 calculated from Table 62

Item	sJIA	AOSD	Description and source
Cyclosporine	£4.46	£13.37	Assumed 4mg/kg for 3 days, cost-per-mg calculated from Table 62
Anakinra	£367.22	£367.22	Assumed 100mg/day for 14 days, cost-per-injection taken from Table 62
IVIG	£4,050.00	£12,150.00	Assumed 1.5g/kg for 2 days, cost-per-g from BNF[139]
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

Key: AOSD, adult-onset Still's disease; ICU, intensive care unit; IVIG, intravenous immunoglobulin; LOS, length of stay; MRU, medical resource use; sJIA, systemic juvenile idiopathic arthritis.

Note: Drug costs calculated assuming average weights of 25kg (sJIA) and 75kg (AOSD).

B.3.5.9. Remission costs

In practice, following confirmation of disease remission some patients may continue treatment (perhaps tapering the dose given over time) for a specific time period. For patients for whom treatment may be gradually reduced, this is expected to take place over a period of approximately 1-3 years. For others, treatment may be given indefinitely (to minimise the risk of losing remission).

To incorporate the possibility that several patients may remain on treatment or undergo dose tapering after remission, it is assumed that within each remission health state a proportion of patients still incur the costs associated with the health state from which they achieved remission. In addition, patients are expected to be seen by a rheumatologist and an immunologist once per year for monitoring.

In the base case this proportion is set to 50% for the remission health states following use of either anakinra or tocilizumab, and 0% for all other health states. A recent study by Sota *et al.* reported cumulative retention rates of anakinra at 12, 24, 48, and 60 months of follow-up of 74.3%, 62.9%, 49.4%, and 49.4%, respectively.[119] These rates do not distinguish between patients in remission and those with persistent active disease, and so should be interpreted with caution. Further to this, the model accounts for patients failing prior regimens and experiencing loss of remission, and so identifying a suitable value to populate the model is challenging. However, the assumed estimate of 50% of patients in remission continuing to receive treatment with either anakinra or tocilizumab until loss of remission or death was considered a reasonable assumption in light of the Sota *et al.* study and clinical opinion provided to Sobi.[21;119]

The assumption of a static proportion of patients in remission still receiving treatment was made in the absence of clear information to model distinct remission health states based on treatment use, and in acknowledgement that it is extremely difficult to populate this model assumption. However, the lack of additional assumed costs for the health states associated with NSAIDs, corticosteroids and csDMARDs, as well as the lack of added costs for patients who achieve remission with BMT from the 'unresolved' state, is considered conservative; and alternative values for these costs are explored within sensitivity analysis.

B.3.5.10. Unresolved disease costs

Unresolved patients are expected to be treated with unlicensed treatment options, enrol within clinical trial, or be in a permanently 'unresolved' state and thus require additional medical resource use. Data to quantify the costs of this health state are not well documented, and so the costs are reliant upon a number of assumptions. In the model base case, canakinumab is not assumed to be used (as it is not recommended).

It is assumed that 1% of patients in this state may undergo BMT per year (0.0193% per model cycle). A cost of £96,956 was taken from NICE TA577 company submission (cost of allogeneic stem cell transplant), and the probability of remission was assumed to be 1 minus the probability of death (estimated at 12.5% based on a study by Silva [2018] – see Section B.3.3.5 for more information).[127;140] If successful, no further costs are expected to be incurred, which is considered to be a conservative estimate of the 'true' costs of follow-up (e.g. ongoing monitoring for patients who develop graft-versus-host disease etc.).

All other patients were estimated to require additional medical resource use costs versus those patients treated with recommended treatment options (such as NSAIDs, corticosteroids, csDMARDs etc.). In TA238, annual resource use costs ranged from £374.16 (Response ACR 90) to £3,640.51 (no response). For "Response ACR 30", the annual cost was £545.60, and so the estimated additional medical resource use costs for 'unresolved' patients may be represented by a multiplier of: $\frac{£3{,}640.51}{£545.60} = 6.67$. This multiplier may be applied to the estimated per-cycle cost of non-treatment specific medical resource use for the recommended treatment options (£53.25) – i.e. all contact with healthcare professionals and hospital admissions, resulting in a cost per week of £355.32.

In the model base-case analysis, the multiplier approach was used as this application allows for consistency between medical resource use estimates taken from NICE TA238 (i.e. the relative increase for unresolved patients is maintained); and allows for ease of stress testing

the added costs required for 'unresolved' patients in sensitivity analysis (i.e. a single value may be varied, as opposed to varying individual unit costs and frequencies). However, for completeness, a micro-costed estimate of the average resource use for 'unresolved' patients is also included within the economic model.

A summary of the costs associated with unresolved disease applied within the model base-case analysis is presented in Table 66.

Table 66. Summary of costs associated with unresolved disease

Category	Application
BMT	Cost of £96,956 applied for 1% of patients per year, equating to £18.62 per week.
Others	Multiplier of 6.67 applied to non-treatment-specific MRU costs = £280.96 per week.
Total	**£299.58**

Key: BMT, bone marrow transplant; MRU, medical resource use.

B.3.6. Summary of base-case analysis inputs and assumptions

B.3.6.1. Base-case analysis inputs

A summary of the variables applied within the economic model base-case analysis ('per-label' versus 'no anakinra'), alongside the corresponding measurement of uncertainty, is provided in Table 67.

Table 67. Summary of variables applied in the economic model

Variable	Value	Distribution (95% CI)	Section
Proportion of AOSD to receive 2nd DMARD	100%	Fixed	B.3.2.3
Proportion of sJIA to receive 2nd DMARD	0%	Fixed	B.3.2.3
Time horizon (years)	30	Fixed	B.3.2.4
Model cycle length (days)	7	Fixed	B.3.2.4
ADR: Costs	3.5%	Fixed	B.3.2.4
ADR: QALYs	3.5%	Fixed	B.3.2.4
ADR: LYs	0%	Fixed	B.3.2.4
Average age: AOSD (years)	39	Normal (35, 43)	B.3.2.5
Average age: sJIA (years)	8.5	Normal (8, 9)	B.3.2.5
Proportion of females	70%	Beta (62.9%, 76.6%)	B.3.2.5
Proportion with monocyclic disease	25.5%	Beta (22.8%, 28.2%)	B.3.2.5
Proportion of patients with AOSD	37.5%	Beta (34.5%, 40.5%)	B.3.2.5
Weekly discontinuation probability for patients treated with NSAIDs+c (monocyclic)	27.3%	Beta (24.6%, 30.1%)	B.3.3.1
Weekly discontinuation probability for patients treated with NSAIDs+c (chronic)	39.3%	Beta (36.3%, 42.3%)	B.3.3.1
Weekly remission probability for patients treated with NSAIDs+c (monocyclic)	12.6%	Beta (10.6%, 14.7%)	B.3.3.1

Variable	Value	Distribution (95% CI)	Section
Weekly remission probability for patients treated with NSAIDs+c (chronic)	0%	Fixed	B.3.3.1
Weekly discontinuation probability for patients treated with csDMARDs (monocyclic)	16.2%	Beta (14.0%, 18.6%)	B.3.3.1
Weekly discontinuation probability for patients treated with csDMARDs (chronic)	17.1%	Beta (14.8%, 19.5%)	B.3.3.1
Weekly remission probability for patients treated with csDMARDs (monocyclic)	0.9%	Beta (0.4%, 1.6%)	B.3.3.1
Weekly remission probability for patients treated with csDMARDs (chronic)	0%	Fixed	B.3.3.1
Weekly remission probability for patients treated with anakinra or tocilizumab (per-label)	4.4%	Beta (3.2%, 5.7%)	B.3.3.1
Weekly remission probability for patients treated with anakinra or tocilizumab (post-csDMARD)	2.9%	Beta (1.9%, 4.0%)	B.3.3.1
Weekly discontinuation probability for patients treated with anakinra or tocilizumab (first biologic)	1.1%	Beta (0.6%, 1.9%)	B.3.3.1
Weekly discontinuation probability for patients treated with anakinra or tocilizumab (second biologic)	2.0%	Beta (1.2%, 3.0%)	B.3.3.1
Relative risk of achieving remission for patients treated with anakinra	1.00	Fixed	B.3.3.1
Weekly remission probability for patients treated with further tx	0.02%	Beta (0.00%, 0.14%)	B.3.3.1
Probability of remission from BMT	100%	Fixed	B.3.3.1
Weekly loss of remission probability for monocyclic patients	0%	Fixed	B.3.3.2
Weekly loss of remission probability for chronic patients	0.54%	Beta (0.18%, 1.07%)	B.3.3.2
Weekly probability of developing MAS for patients not treated with anakinra	0.10%	Beta (0.00%, 0.37%)	B.3.3.3
Relative risk of developing MAS for patients treated with anakinra	1.00	Fixed	B.3.3.3
Probability of developing MAS in remission states	0%	Fixed	B.3.3.3
sJIA per-administration probability of ISR for tocilizumab	0%	Beta (0.0%, 0.0%)	B.3.3.4
AOSD per-administration probability of ISR for tocilizumab	0%	Beta (0.0%, 0.0%)	B.3.3.4
sJIA per-administration probability of ISR for anakinra	0.43%	Beta (0.119%, 0.905%)	B.3.3.4
AOSD per-administration probability of ISR for anakinra	0.16%	Beta (0.013%, 0.485%)	B.3.3.4
Probability MAS is fatal (per episode)	10%	Beta (8.2%, 11.9%)	B.3.3.5
Probability BMT is fatal (per procedure)	12.5%	Beta (10.5%, 14.6%)	B.3.3.5
Utility: Remission health states	0.715	Beta (0.987, 0.743)	B.3.4.4
Utility: Non-remission health states	0.567	Beta (0.537, 0.598)	B.3.4.4
Utility: <30 years	0.938	Beta (0.933, 0.943)	B.3.4.4
Utility: 30 years	0.915	Beta (0.905, 0.923)	B.3.4.4
Utility: 35 years	0.907	Beta (0.898, 0.916)	B.3.4.4
Utility: 40 years	0.882	Beta (0.872, 0.893)	B.3.4.4
Utility: 45 years	0.864	Beta (0.852, 0.875)	B.3.4.4
Utility: 50 years	0.834	Beta (0.821, 0.847)	B.3.4.4
Utility: 55 years	0.822	Beta (0.809, 0.835)	B.3.4.4

Variable	Value	Distribution (95% CI)	Section
Utility: 60 years	0.807	Beta (0.792, 0.822)	B.3.4.4
Utility: 65 years	0.804	Beta (0.790, 0.818)	B.3.4.4
Utility: 70 years	0.779	Beta (0.763, 0.795)	B.3.4.4
Utility: 75 years	0.753	Beta (0.734, 0.772)	B.3.4.4
Utility: 80 years	0.699	Beta (0.672, 0.724)	B.3.4.4
Disutility: ISR (per-administration)	-0.010	Beta (-0.076, 0.000)	B.3.4.5
Disutility: MAS (per episode)	-0.468	Normal (-0.515, -0.421)	B.3.4.6
PAS: Tocilizumab	[redacted]	Fixed	B.3.5.2
Cost: Naproxen (500mg)	£3.58	Normal (£3.23, £3.93)	B.3.5.2
Cost: Ibuprofen (200mg)	£0.31	Normal (£0.28, £0.34)	B.3.5.2
Cost: Prednisolone (5mg)	£0.26	Normal (£0.23, £0.29)	B.3.5.2
Cost: Methylprednisolone (1,000mg)	£6.42	Normal (£5.79, £7.05)	B.3.5.2
Cost: Azathioprine (50mg)	£1.59	Normal (£1.43, £1.75)	B.3.5.2
Cost: Cyclosporine (25mg)	£11.14	Fixed	B.3.5.2
Cost: Leflunomide (20mg)	£3.57	Normal (£3.22, £3.92)	B.3.5.2
Cost: Methotrexate (2.5mg)	£0.86	Normal (£0.78, £0.94)	B.3.5.2
Cost: Anakinra (100mg/0.67ml)	£183.61	Fixed	B.3.5.2
Cost: Tocilizumab (80mg/4ml, IV)*	[redacted]	Fixed	B.3.5.2
Cost: Tocilizumab (162mg/0.9ml, SC)*	[redacted]	Fixed	B.3.5.2
Cost: Canakinumab (150mg/1ml)	£9,927.80	Fixed	B.3.5.2
MS: Naproxen	50%	Beta (46.9%, 53.1%)	B.3.5.2
MS: Ibuprofen	50%	Beta (46.9%, 53.1%)	B.3.5.2
MS: Prednisolone	50%	Beta (46.9%, 53.1%)	B.3.5.2
MS: Methylprednisolone	50%	Beta (46.9%, 53.1%)	B.3.5.2
MS: Azathioprine (1st or 2nd choice of csDMARD)	0%	Fixed	B.3.5.2
MS: Cyclosporine as 1st choice of csDMARD (no anakinra and post-csDMARD)	0%	Fixed	B.3.5.2
MS: Cyclosporine as 2nd choice of csDMARD (no anakinra and post-csDMARD)	100%	Fixed	B.3.5.2
MS: Leflunomide (1st or 2nd choice of csDMARD)	0%	Fixed	B.3.5.2
MS: Methotrexate as 1st choice of csDMARD (no anakinra and post-csDMARD)	100%	Fixed	B.3.5.2
MS: Methotrexate as 2nd choice of csDMARD (no anakinra and post-csDMARD)	0%	Fixed	B.3.5.2
MS: Anakinra as 1st choice biologic (per-label)	100%	Fixed	B.3.5.2
MS: Anakinra as 2nd choice biologic (per-label)	0%	Fixed	B.3.5.2
MS: Anakinra as 1st choice biologic for AOSD (post-csDMARD)	50%	Beta (46.9%, 53.1%)	B.3.5.2
MS: Anakinra as 2nd choice biologic for AOSD (Post-csDMARD)	50%	Beta (46.9%, 53.1%)	B.3.5.2
MS: Anakinra as 1st choice biologic for sJIA (post-csDMARD)	0%	Fixed	B.3.5.2
MS: Anakinra as 2nd choice biologic for sJIA (post-csDMARD)	100%	Fixed	B.3.5.2
MS: Tocilizumab ('no anakinra')	100%	Fixed	B.3.5.2
MS: Tocilizumab as 1st choice biologic (per-label)	0%	Fixed	B.3.5.2
MS: Tocilizumab as 2nd choice biologic (per-label)	100%	Fixed	B.3.5.2
MS: Tocilizumab as 1st choice biologic for AOSD (post-csDMARD)	50%	Beta (46.9%, 53.1%)	B.3.5.2

Variable	Value	Distribution (95% CI)	Section
MS: Tocilizumab as 2nd choice biologic for AOSD (Post-csDMARD)	50%	Beta (46.9%, 53.1%)	B.3.5.2
MS: Tocilizumab as 1st choice biologic for sJIA (post-csDMARD)	100%	Fixed	B.3.5.2
MS: Tocilizumab as 2nd choice biologic for sJIA (Post-csDMARD)	0%	Fixed	B.3.5.2
Dosing: Naproxen, AOSD (mg/cycle)	5,250	Fixed	B.3.5.3
Dosing: Naproxen, sJIA (mg/cycle)	1,093.75	Fixed	B.3.5.3
Dosing: Ibuprofen, AOSD (mg/cycle)	6,300	Fixed	B.3.5.3
Dosing: Ibuprofen, sJIA (mg/cycle)	7,875	Fixed	B.3.5.3
Dosing: Prednisolone, AOSD (mg/cycle)	472.5	Fixed	B.3.5.3
Dosing: Prednisolone, sJIA (mg/cycle)	262.5	Fixed	B.3.5.3
Dosing: Methylprednisolone, AOSD (mg/cycle)	3,000	Fixed	B.3.5.3
Dosing: Methylprednisolone, sJIA (mg/cycle)	1,125	Fixed	B.3.5.3
Dosing: Azathioprine, AOSD (mg/cycle)	1,050	Fixed	B.3.5.3
Dosing: Azathioprine, sJIA (mg/cycle)	350	Fixed	B.3.5.3
Dosing: Cyclosporine, AOSD (mg/cycle)	2,100	Fixed	B.3.5.3
Dosing: Cyclosporine, sJIA (mg/cycle)	700	Fixed	B.3.5.3
Dosing: Leflunomide, AOSD (mg/cycle)	105	Fixed	B.3.5.3
Dosing: Leflunomide, sJIA (mg/cycle)	87.5	Fixed	B.3.5.3
Dosing: Methotrexate, AOSD (mg/cycle)	16.25	Fixed	B.3.5.3
Dosing: Methotrexate, sJIA (mg/cycle)	11.66	Fixed	B.3.5.3
Dosing: Anakinra, AOSD (mg/cycle)	700	Fixed	B.3.5.3
Dosing: Anakinra, sJIA (mg/cycle)	262.5	Fixed	B.3.5.3
Dosing: Tocilizumab, AOSD (mg/cycle)	150	Fixed	B.3.5.3
Dosing: Tocilizumab, sJIA (mg/cycle)	150	Fixed	B.3.5.3
Dosing: Canakinumab, AOSD (mg/cycle)	75	Fixed	B.3.5.3
Dosing: Canakinumab, sJIA (mg/cycle)	25	Fixed	B.3.5.3
Average weight: AOSD	75kg	Normal (67.65kg, 82.35kg)	B.3.5.3
Average weight: sJIA	25kg	Normal (22.55kg, 27.45kg)	B.3.5.3
Average BSA: sJIA	0.95m²	Normal (0.86 m², 1.04 m²)	B.3.5.3
Cost: Administration of methylprednisolone	£154.64	Normal (£139.33, £169.60)	B.3.5.4
Cost: Administration of tocilizumab (IV)	£154.64	Normal (£139.33, £169.60)	B.3.5.4
Cost: Tocilizumab as IV (remainder SC)	50%	Beta (46.9%, 53.1%)	B.3.5.4
Cost: Full blood count	£2.51	Normal (£2.26, £2.76)	B.3.5.5
Cost: Liver function test	£1.11	Normal (£1.00, £1.22)	B.3.5.5
Cost: Erythrocyte sedimentation rate	£2.51	Normal (£2.26, £2.76	B.3.5.5
Cost: C-reactive protein	£2.51	Normal (£2.26, £2.76)	B.3.5.5
Cost: Urea, electrolytes and creatinine	£1.11	Normal (£1.00, £1.22)	B.3.5.5
Cost: Lipid test	£2.51	Normal (£2.26, £2.76)	B.3.5.5
Cost: GP appointment	£31.00	Normal (£27.96, £34.04)	B.3.5.5
Cost: AOSD Haematology	£160.00	Normal (£144.32, £175.68)	B.3.5.5
Cost: sJIA Haematology	£288.00	Normal (£259.78, £316.22)	B.3.5.5
Cost: AOSD Radiology	£145.00	Normal (£130.79, £175.68)	B.3.5.5
Cost: sJIA Radiology	£192.00	Normal (£173.18, £210,82)	B.3.5.5
Cost: AOSD Ophthalmology	£98.00	Normal (£88.40, £107.60)	B.3.5.5
Cost: sJIA Ophthalmology	£102.00	Normal (£92.00, £112.00)	B.3.5.5
Cost: AOSD Rheumatology	£146.00	Normal (£131.69, £160.31)	B.3.5.5

Variable	Value	Distribution (95% CI)	Section
Cost: sJIA Rheumatology	£245.00	Normal (£220.99, £269.01)	B.3.5.5
Cost: AOSD Psychology	£170.00	Normal (£153.34, £186.66)	B.3.5.5
Cost: sJIA Psychology	£243.00	Normal (£219.19, £266.81)	B.3.5.5
Cost: AOSD Immunology	£269.00	Normal (£242.64, £295.36)	B.3.5.5
Cost: sJIA Immunology	£219.00	Normal (197.54, £240.46)	B.3.5.5
Cost: Occupational therapy	£73.00	Normal (£65.85, £80.15)	B.3.5.5
Cost: Physiotherapy	£55.00	Normal (£49.61, £60.39)	B.3.5.5
Cost: Inpatient stay (per day)	£339.00	Normal (£305.78, £372.22)	B.3.5.5
MRU: Full blood count (all tx)	18 per year	Fixed	B.3.5.6
MRU: Liver function test (all tx)	18 per year	Fixed	B.3.5.6
MRU: Erythrocyte sedimentation rate (all tx)	18 per year	Fixed	B.3.5.6
MRU: C-reactive protein (all tx)	18 per year	Fixed	B.3.5.6
MRU: Urea, electrolytes and creatinine (all tx)	18 per year	Fixed	B.3.5.6
MRU: Lipid test (tocilizumab only)	18 per year	Fixed	B.3.5.6
MRU: GP appointment (all tx)	3.5 per year	Fixed	B.3.5.6
MRU: Haematology (all tx)	2 per year	Fixed	B.3.5.6
MRU: Radiology (all tx)	0.4 per year	Fixed	B.3.5.6
MRU: Ophthalmology (all tx)	0 per year	Fixed	B.3.5.6
MRU: Rheumatology (all tx)	1.5 per year	Fixed	B.3.5.6
MRU: Psychology (all tx)	0.4 per year	Fixed	B.3.5.6
MRU: Immunology (all tx)	1.5 per year	Fixed	B.3.5.6
MRU: Occupational therapy (all tx)	3.5 per year	Fixed	B.3.5.6
MRU: Physiotherapy (all tx)	3.5 per year	Fixed	B.3.5.6
MRU: Inpatient stay (all tx)	1.7 per year	Fixed	B.3.5.6
Cost: ISR resolution	£0.00	Fixed	B.3.5.7
Cost: resolve MAS (sJIA)	£22,482.13	Normal (£20,279, £24,685)	B.3.5.8
Cost: resolve MAS (AOSD)	£27,031.30	Normal (£24,382, £29,680)	B.3.5.8
Proportion of health state cost applied to remission health states (achieved remission on NSAIDs+c or csDMARDs)	0%	Fixed	B.3.5.9
Proportion of health state cost applied to remission health states (achieved remission on biologics)	50%	Beta (46.9%, 53.1%)	B.3.5.9
MRU: Rheumatology (remission health states)	4 per year	Fixed	B.3.5.9
MRU: Immunology (remission health states)	4 per year	Fixed	B.3.5.9
Proportion of patients treated with canakinumab in 'unresolved' health state (per cycle)	0%	Fixed	B.3.5.10
Proportion of patients to undergo BMT in 'unresolved' health state (per cycle)	0.0193%	Beta (0.0%, 0.15%)	B.3.5.10
Cost: BMT (per procedure)	£96,956	Normal (£87,454, £106,458)	B.3.5.10
Multiplier applied to non-tx-specific MRU costs to inform 'other costs' in the 'unresolved' health state	6.67	Normal (6.02, 7.33)	B.3.5.10

Key: ADR, annual discount rate; AOSD, adult-onset Still's disease; BMT, bone-marrow transplant; BSA, body surface area; CI, confidence interval; csDMARD, conventional systemic disease-modifying anti-rheumatic drug; ICU, intensive care unit; ISR, injection site reaction; LYs, life years; MAS, macrophage activation syndrome; MRU, medical resource use; MS, market share; NSAID+c, nonsteroidal anti-inflammatory drug + corticosteroid; PAS, Patient Access Scheme; QALYs, quality-adjusted life year; sJIA, systemic juvenile idiopathic arthritis; tx, treatment(s).

Note: *Assuming a PAS discount of [redacted]. Price excluding PAS: £102.40 (1x vial for infusion), £913.12 (4x syringe for injection)

B.3.6.2. Assumptions

A summary of the key assumptions made within the cost-effectiveness model used to inform this submission is provided in Table 68.

Table 68. Summary of key assumptions made in the economic model

Assumption	Rationale	Section(s)
Weight (and by extension, BSA) is assumed to be fixed for sJIA patients aged under 18 years, and for AOSD or sJIA patients over the age of 18 years.	The key model parameters affected by weight relate to the acquisition of tocilizumab (as most other affected parameters are associated with similar costs for each 'state of the world', and nearly all patients treated with anakinra will require exactly one 100mg vial per administration, regardless of weight). An average sJIA patient may require anywhere between 2 and 8 vials of tocilizumab per administration, and so average weight is varied within sensitivity analysis to assess the potential influence of this assumption on cost-effectiveness results. The assumption of fixed weight within a group was chosen for simplicity (as tracking changes in weight over time would increase model complexity).	B.3.2, B.3.5.
Majority of model inputs for sJIA patients over the age of 18 are assumed to be the same as per the AOSD population (e.g. MRU).	Due to the growing understanding that sJIA and AOSD are the same disease, it was considered most appropriate for model inputs to be the same when sJIA patients reach adulthood (18 years), with the following exceptions: (1) requirement for at least one or two csDMARDs prior to use of biologics (as diagnosis of sJIA continues into adulthood), and (2) transition probabilities (as health state occupancy prior to age of 18 years based on sJIA probabilities, and so determining proportion of patients over the age of 18 years to weight-average transition probabilities would be highly complex).	B.3.2, B.3.3.
Markov structure of the model exhibits the 'memoryless' property, and so a treatment history is not explicitly modelled.	This model structure was chosen for several reasons. Firstly, it is a relatively simple model structure that may be adjusted to reflect a number of possible treatment pathways; allowing a transparent presentation of model assumptions and making best use of the (limited) data. This includes allowing patients to enter the model at different parts of the pathway, conducting extensive sensitivity analysis by varying individual or even groups of parameters, and omitting parts of the treatment pathway simply. Secondly, it is unknown how treatment history may affect specific model parameters. The incorporation of several additional parameters to quantify time-dependency would rely on clinical assumption that would be impossible to validate with currently-available evidence. Finally, a Markovian structure was adopted and considered in the previous NICE assessment of tocilizumab for sJIA. This model structure was ultimately accepted as appropriate for decision making.	B.3.2, B.3.3.
Markov structure of the model means that transitions are informed using constant probabilities.	Transition probabilities were assumed to be fixed as there is highly limited evidence to incorporate time-dependency, and to align with the memoryless property of the Markov structure. This allows for simple incorporation of disease reoccurrence into the model. Constant probabilities of discontinuation were applied within the previous NICE assessment of tocilizumab for sJIA. It is acknowledged that the use of constant probabilities is imperfect, as this may lead to an over-estimation of patients on treatment beyond what may be typically considered a maximum plausible duration before adding/ switching treatments (e.g. 4-6 weeks for those receiving corticosteroids). However, were time dependency implemented (e.g. through the use of tunnel states), this would have added substantial complexity to the model calculations for relatively little additional benefit.	B.3.3

Assumption	Rationale	Section(s)
Only AE captured by the model is ISRs.	The most common AE associated with anakinra is ISR. All other AEs were excluded for simplicity, and it is understood that if patients were to develop severe AEs this may lead to treatment discontinuation (which is captured by the model). All AEs were excluded from the model used to inform the previous NICE assessment of tocilizumab for sJIA, however it was considered necessary to acknowledge the difference in the number of ISRs associated with anakinra versus tocilizumab treatment.	B.3.3, B.3.4.
Disease-specific mortality only captured via MAS and BMT.	The model does not capture all disease-specific mortality, as to capture other effects would rely upon extensive clinical assumptions. The omission of these other mortality effects is considered conservative, as the use of anakinra is expected to reduce the risk of death through unresolved disease and/or long-term complications associated with inferior treatment option (such as corticosteroids)	B.3.3
Efficacy of canakinumab assumed to be equivalent to anakinra or tocilizumab.	No clear data regarding the long-term efficacy of canakinumab were identified (in relation to a matched comparison versus anakinra and/or tocilizumab). The positioning of canakinumab means that it may follow anakinra, both of which target IL-1 and so the efficacy of canakinumab is expected to be lower than it would be were canakinumab used in a population that has not previously failed treatment with anakinra. In the absence of clear data to suggest otherwise, it was assumed that canakinumab was equivalently efficacious as anakinra and tocilizumab. The model base-case analysis excludes canakinumab use given that it is not routinely used in NHS practice.	B.3.3
Probability of remission achieved through use of non-recommended, unlicensed and/or experimental treatments assumed to be zero	There is extremely limited evidence available in support of the efficacy of unlicensed, non-recommended treatment options used following the failure of all other regimens (i.e. NSAIDs, corticosteroids, csDMARD[s], anakinra and tocilizumab). While there is evidence available for canakinumab and BMT, this does not apply to other treatments (in an sJIA and/or AOSD population, specifically after all other options have failed).	B.3.3
The same utility value is assumed to apply for all patients receiving a recommended treatment option.	By definition, patients whom reside within the 'on active treatment' health states have not yet achieved remission which is the key goal of treatment. This application of utility values is simplified, aligned with current treatment goals, and avoids several issues relating to treatment sequencing, cross-comparability of trial populations (which may be required were treatment-specific utilities incorporated), and data availability (i.e. the availability of [C]HAQ and ACR scores for each relevant treatment).	B.3.4
The same utility values are assumed to apply for sJIA and AOSD (excluding the impact of age).	Data to quantify health-related quality of life for sJIA and AOSD patients are sparsely reported, and where available were not considered relevant to the decision problem. Sensitivity analysis has been conducted to ascertain the impact of alternative utility values on cost-effectiveness results.	B.3.4
Costs incurred within remission are assumed to be a proportion of those incurred in non-remission.	The previously-highlighted limitation relating to the ability to track individual patient transitions applies also to the costing of remission. Patients may enter remission at different points in time and may fail to maintain remission at any subsequent cycle. Therefore, applying a cost upon entry to remission may be inappropriate. A proportion of costs maintained was assumed to apply, which is varied in sensitivity analysis.	B.3.5

Key: ACR, American College of Rheumatology; AE, adverse event; AOSD, adult-onset Still's disease; BMT, bone marrow transplant; BSA, body surface area; (C)HAQ, (Childhood) Health Assessment Questionnaire; csDMARD, conventional systemic disease-modifying anti-rheumatic drug; IL-1, interleukin-1; ISR, injection site reaction; MAS, macrophage activation syndrome; mg, milligram(s); MRU, medical resource use; NICE, National Institute for Health and Care Excellence; NSAID, nonsteroidal anti-inflammatory drug; QALY, quality-adjusted life year.

B.3.7. Base-case results

Pairwise results for the base-case analysis ('per-label' versus 'no anakinra') are presented in Table 70. The 'per-label' use of anakinra is associated with cost savings of approximately £56,790 and an incremental QALY gain of 0.666 and is therefore shown to be a dominant treatment strategy, versus no use of anakinra. The incremental net monetary benefit (INMB) demonstrates the extent to which the 'per-label' state of the world dominates the 'no anakinra' state of the world. Disaggregated results are provided in Appendix J.

Table 69. Base case pairwise results ('per-label' versus 'no anakinra')

Arm	Total			Incremental			ICER	INMB (£)
	Costs (£)	QALYs	LYs	Costs (£)	QALYs	LYs		
No anakinra	258,107	11.304	28.202					
Per-label	201,317	11.970	28.774	-56,790	0.666	0.572	Dominant	70,102

Key: ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; LY, life year; QALY, quality-adjusted life year.

Note: These results take into account the assumed commercially-sensitive simple patient access scheme discount for tocilizumab ([redacted]). INMB calculated assuming a willingness-to-pay threshold of £20,000 per QALY gained.

Incremental cost-effectiveness results for all three modelled states of the world are presented in Table 70. The use of anakinra following csDMARDs ('post-csDMARD') is associated with cost savings and additional QALYs versus the 'no anakinra' state of the world, yet the 'per label' positioning of anakinra is associated with further benefits (and therefore, the 'per-label' positioning dominates both the 'no anakinra' and 'post-csDMARD' states of the world). ICERs are not presented owing to the fact that all relevant ICERs are dominant. Disaggregated results are provided in Appendix J.

Table 70. Base case incremental results (all states of the world)

Arm	Total			Incremental			INMB (£), vs.	
	Costs (£)	QALYs	LYs	Costs (£)	QALYs	LYs	1)	2)
1) No anakinra	258,107	11.304	28.202					
2) Post-csDMARD	224,343	11.657	28.509	-33,764	0.353	0.307	40,817	
3) Per-label	201,317	11.970	28.774	-23,026	0.313	0.265	70,102	29,285

Key: csDMARD, conventional systemic disease-modifying anti-rheumatic drug; INMB, incremental net monetary benefit; LY, life year; QALY, quality-adjusted life year.

Note: Treatments ranked according to increasing QALYs. These results take into account the assumed commercially-sensitive simple patient access scheme discount for tocilizumab ([redacted]). INMB calculated assuming a willingness-to-pay threshold of £20,000 per QALY gained.

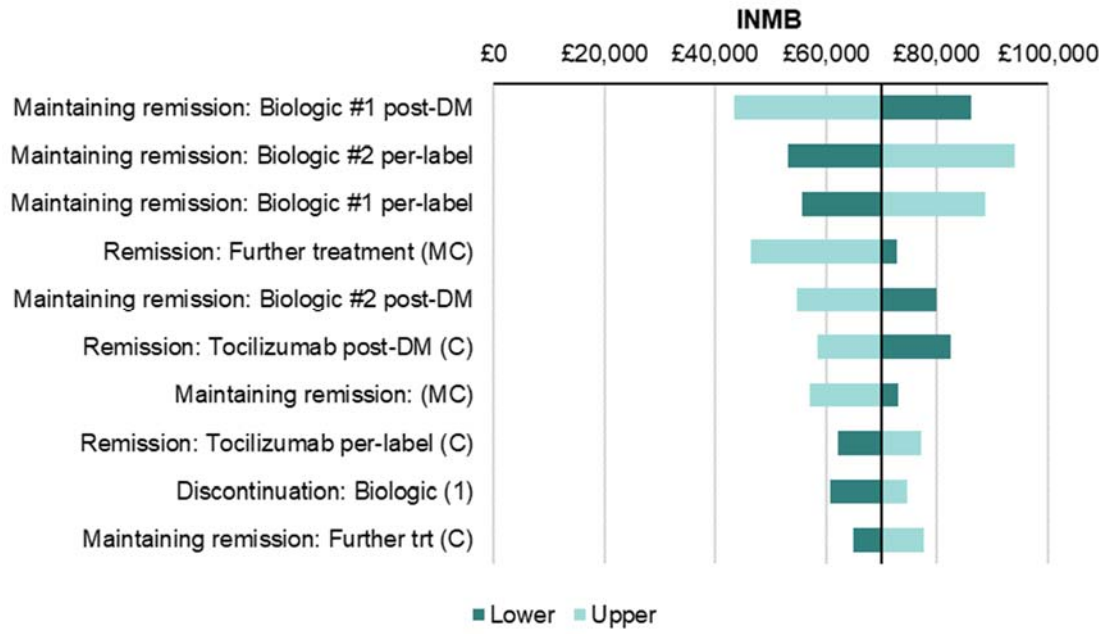
B.3.8. Sensitivity analyses

B.3.8.1. Deterministic one-way sensitivity analysis

Deterministic one-way sensitivity analysis (OWSA) was undertaken to demonstrate the influence of key model parameters on cost-effectiveness results. Model parameters subject to parameter uncertainty were sampled at the extremes of their plausible bounds and the cost-effectiveness results were recorded. The top 10 most influential parameters were identified and the associated impact on cost-effectiveness results is shown in a tornado diagram.

The tornado diagrams are presented in Figure 14 and Figure 15 for comparisons of the 'per-label' and 'post-csDMARD' states of the world versus the 'no anakinra' state of the world. Overall, the results show that the results are most sensitive to the assumptions concerning the probability of maintaining or achieving remission, as well as discontinuing a given treatment. No individual parameter included within the OWSA led to a negative net monetary benefit (NMB), as the use of anakinra was dominant in all sensitivity analyses.

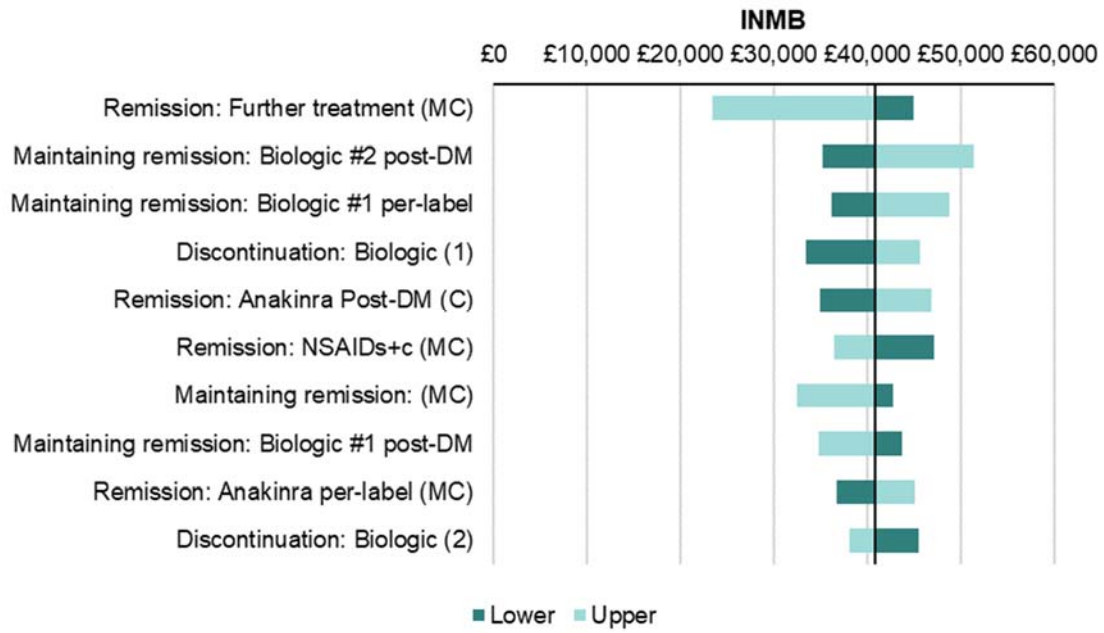
Figure 14. Tornado diagram – 'per-label' versus 'no anakinra'



Key: C, chronic; DM, (conventional synthetic) disease-modifying anti-rheumatic drug; MC, monocyclic; trt, treatment.

Note: INMB calculated assuming a willingness-to-pay threshold of £20,000 per QALY gained. These results take into account the assumed commercially-sensitive simple patient access scheme discount for tocilizumab ([redacted]).

Figure 15. Tornado diagram – 'post-csDMARD' versus 'no anakinra'



Key: C, chronic; DM, (conventional synthetic) disease-modifying anti-rheumatic drug; MC, monocyclic; NSAID, nonsteroidal anti-inflammatory drug; trt, treatment.

Note: INMB calculated assuming a willingness-to-pay threshold of £20,000 per QALY gained. These results take into account the assumed commercially-sensitive simple patient access scheme discount for tocilizumab ([redacted]).

B.3.8.2. Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was undertaken to ascertain the influence of parameter uncertainty on cost-effectiveness results. Model parameters subject to parameter uncertainty were randomly sampled within their plausible bounds and the cost-effectiveness results were recorded over a total of 1,000 iterations.

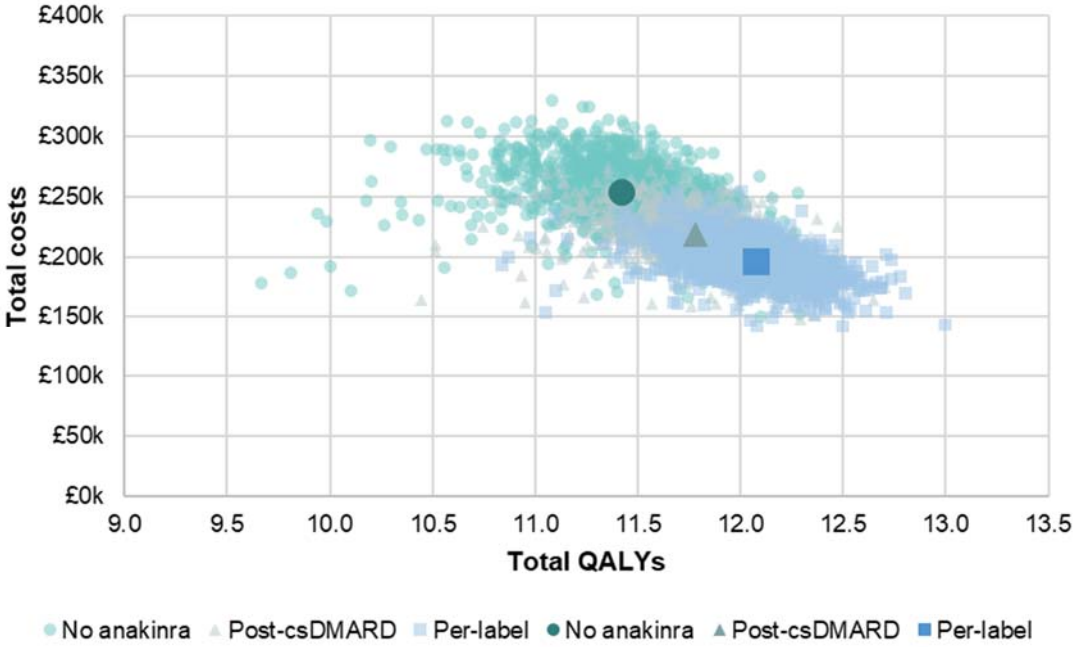
A comparison of the deterministic and probabilistic cost-effectiveness results is provided in Table 71, and the scatterplot of individual iteration costs and QALYs is presented in Figure 16. Like the base-case deterministic analysis, the mean results of the probabilistic analysis show that increased use of anakinra leads to lower costs and additional QALYs.

Table 71. Comparison of deterministic and probabilistic results

	Per-label			Post-csDMARD			No anakinra		
	Costs (£)	**QALYs**	**LYs**	**Costs (£)**	**QALYs**	**LYs**	**Costs (£)**	**QALYs**	**LYs**
Det.	201,317	11.970	28.774	224,343	11.657	28.509	258,107	11.304	28.202
Prob.	195,913	12.074	28.865	218,425	11.778	28.644	254,330	11.419	28.364

Key: Det., deterministic; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; LY, life year; Prob., probabilistic; QALY, quality-adjusted life year

Figure 16. PSA scatterplot



Key: csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Note: Larger points in plot denote the mean result.

A cost-effectiveness acceptability curve is not provided as in each of the 1,000 probabilistic scenarios, the use of anakinra was shown to provide the most QALYs and the lowest overall costs. However, in approximately 5.5% of iterations, the 'post-csDMARD' state was associated with larger overall QALYs (though this is expected to be due to the independent sampling of parameters to inform the PSA).

B.3.8.3. Scenario analyses

Scenario analyses were conducted to explore the impact of key model settings and assumptions on the cost-effectiveness results. A summary of the scenario analyses performed is provided in Table 72.

Table 72. Scenario analyses performed

Scenario	Description	Results
Analysis perspective		
Time horizon	Varied time horizon from 5 to 30 years	Table 73
Discounting	Varied discount rates for costs and QALYs	Table 74
Patient characteristics		
% Female	Assume % female per clinical studies of anakinra	Table 75
Age	Vary average age for sJIA and AOSD patients	Table 76

Scenario	Description	Results
Weight	Vary average weight for sJIA and AOSD patients	Table 77
Disease course	Vary ratio of monocyclic to chronic patients	Table 78
Treatment pathway		
Loss of remission	Assume patients return to first treatment or progress to next treatment after loss of remission	Table 79
First biologic	For 'per-label' and 'post-csDMARD' states of the world, vary proportion of patients that first receive anakinra or tocilizumab	Table 80
Duration of treatment	Assume lifelong use of anakinra and/or tocilizumab	Table 81
Clinical inputs and assumptions		
Anakinra efficacy	Use alternative source for remission probability	Table 82
Utility source	Apply different utility equations from TA238	Table 83
Age-adjustment	Disable age-adjusted utility values	Table 84
AE disutilities	Disable disutility due to ISRs and double its impact	Table 85
Unresolved utility	Vary utility value for patients in 'unresolved' state	Table 86
Macrophage activation syndrome		
Baseline risk of MAS	Uplift probability of experiencing MAS	Table 87
Relative risk of MAS	Vary relative risk of developing MAS if receiving anakinra	Table 88
MAS-related death	Increase probability MAS is fatal and disutility	Table 89
Duration of MAS	Vary duration over which MAS impacts utility	Table 90
Costs		
Other treatment	Vary cost of other treatment used	Table 91
Tocilizumab PAS	Vary volume of assumed simple PAS discount for tocilizumab	Table 92

Key: AOSD, adult-onset Still's disease; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; ISR, injection site reaction; PAS, patient access scheme; QALY, quality-adjusted life year; sJIA, systemic juvenile idiopathic arthritis

B.3.8.3.1. Analysis perspective scenarios

Scenario analyses were performed which shortened the time horizon from the base-case setting (30 years), with results presented in Table 73. A shorter time horizon leads to smaller overall costs and QALYs, though the overall conclusion reached by the model remains unchanged (i.e. use of anakinra dominates). Discount rates were also varied in scenario analyses, with results displayed in Table 74. Like the time horizon analyses, alternative discount rates affected total costs and QALYs but not change the overall conclusion.

Table 73. Scenario analyses - Length of time horizon

Time horizon (years)	Totals						INMB		
	No anakinra		Per-label		Post-csDMARD		Per-label vs.		Post-csDMARD vs.
	Costs	QALYs	Costs	QALYs	Costs	QALYs	No anakinra	Post-csDMARD	No anakinra
5	£41,647	3.03	£33,381	3.14	£35,540	3.09	£10,469	£3,280	£7,189
10	£88,965	5.49	£68,670	5.73	£74,839	5.62	£25,133	£8,354	£16,779
20	£185,088	9.04	£141,002	9.53	£157,211	9.31	£53,891	£20,653	£33,238
30	**£258,107**	**11.30**	**£201,317**	**11.97**	**£224,343**	**11.66**	**£70,102**	**£29,285**	**£40,817**

Key: csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; INMB, Incremental Net Monetary Benefit; LY, life year; QALY, quality-adjusted life year

Table 74. Scenario analyses – Discounting

Discount rates	Totals						INMB		
	No anakinra		Per-label		Post-DMARD		Per-label vs.		Post-DMARD vs.
	Costs	QALYs	Costs	QALYs	Costs	QALYs	No anakinra	Post-DMARD	No anakinra
All 0%	£439,727	17.69	£345,831	18.80	£386,238	18.27	£116,256	£51,062	£65,195
All 1.5%	£345,775	14.42	£270,867	15.30	£302,293	14.88	£92,601	£39,803	£52,798
All 3.5%	**£258,107**	**11.30**	**£201,317**	**11.97**	**£224,343**	**11.66**	**£70,102**	**£29,285**	**£40,817**
All 6%	£186,868	8.69	£145,210	9.18	£161,401	8.95	£51,381	£20,739	£30,642

Key: csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; INMB, Incremental Net Monetary Benefit; LY, life year; QALY, quality-adjusted life year

B.3.8.3.2. Patient characteristics scenarios

Table 75 displays the cost-effectiveness results for alternative proportions of females considered in the model. Nordstrom et al. (2012)[92] and Quartier et al (2011)[4] reported 50% and 62.5% of females within their studies respectively. The results show a lower proportion of females is associated with marginally lower costs, LYs and QALYs.

Table 75. Scenario analyses - Proportion of females

Source for proportion female – Author (year)	Totals						INMB		
	No anakinra		Per-label		Post-DMARD		Per-label vs.		Post-DMARD vs.
	Costs	QALYs	Costs	QALYs	Costs	QALYs	No anakinra	Post-DMARD	No anakinra
Efthmiou et al. (2006),[26] Gerfaud-Valentin (2014),[10] Lebrun,[28] Ruscitti (2016),[27]	**£258,107**	**11.30**	**£201,317**	**11.97**	**£224,343**	**11.66**	**£70,102**	**£29,285**	**£40,817**
Nordstrom (2012)[92]	£257,694	11.29	£200,982	11.96	£223,971	11.64	£70,003	£29,238	£40,766
Quartier (2011)[4]	£257,952	11.30	£201,191	11.96	£224,203	11.65	£70,065	£29,267	£40,798

Key: csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; INMB, Incremental Net Monetary Benefit; QALY, quality-adjusted life year; vs, versus

The cost-effectiveness results when age is adjusted are displayed in Table 76. Increasing the average age for the AOSD population reduces the costs incurred which is likely due to a greater number of deaths occurring earlier on, resulting in less time on treatment and therefore fewer costs. A reduction in QALY gain is also apparent as the average age of AOSD patients is increased due to the base-case age-adjusted utility values. Increasing the average age of the sJIA population results in greater costs and less QALYs.

Table 76. Scenario analyses - Average patient age

Age at baseline (years)	Totals						INMB		
	No anakinra		Per-label		Post-DMARD		Per-label vs.		Post-DMARD vs.
	Costs	QALYs	Costs	QALYs	Costs	QALYs	No anakinra	Post-DMARD	No anakinra
Base case (39, 8.5)	**£258,107**	**11.30**	**£201,317**	**11.97**	**£224,343**	**11.66**	**£70,102**	**£29,285**	**£40,817**
AOSD: 20	£260,428	11.57	£203,216	12.25	£226,439	11.93	£70,876	£29,650	£41,226
AOSD: 30	£259,995	11.49	£202,853	12.17	£226,045	11.85	£70,689	£29,562	£41,127
AOSD: 50	£252,152	11.24	£196,458	11.90	£218,961	11.59	£68,883	£28,694	£40,189
AOSD: 60	£235,324	10.65	£182,669	11.26	£203,702	10.97	£64,968	£26,784	£38,184
sJIA: 4	£253,456	11.33	£199,306	12.00	£221,493	11.69	£67,503	£28,466	£39,037
sJIA: 12	£262,112	11.27	£202,914	11.93	£226,631	11.62	£72,458	£29,950	£42,507
sJIA: 16	£265,597	11.21	£204,155	11.87	£228,443	11.56	£74,620	£30,480	£44,140

Key: AOSD, adult-onset Still's disease; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; INMB, Incremental Net Monetary Benefit; QALY, quality-adjusted life year; sJIA, systemic juvenile idiopathic arthritis

The results from the scenario analyses adjusting AOSD and sJIA average weights are displayed in Table 77. For both populations, increasing weight is associated with greater costs and decreasing average weight with lower costs when compared to the base case.

Table 77. Scenario analyses - Average patient weight

Average weight (kg) for (AOSD, sJIA) patients	Totals						INMB		
	No anakinra		Per-label		Post-DMARD		Per-label vs.		Post-DMARD vs.
	Costs	QALYs	Costs	QALYs	Costs	QALYs	No anakinra	Post-DMARD	No anakinra
(75, 12.5)	£255,390	11.30	£200,390	11.97	£221,607	11.66	£68,312	£27,476	£40,836
(65, 25)	£257,393	11.30	£200,753	11.97	£223,705	11.66	£69,951	£29,211	£40,740
(75, 25)	**£258,107**	**11.30**	**£201,317**	**11.97**	**£224,343**	**11.66**	**£70,102**	**£29,285**	**£40,817**
(75, 50)	£261,066	11.30	£202,492	11.97	£227,339	11.66	£71,886	£31,106	£40,780
(85, 25)	£274,632	11.30	£209,968	11.97	£236,362	11.66	£77,976	£32,653	£45,323

Key: AOSD, adult-onset Still's disease; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; INMB, Incremental Net Monetary Benefit; kg, kilogram; QALY, quality-adjusted life year; sJIA, systemic juvenile idiopathic arthritis

The proportion of monocyclic patients was varied within the scenario analyses given the uncertainty in its estimation, with results provided in Table 78. A greater proportion of monocyclic patients is correlated with an increased total QALYs and reduced total costs, though a lower overall INMB. The lower INMB is due to the fact that monocyclic patients will never experience loss of remission (and therefore do not need further treatment and do not experience detrimental disease-related health effects).

Table 78. Scenario analyses - Proportion of monocyclic patients

Proportion with monocyclic disease	Totals						INMB		
	No anakinra		Per-label		Post-DMARD		Per-label vs.		Post-DMARD vs.
	Costs	QALYs	Costs	QALYs	Costs	QALYs	No anakinra	Post-DMARD	No anakinra
12.5%	£275,110	11.14	£214,194	11.85	£240,590	11.51	£75,065	£33,296	£41,769
25.5%	**£258,107**	**11.30**	**£201,317**	**11.97**	**£224,343**	**11.66**	**£70,102**	**£29,285**	**£40,817**
50%	£226,063	11.61	£177,048	12.19	£193,724	11.94	£60,749	£21,725	£39,024
75%	£193,365	11.92	£152,285	12.42	£162,480	12.23	£51,206	£14,011	£37,194

Key: csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; INMB, Incremental Net Monetary Benefit; QALY, quality-adjusted life year

B.3.8.3.3. Treatment pathway scenarios

The cost-effectiveness results when varying the treatment administered after loss of remission are shown in Table 79. Returning to the first treatment in the pathway resulted in lower costs and higher QALYs than in the base case setting and, greater costs and fewer QALYs resulted from progressing to the next treatment line versus returning to previous treatment (base case). As discussed previously, these results should be interpreted with caution, as it is unlikely that all patients would restart the treatment pathway or progress immediately to the next line (the latter of which is especially unlikely in the case where patients may have exhausted all recommended options).

Table 79. Scenario analyses - Treatment given following loss of remission

Structural assumption	Totals						INMB		
	No anakinra		Per-label		Post-DMARD		Per-label vs.		Post-DMARD vs.
	Costs	QALYs	Costs	QALYs	Costs	QALYs	No anakinra	Post-DMARD	No anakinra
Return to previous tx	**£258,107**	**11.30**	**£201,317**	**11.97**	**£224,343**	**11.66**	**£70,102**	**£29,285**	**£40,817**
Return to first tx	£219,376	11.55	£138,228	12.35	£160,798	12.04	£97,179	£28,637	£68,542
Progress to next tx	£313,944	10.76	£288,920	11.16	£291,538	11.05	£32,994	£4,874	£28,120
Key: DMARD, disease-modifying anti-rheumatic drug; INMB, Incremental Net Monetary Benefit; QALY, quality-adjusted life year; tx, treatment									

Key: csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; INMB, Incremental Net Monetary Benefit; QALY, quality-adjusted life year; tx, treatment

In the base-case analysis ('per-label), it is assumed that all patients receive anakinra as a first-line biologic. In the 'post-DMARD' state of the world, it is assumed that 50% of AOSD patients receive anakinra as a first-line biologic (remainder receive tocilizumab), and all sJIA patients are first treated with tocilizumab (based on NICE TA238). The proportion of patients to receive tocilizumab as the first biologic was varied in scenario analyses and the cost-effectiveness results presented in Table 80. Increased costs are associated with greater proportions of patients receiving tocilizumab first, yet as the efficacy of both biologics is assumed to be equal there is no change in QALYs.

Table 80. Scenario analyses - Proportion of patients receiving tocilizumab as first biologic

Use of tocilizumab first-line	Totals						INMB		
	No anakinra		Per-label		Post-DMARD		Per-label vs.		Post-DMARD vs.
	Costs	QALYs	Costs	QALYs	Costs	QALYs	No anakinra	Post-DMARD	No anakinra
Base case	**£258,107**	**11.30**	**£201,317**	**11.97**	**£224,343**	**11.66**	**£70,102**	**£29,285**	**£40,817**
Post-DMARD: 0%	£258,107	11.30	£201,317	11.97	£223,647	11.66	£70,102	£28,596	£41,506
Post-DMARD: 50%	£258,107	11.30	£201,317	11.97	£223,930	11.66	£70,102	£28,875	£41,227
Post-DMARD: 100%	£258,107	11.30	£201,317	11.97	£224,213	11.66	£70,102	£29,153	£40,949
Per-label: 50%	£258,107	11.30	£201,823	11.97	£224,343	11.66	£69,603	£28,786	£40,817
Per-label: 100%	£258,107	11.30	£202,329	11.97	£224,343	11.66	£69,105	£28,288	£40,817

Key: csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; INMB, Incremental Net Monetary Benefit; QALY, quality-adjusted life year

The base-case analysis assumes 50% of costs incurred prior to remission (for patients receiving treatment with biologics) are continued into remission. Scenario analyses were conducted to establish the impact on results if all costs were assumed to continue into remission or all costs were assumed to cease following remission (shown in Table 81). A higher proportion of costs carried over into remission is associated with increased total costs, and lower INMB results, though clinical expert advice provided to Sobi suggests the proportion of patients expected to remain on treatment after remission for the remainder of their lifetime is substantially less than 100%.

Table 81. Scenario analyses - Proportion of biologic treatment used in remission

Proportion of costs maintained in remission	Totals						INMB		
	No anakinra		Per label		Post-DMARD		Per label vs.		Post-DMARD vs.
	Costs	QALYs	Costs	QALYs	Costs	QALYs	No anakinra	Post-DMARD	No anakinra
0%	£221,140	11.30	£138,111	11.97	£173,476	11.66	£96,355	£41,634	£54,721
50%	**£258,107**	**11.30**	**£201,317**	**11.97**	**£224,343**	**11.66**	**£70,102**	**£29,285**	**£40,817**
100%	£295,074	11.30	£264,523	11.97	£275,210	11.66	£43,849	£16,935	£26,913

Key: csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; INMB, Incremental Net Monetary Benefit; QALY, quality-adjusted life year

B.3.8.3.4. Clinical input and assumption scenarios

Table 82 displays the cost-effectiveness results for the alternative efficacy source for anakinra considered in the model (applicable only to the 'Post-DMARD' and 'no anakinra' states of the world). Pardeo 2015[87] allowed for the estimation of a 3.1% rate of remission with anakinra per week with the Nordstrom et al. (2012)[92] rate of 2.85% used in the base case. The results show a higher rate of remission with anakinra associated with fewer costs and QALYs in both the 'post-DMARD' and 'no anakinra' states of the world.

Table 82. Scenario analyses - Anakinra efficacy source

Source for anakinra efficacy	Totals						INMB		
	No anakinra		Per label		Post-DMARD		Per label vs.		Post-DMARD vs.
	Costs	QALYs	Costs	QALYs	Costs	QALYs	No anakinra	Post-DMARD	No anakinra
Nordstrom (2012)[92]	**£258,107**	**11.30**	**£201,317**	**11.97**	**£224,343**	**11.66**	**£70,102**	**£29,285**	**£40,817**
Pardeo (2015)[87]	£254,036	11.35	£201,317	11.97	£219,456	11.72	£65,050	£23,231	£41,819

Key: csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; INMB, Incremental Net Monetary Benefit; QALY, quality-adjusted life year

Table 83 displays the cost-effectiveness results for the alternative utility sources considered in the model. TA195 addendum, TA238 linear and Boggs (2002) linear each reported lower utility values than those considered in the base case (TA238). For example, the non-remission utility values are 0.5674 (base case), 0.4736 (TA195 addendum), 0.5344 (TA238 linear), and 0.4394 (Boggs, 2002). The lower utility values are associated with fewer total QALYs across all states of the world, yet also lead to larger estimates of the INMB – this is due to the base-case utility equation offering the lowest estimated utility benefit experienced upon remission (+0.1476) versus the scenarios conducted (range: 0.1682 to 0.1744).

Table 83. Scenario analyses - Utility source

Utility regression applied	Totals						INMB		
	No anakinra		Per label		Post-DMARD		Per label vs.		Post-DMARD vs.
	Costs	QALYs	Costs	QALYs	Costs	QALYs	No anakinra	Post-DMARD	No anakinra
TA238[77] quadratic	**£258,107**	**11.30**	**£201,317**	**11.97**	**£224,343**	**11.66**	**£70,102**	**£29,285**	**£40,817**
TA195[141] addendum	£258,107	9.94	£201,317	10.67	£224,343	10.33	£71,379	£29,900	£41,479
TA238[77]ta linear	£258,107	10.94	£201,317	11.66	£224,343	11.32	£71,309	£29,861	£41,448
Boggs (2002)[142] linear	£258,107	9.29	£201,317	9.99	£224,343	9.66	£70,765	£29,611	£41,154

Key: csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; INMB, Incremental Net Monetary Benefit; QALY, quality-adjusted life year

In the base-case utility values are adjusted for age with this setting disabled in scenario analysis. The cost-effectiveness results are displayed in Table 84. By not adjusting for age there are more QALYs accrued in each ‘state of the world’, and therefore (given that more overall QALYs will be gained in states of the world where a LY improvement is modelled), the INMB estimates improve.

Table 84. Scenario analyses - Use of age-adjusted utility values

Application of age-adjusted utilities	Totals						INMB		
	No anakinra		Per label		Post-DMARD		Per label vs.		Post-DMARD vs.
	Costs	QALYs	Costs	QALYs	Costs	QALYs	No anakinra	Post-DMARD	No anakinra
Enable	**£258,107**	**11.30**	**£201,317**	**11.97**	**£224,343**	**11.66**	**£70,102**	**£29,285**	**£40,817**
Disable	£258,107	11.61	£201,317	12.29	£224,343	11.97	£70,514	£29,484	£41,030

Key: csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; INMB, Incremental Net Monetary Benefit; QALY, quality-adjusted life year

Table 85 displays the cost-effectiveness results when the disutility of ISRs is varied – either twice the impact, or through disabling the disutility from the model entirely. The results show marginal differences in the INMB when the impact is either removed or doubled, as expected.

Table 85. Scenario analyses – Impact of ISR on utility

Disutility for ISR	Totals						INMB		
	No anakinra		Per label		Post-DMARD		Per label vs.		Post-DMARD vs.
	Costs	QALYs	Costs	QALYs	Costs	QALYs	No anakinra	Post-DMARD	No anakinra
0% of base case (0.00)	£258,107	11.30	£201,317	11.97	£224,343	11.66	£70,119	£29,296	£40,823
Base case (0.01)	**£258,107**	**11.30**	**£201,317**	**11.97**	**£224,343**	**11.66**	**£70,102**	**£29,285**	**£40,817**
200% of base case (0.02)	£258,107	11.30	£201,317	11.97	£224,343	11.66	£70,084	£29,273	£40,811

Key: csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; ISR, injection site reaction; INMB, Incremental Net Monetary Benefit; QALY, quality-adjusted life year

The ‘unresolved’ utility in the base-case analysis is 0.567 (as per all patients not in remission). However, as previously noted, after exhausting all recommended treatment options patients may have poorer utility. The cost-effectiveness results when halving the utility value for ‘unresolved’ disease are displayed in Table 86. By reducing the utility value for unresolved disease, the INMB increases markedly.

Table 86. Scenario analyses – Utility value for the 'unresolved' state

Utility for 'unresolved' state	Totals						INMB		
	No anakinra		Per label		Post-DMARD		Per label vs.		Post-DMARD vs.
	Costs	QALYs	Costs	QALYs	Costs	QALYs	No anakinra	Post-DMARD	No anakinra
50% of base case (0.284)	£258,107	9.50	£201,317	11.05	£224,343	10.41	£87,914	£35,829	£52,086
Base case (0.567)	**£258,107**	**11.30**	**£201,317**	**11.97**	**£224,343**	**11.66**	**£70,102**	**£29,285**	**£40,817**

Key: csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; ISR, injection site reaction; INMB, Incremental Net Monetary Benefit; QALY, quality-adjusted life year

B.3.8.3.5. Macrophage activation syndrome (MAS) scenarios

In the base-case, the weekly probability of developing MAS is 0.1% (for all health states excluding 'remission'). Scenario analyses, results displayed in Table 87, were performed assuming a 10% decrease and 10% increase in the base-case weekly probability of developing MAS on any treatments. Increased probability of developing MAS is associated will fewer QALYs and costs. The INMB is shown to change marginally, as changing the risk of developing MAS affects a multitude of aspects within the model (e.g. reducing the risk of MAS causes a reduction in the costs for its resolution, yet an increase in QALYs).

Table 87. Scenario analyses - Probability of developing MAS

Probability of developing MAS	Totals						INMB		
	No anakinra		Per label		Post-DMARD		Per label vs.		Post-DMARD vs.
	Costs	QALYs	Costs	QALYs	Costs	QALYs	No anakinra	Post-DMARD	No anakinra
90% of base case (0.09%)	£258,488	11.34	£201,438	11.99	£224,563	11.68	£70,097	£29,252	£40,845
Base case (0.1%)	**£258,107**	**11.30**	**£201,317**	**11.97**	**£224,343**	**11.66**	**£70,102**	**£29,285**	**£40,817**
110% of base case (0.11%)	£257,727	11.27	£201,196	11.95	£224,123	11.63	£70,105	£29,317	£40,788

Key: csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; INMB, Incremental Net Monetary Benefit; MAS, macrophage activation syndrome; QALY, quality-adjusted life year

In the base-case, the risk of MAS for patients on anakinra is assumed to be equal to the risk of MAS for patients who are not receiving anakinra. A scenario analysis was performed where it was assumed the relative risk of MAS on anakinra was 10% lower than that for those who do not receive anakinra (based on current clinical opinion concerning the role of IL-1). The cost-effectiveness results are displayed in Table 88, which illustrates that a reduced risk of MAS for patients receiving anakinra leads to a slightly larger estimate of the INMB.

Table 88. Scenario analyses - Relative risk of MAS for patients on anakinra

Relative risk of MAS for anakinra versus others	Totals						INMB		
	No anakinra		Per label		Post-DMARD		Per label vs.		Post-DMARD vs.
	Costs	QALYs	Costs	QALYs	Costs	QALYs	No anakinra	Post-DMARD	No anakinra
0.9	£258,107	11.30	£201,318	11.97	£224,342	11.66	£70,196	£29,328	£40,868
1.0	**£258,107**	**11.30**	**£201,317**	**11.97**	**£224,343**	**11.66**	**£70,102**	**£29,285**	**£40,817**

Key: csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; INMB, Incremental Net Monetary Benefit; MAS, macrophage activation syndrome; QALY, quality-adjusted life year.

Scenario analyses were also performed where the base-case inputs for MAS-related mortality and the disutility in non-fatal cases were both increased by 10% and 20%. The cost-effectiveness results are displayed in Table 89, which illustrate that as the detrimental effect of MAS is assumed to increase, the estimates of the INMB decrease slightly. As per the scenarios concerning the risk of developing MAS, inputs relating to MAS affect a multitude of aspects within the model, and so while the INMB estimates decrease, the impact is relatively small and overall conclusions remain unchanged.

Table 89. Scenario analyses – Increase mortality and disutility from MAS

Assumptions regarding MAS (mortality rate, disutility)	Totals						INMB		
	No anakinra		Per label		Post-DMARD		Per label vs.		Post-DMARD vs.
	Costs	QALYs	Costs	QALYs	Costs	QALYs	No anakinra	Post-DMARD	No anakinra
Base case (12.9%, -0.47)	**£258,107**	**11.30**	**£201,317**	**11.97**	**£224,343**	**11.66**	**£70,102**	**£29,285**	**£40,817**
110% of base case (14.2%, -0.52)	£256,690	11.27	£200,588	11.95	£223,310	11.63	£69,675	£29,111	£40,564
120% of base case (15.9%, -0.56)	£255,286	11.24	£199,865	11.93	£222,286	11.61	£69,253	£28,940	£40,313

Key: DMARD, disease-modifying anti-rheumatic drug; INMB, Incremental Net Monetary Benefit; MAS, macrophage activation syndrome; QALY, quality-adjusted life year

The time over which MAS is expected to affect utility could last anywhere between a few days to several months, and so the estimated mean duration was varied in the scenario analyses. The cost-effectiveness results for these scenarios are presented in Table 90. Increased duration of MAS is associated with greater costs, fewer QALYs, and higher estimates of the INMB (as a greater impact of MAS is associated with a greater benefit predicted for states of the world wherein MAS is avoided).

Table 90. Scenario analyses – Vary duration of impact for MAS

Duration of impact for MAS	Totals						INMB		
	No anakinra		Per label		Post-DMARD		Per label vs.		Post-DMARD vs.
	Costs	QALYs	Costs	QALYs	Costs	QALYs	No anakinra	Post-DMARD	No anakinra
7 days	£258,034	11.31	£201,274	11.97	£224,285	11.66	£70,038	£29,257	£40,782
14 days	**£258,107**	**11.30**	**£201,317**	**11.97**	**£224,343**	**11.66**	**£70,102**	**£29,285**	**£40,817**
28 days	£258,254	11.30	£201,403	11.97	£224,458	11.65	£70,229	£29,341	£40,888

Key: DMARD, disease-modifying anti-rheumatic drug; INMB, Incremental Net Monetary Benefit; Multi, Multiplier; QALY, quality-adjusted life year

B.3.8.3.6. Cost scenarios

Scenario analyses explored the effect of varying the costs associated with unresolved disease in the 'unresolved' health state on the cost-effectiveness results, displayed in Table 91. The multiplier base-case (6.67) was varied assuming arbitrary values of 3 and 10. In both alternative scenarios, costs are higher with no use of anakinra versus positioning anakinra following csDMARDs (post-csDMARD) or before csDMARDs (per-label).

Table 91. Scenario analyses - Cost of 'unresolved' disease

Multiplier for costs incurred in unresolved state	Totals						INMB		
	No anakinra		Per label		Post-DMARD		Per label vs.		Post-DMARD vs.
	Costs	QALYs	Costs	QALYs	Costs	QALYs	No anakinra	Post-DMARD	No anakinra
3	£199,133	11.30	£171,242	11.97	£183,593	11.66	£41,203	£18,610	£22,593
6.67	**£258,107**	**11.30**	**£201,317**	**11.97**	**£224,343**	**11.66**	**£70,102**	**£29,285**	**£40,817**
10	£311,542	11.30	£228,567	11.97	£261,265	11.66	£96,286	£38,957	£57,329

Key: DMARD, disease-modifying anti-rheumatic drug; INMB, Incremental Net Monetary Benefit; Multi, Multiplier; QALY, quality-adjusted life year

There is an approved patient access scheme (PAS) simple discount in effect for tocilizumab, yet the volume of discount offered is commercially sensitive and therefore unknown to Sobi. The cost-effectiveness results for varying assumed PAS discounts for tocilizumab (in 5% increments) are displayed in Table 92. A larger PAS discount for tocilizumab is shown to lead to a lower INMB in comparisons of states of the world where anakinra is used more versus less (e.g. 'per-label' versus 'no anakinra').

Table 92. Scenario analyses - Assumed tocilizumab PAS

PAS discount for tocilizumab	Totals						INMB		
	No anakinra		Per label		Post-DMARD		Per label vs.		Post-DMARD vs.
	Costs	QALYs	Costs	QALYs	Costs	QALYs	No anakinra	Post-DMARD	No anakinra
0%	[redacted]	11.30	[redacted]	11.97	[redacted]	11.66	[redacted]	[redacted]	[redacted]
5%	[redacted]	11.30	[redacted]	11.97	[redacted]	11.66	[redacted]	[redacted]	[redacted]
10%	[redacted]	11.30	[redacted]	11.97	[redacted]	11.66	[redacted]	[redacted]	[redacted]
15%	[redacted]	11.30	[redacted]	11.97	[redacted]	11.66	[redacted]	[redacted]	[redacted]
20%	[redacted]	11.30	[redacted]	11.97	[redacted]	11.66	[redacted]	[redacted]	[redacted]
25%	[redacted]	11.30	[redacted]	11.97	[redacted]	11.66	[redacted]	[redacted]	[redacted]
30%	[redacted]	11.30	[redacted]	11.97	[redacted]	11.66	[redacted]	[redacted]	[redacted]
35%	[redacted]	11.30	[redacted]	11.97	[redacted]	11.66	[redacted]	[redacted]	[redacted]
40%	[redacted]	11.30	[redacted]	11.97	[redacted]	11.66	[redacted]	[redacted]	[redacted]
45%	[redacted]	11.30	[redacted]	11.97	[redacted]	11.66	[redacted]	[redacted]	[redacted]
50%	[redacted]	11.30	[redacted]	11.97	[redacted]	11.66	[redacted]	[redacted]	[redacted]
55%	[redacted]	11.30	[redacted]	11.97	[redacted]	11.66	[redacted]	[redacted]	[redacted]
60%	[redacted]	11.30	[redacted]	11.97	[redacted]	11.66	[redacted]	[redacted]	[redacted]
65%	[redacted]	11.30	[redacted]	11.97	[redacted]	11.66	[redacted]	[redacted]	[redacted]
70%	[redacted]	11.30	[redacted]	11.97	[redacted]	11.66	[redacted]	[redacted]	[redacted]
75%	[redacted]	11.30	[redacted]	11.97	[redacted]	11.66	[redacted]	[redacted]	[redacted]
80%	[redacted]	11.30	[redacted]	11.97	[redacted]	11.66	[redacted]	[redacted]	[redacted]
85%	[redacted]	11.30	[redacted]	11.97	[redacted]	11.66	[redacted]	[redacted]	[redacted]
90%	[redacted]	11.30	[redacted]	11.97	[redacted]	11.66	[redacted]	[redacted]	[redacted]
95%	[redacted]	11.30	[redacted]	11.97	[redacted]	11.66	[redacted]	[redacted]	[redacted]
100%	[redacted]	11.30	[redacted]	11.97	[redacted]	11.66	[redacted]	[redacted]	[redacted]

Key: DMARD, disease-modifying anti-rheumatic drug; INMB, Incremental Net Monetary Benefit; PAS, patient access scheme; QALY, quality-adjusted life year

B.3.9. Subgroup analysis

This appraisal considers the sJIA and AOSD populations separately. Therefore, while these constitute subgroups of the overall Still's disease population, their results are presented separately within this section. Table 70 details the cost-effectiveness results for each subgroup. The total QALYs are larger for patients with sJIA primarily due to the role of age adjustment. Total costs for sJIA patients are also marginally higher, though this is a trade-off between slightly lower drug costs (due to differences in weight and dosing, see Section B.3.5.3) and slightly larger MRU costs (due to the increased cost of paediatric appointments, see Section B.3.5.5).

Table 93. Subgroup cost-effectiveness results

Arm	Total			Incremental			ICER	
	Costs (£)	QALYs	LYs	Costs (£)	QALYs	LYs	vs. No Ana	vs. Post-DM
Base-case analysis (37.5% AOSD, 62.5% sJIA)								
No Ana	258,107	11.304	28.202					
Post-DM	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								
No Ana	254,071	10.698	27.549					
Post-DM	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								
No Ana	260,529	11.668	28.593					
Post-DM	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

Key: Ana, anakinra; AOSD, adult-onset Still's disease; DM, conventional synthetic disease-modifying anti-rheumatic drug; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year; sJIA, systematic juvenile idiopathic arthritis.

Note: These results take into account the assumed commercially-sensitive simple patient access scheme discount for tocilizumab ([redacted]).

B.3.10. Validation

The cost-effectiveness model was subject to a number of internal quality-control (QC) checks throughout development. QC checks of the model covered a validation of the logic underpinning the model calculations, a sense check that the model calculations produced the intended results, and identification of any modelling errors introduced through misspecification of input and/or output ranges.

An independent QC of the economic model was conducted by a health economics and outcomes research consultancy not involved with model development. The objective of the QC was to identify any programming errors, highlight they key challenges associated with quantifying the cost-effectiveness of anakinra for Still's disease, and ensure model calculations are clearly presented. Any errors identified by the QC (as well as any areas where additional clarity were suggested) were rectified ahead of submission.

The assumptions made within the economic model were presented at two advisory board meetings held by Sobi in April and September 2019. The advisory boards were held to gain further insight into the treatment of Still's disease within modern UK clinical practice (given that NICE TA238 was published in 2012, prior to the routine use of biologic therapies). The meeting notes recorded are presented within the reference pack as part of this submission.

B.3.11. Interpretation and conclusions of economic evidence

This submission presents a *de novo* economic analysis regarding the use of anakinra for active Still's disease. Prior to this appraisal, there have been no published studies regarding the cost effectiveness of anakinra for the treatment of Still's disease. The analysis presented in this submission draws from the available evidence base combined with current clinical expert opinion and experience to illustrate the likely cost-effectiveness of anakinra in NHS practice.

Data from a variety of sources were identified to inform the economic analysis. Anakinra has been used in NHS practice for over a decade, and so clinical expert opinion was vital to ensure the model developed to inform this submission was relevant to modern practice (as some features of the previous NICE assessment of TA238 are no longer considered representative).The constructed economic model adopted a simple and transparent structure such that key assumptions and limitations may be understood and (subsequently) explored.

The results of the base-case analysis demonstrate improved patient outcomes (in the form of additional QALYs and LYs) at a reduced cost when anakinra is used per its licensed indication ('per-label') versus the 'no anakinra' state of the world. The INMB was £70,102 for the 'per-label' versus 'no anakinra', assuming a willingness-to-pay threshold of £20,000 per QALY gained. In a sensitivity analysis comparing the 'per-label' to 'post-csDMARD' positionings, the INMB was £29,285. The cost-effectiveness results are driven primarily by the reduction in the development of MAS (and its longer-term sequalae), increased

probability of achieving disease remission, and the reduction in the number of unresolved patients (for whom extensive medical resource use is required).

The primary limitation of the submitted cost-effectiveness analysis is the paucity of evidence available to address all aspects of the decision problem. The EMA extended the license for anakinra to cover the sJIA and AOSD populations specifically in April 2018. The safety and efficacy of anakinra has been studied in three RCTs in Still's disease and reported in a large number of uncontrolled studies. However, these studies were not designed to provide information regarding the likely long-term outcomes associated with anakinra when used in a variety of different positions (and either before or after tocilizumab). Anakinra has been used in sJIA and AOSD within UK NHS practice for several years, and so where clinical trial evidence was not available to inform the economic model clinical expert opinion was sought to address data gaps and inform modelling assumptions.

The majority of evidence available within the Still's disease population comes from the sJIA group. Clinical opinion supports the fact that sJIA and AOSD groups are considered 'the same disease' (and that the separation of the two is an artefact of how Still's disease was first discovered), thus the model relies upon the generalisability of input parameters between the sJIA and AOSD groups. Nevertheless, the model allows the exploration of alternative settings for the two groups where required, and differences in the management and/or characteristics of sJIA and AOSD patients have been captured where possible (e.g. acknowledging differences in average weight).

There are several aspects of the submitted model that may underestimate the benefit that anakinra provides, primarily due data availability. For example, long-term health and side effects for all other treatments (such as stunted growth for corticosteroids) were not explicitly modelled, and other long-run consequences of poor disease control (such as the development of osteoarthritis) were also omitted from the analysis. While not captured within the economic analysis, the increased risk of such negative health effects are nonetheless real consequences of poor disease control, for which the use of anakinra is expected to reduce the number of patients affected.

The economic analysis presented in this submission supports the conclusion that anakinra offers a clinically-effective treatment for patients with Still's disease (including AOSD and sJIA), with anticipated cost savings associated with its use following NSAIDs + corticosteroids, owing to its increased efficacy versus csDMARDs (such as methotrexate) and the reduced risk of developing MAS while disease is controlled. This conclusion was

reached when considering the use of anakinra per its licensed indication versus both the ‘no anakinra’ and ‘post-csDMARD’ states of the world. Anakinra therefore offers a valuable treatment option for patients with Still’s disease, and is associated with cost savings across the NHS and PSS.

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B.5. Appendices

Please see separate standalone documents.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Anakinra for treating Still's disease [ID1463]

Clarification questions

November 2019

File name	Version	Contains confidential information	Date
ID1463 anakinra clarification response for ERG	For the ERG	No	21 November 2019

Section A: Clarification on effectiveness data

A1. In Table 29 of the company submission, median erythrocyte sedimentation rate (ESR) level at baseline for the systematic juvenile idiopathic arthritis (sJIA) population of the Ilowite (2009) trial is quoted to be 50.0 mm/hour. However, in the text accompanying the table (submission, p79), median ESR level at baseline is quoted to be 45.5 mm/hour. Neither of these values are provided in the trial publication. Please clarify which value is correct.

In the Ilowite study,[1] ESR was recorded at the following timepoints: Screening, Baseline (Day 1), Week 2, Week 4, Week 8, and Week 12 (where screening was performed up to 4 weeks prior study enrolment). In the CS, the text refers to the Baseline (Day 1) measure, whereas the table mistakenly presents the Screening measure. In addition, Sobi has identified two other minor transcription errors relating to the upper quartile values in the table for ESR and C-reactive protein (CRP).

For completeness, Table 1 contains the values recorded for both CRP and ESR at each of the previously mentioned time points. Please consider this table as a direct replacement for Table 29 in the CS. Table 1 includes measures at both screening and baseline, as well as the edited upper quartile values (which are shown in bold).

Table 1. CRP and ESR over time (study 990758, sJIA ITT Population, Open-label run-in phase)

Marker	Screening[a]	Baseline[b]	Week 2	Week 4	Week 8	Week 12
N	13/12[c]	13	13	13	12	12
Median CRP (Q1, Q3)	114.0 (41.0, **140.0**)	94.0 (36.0, 147.0)	3.0 (1.0, 26.0)	1.0 (1.0, 22.0)	1.0 (1.0, 37.0)	1.5 (1.0, 96.5)
Median ESR (Q1, Q3)	45.5 (21.0, 68.5)	50.0 (20.0, 70.0)	14.0 (10.0, **20.0**)	7.0 (6.0, 20.0)	6.0 (4.5, 25.0)	7.5 (4.5, 32.0)

[a]Screening was performed up to 4 weeks prior study enrolment.
[b]Baseline measurement taken at Day 1.
[c]CRP was measured in 13 anakinra-treated patients, and ESR was measured in 12 anakinra-treated patients.
Key: CRP, C-reactive protein (mg/l); ESR, Erythrocyte sedimentation rate (mm/hour); ITT, Intent to treat; n, Number of patients for which inflammatory markers were measured; Q1, lower quartile; Q3, upper quartile; sJIA, Systemic juvenile idiopathic arthritis.

A2. Please provide a copy of the Statistical Report 990758, which is referred to in the reference: 105. Sobi. Data on File: Summary of clinical efficacy – Still´s disease. Sobi, 2017/18.

Please find alongside this response a copy of the requested statistical report.

A3. Please provide a copy of the publication where data are reported to support the following statement (submission, p82) regarding the Quartier (2011) trial: "Loss of response in respect of number of joints with active or limited disease, childhood HAQ (CHAQ), PGA, PGE, PGE pain, CRP, ESR and SAA was observed in most patients over the longer term." The reference provided (Quartier 2011) does not appear to include a statement or any data to support the statement in the company submission.

In the study by Quartier *et al.*,[2] the authors state the following in their discussion:

> *"This double-blind, placebo-controlled study demonstrated the efficacy of anakinra in treating corticosteroid-dependent patients with sJIA, as a significantly higher proportion of responders was observed after 1 month of treatment compared with placebo. However, a loss of response was observed in most patients over time."*

As the definition of response has changed over time in studies conducted in Still's disease (and indeed differs between studies conducted in sJIA and AOSD), Sobi clarified the authors' statement to reflect the measures of response that were captured in the study. Values for these measures (and others) are provided in the supplementary material within the Quartier *et al.* study, which for completeness are presented in Table 2.

Table 2. Clinical and biological parameters before and at the latest follow-up on anakinra treatment (taken from Quartier *et al.*, supplementary table 3)

	Group 1 (Anakinra started at D1)						Group 2 (Placebo at D1, Anakinra at M1)					
Visit	D1	M1	M2	M3	M6	M12	D1	M1	M2	M3	M6	M12
Number of patients in the trial	12	12	12	11	8	7	12	12	10	10	9	9
Fever (number of patients)	4	0	2	2	1	0	5	3	0	0	1	2
Active joint count*	16	2.5	1	1	0	1	16	7	3	3	0	0
Joints with limitation of motion*	16	3	6.5	1.5	3.5	2	17	9.5	5	4	2	2
Physician global assessment*	63	14	15	15.5	5.5	7	57	40	14	4	4	7
Parents' global assessment*	50	29.5	21.5	20.5	11.5	14	55	50	16	21	10	7
Parent's assessment of pain*	50	21	18.5	20	10	9	53	50	17	12	6	9
CHAQ*	1.67	1	0.88	0.69	0.44	0.50	1.44	1.25	0.94	0.44	0.38	0.50
First hour ESR, mm/hour*	44	9	17	18	13	17	75	39	12	21	27	17
CRP, mg/l*	66	6	16	24	23	10	50	63	6	12	9	14
SAA*	366	43	70	ND	98	ND	367	397	11	ND	72	ND
Leukocyte counts (x 10^9/L)*	13.5	10.4	9.5	9.4	8.1	8.1	13.9	13.4	10.8	9.4	8.1	7.7
Neutrophils (%)*	67	59	60	62	53	46	69	64	52	54	50	55
Hemoglobin (g/L)*	107	111	116	113	112	116	103	97	118	114	112	115
Platelets (x 10^9/L)*	499	392	395	393	371	407	581	566	489	509	460	400
Daily predniso(lo)ne dose (mg)*	14.2	14.2	9.5	8.0	3.7	2.9	12.1	12.1	11.8	8.0	3.0	2.4
Daily predniso(lo)ne dose (mg/kg)*	0.52	0.52	0.35	0.30	0.14	0.13	0.65	0.65	0.64	0.48	0.20	0.16

*Values indicated are mean values.

The finding by Quartier *et al.* concerning loss of response over time is discussed in detail within the study itself, which states:

> *"The lack of sustained response in several patients may have been related to several factors. First, most patients had diffuse polyarthritis at enrolment but no fever; as previously reported, anakinra seemed less effective on the arthritis than on systemic features. Second, PK data suggested that low-weight children might have benefited from a higher anakinra dosage. Third, we included patients with active SJIA, steroid-dependency and a minimal disease duration of 6 months, therefore difficult to treat; loss of responses may have been favoured by the study design that precluded the use of associated DMARDs and allowed tapering of the corticosteroid dose at an early stage, a strategy designed to minimise the risk of treatment-related complications."*

It should also be noted that some variables are expected to fluctuate over time. For example, as shown in Table 2, median ESR for patients treated with anakinra initially decreased rapidly, but then fluctuated over the remaining follow up. This is also related to the extent of follow up (and how not all patients were followed up for the full 12-month study period), and so these findings should be interpreted with caution. In addition, the Quartier *et al.* study considers a mixed population of pre-treated patients which is not aligned with the per-label positioning of anakinra per Sobi's submission.

In contrast to the Quartier *et al.* study population initiated on anakinra after a mean disease duration of 3.7 years (after 3.3 years treated with corticosteroids), a recent study (by ter Haar *et al.*) of patients treated with anakinra after a median disease duration of 30 days illustrates very different outcomes in patients treated with anakinra earlier in the pathway.[3] In this study, 32 patients (76%) had clinically inactive disease one year after initiation of rIL1-RA (primary endpoint), of which 28 used rIL-1RA monotherapy[*]. The authors also described a tapering strategy which allowed 22 patients (52% of the whole cohort) to stop therapy and be in drug-free remission at 1 year. 96% of patients followed up until 5 years (n=24 of 25) had inactive disease, of which 75% (n=18 of 24) had inactive disease off medication (i.e.

[*] In total, 32 patients (76%) had inactive disease 1 year after the initiation of rIL1-Ra; 22 of these patients (52% of the whole cohort) were not receiving therapy. Of these 32 patients, 28 had only received rIL-1Ra, 2 had received rIL-1Ra and prednisolone, 1 had received MTX and prednisolone (in addition to previously receiving rIL-1Ra), and 1 patient switched to tocilizumab and prednisolone. For further information, please see the ter Haar *et al.* publication.

no use of biologics, disease-modifying antirheumatic drugs [DMARDs], or corticosteroids).

Notwithstanding the issues highlighted above, Sobi presented this statement within the CS to accurately reflect the conclusions reached by the original Quartier *et al.* study authors, and added clarification of the measures that were captured within the study itself. The supplementary materials referenced above may be freely-accessed via the following weblink, should the ERG wish to find further information: https://ard.bmj.com/content/70/5/747.long (please scroll to the bottom of this webpage to find the supplementary material).

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Anakinra for treating Still's disease [ID1463]

Additional clarification questions – company response

February 2020

File name	Version	Contains confidential information	Date
2020-02-12_ID1463 anakinra additional clarification letter - Sobi response	v1-0	Yes	12/02/20

Introduction

Sobi thanks NICE and the ERG for the opportunity to provide clarification concerning the submission and supporting economic model. Following the informal discussion concerning the clarification questions on 29 January, Sobi respectfully wishes to clarify three points which may supplement understanding and assist review.

1. Still's disease (systemic juvenile idiopathic arthritis [sJIA] and adult-onset Still's disease [AOSD]) is an autoinflammatory disease; rheumatoid arthritis (RA) and other juvenile idiopathic arthritis (JIA) subtypes are autoimmune diseases.

Still's disease is understood to be a polygenic *autoinflammatory* disease – a disease of the innate immune system driven predominantly by interleukin-1 (IL-1) and IL-6. In this regard it is entirely distinct from RA, an *autoimmune* disease driven by pathology in the adaptive immune system driven predominantly by tumour necrosis factor (TNF) and IL-6.

Anakinra was first licensed for use in RA by the European Medicines Agency (EMA) in March 2002, and its use in rheumatology spans nearly two decades. RA is a chronic autoimmune disease which benefits from an array of new treatments targeting specific cytokines relevant in autoimmune pathogenesis. Use of anakinra in RA in the UK is extremely limited, aligned with NICE Guideline 100 and with the modern understanding of the limited role of IL-1 in autoimmune disease.

A summary of the key differences in autoinflammatory and autoimmune disease is provided below:

Disease	Autoinflammatory	Autoimmune
Immunological basis	Innate (non-specific) immune dysfunction	Adaptive (specific) immune dysfunction
Predominant cytokines increased	IL-1, IL-6	TNF, IL-6

2. Systemic JIA distinct in pathogenesis from JIA and AOSD distinct from RA

Following increased understanding of disease pathogenesis, the International League of Associations for Rheumatology (ILAR) classification of juvenile arthritis was updated in 2019 to the Paediatric Rheumatology International Trials Organisation (PRINTO) classification.[1] In this updated classification, the systemic features of sJIA were attributed to the disease's underlying autoinflammatory pathogenesis and accounted for the difference in response to inhibitors of IL-1/ IL-6.

The new PRINTO classification also removed the requirement for arthritis to diagnose sJIA, acknowledging the paradox of a classification of "arthritis" with systemic features only and no arthritis. (*"There was consensus to keep the term systemic JIA, even though some patients may not have arthritis, to be consistent with the current accepted terminology. Similarly, there was consensus to keep systemic JIA among the JIA disorders rather than grouping it with autoinflammatory*

diseases"). Rather than arthritis, the dominant features of sJIA include fever, rash, lymphadenopathies, marked systemic inflammation and a risk of developing macrophage activation syndrome (MAS).

Lopalco *et al.*, (2015) provides a helpful description of the differences between RA and AOSD.[2] As described above, RA is an autoimmune disorder that predominantly affects joints. TNF-α, IL-1β, and IL-6, are all involved in the pathogenesis of RA. For the autoinflammatory disorder AOSD, the main cytokine increased is IL-1β.

3. Clinical evidence for anakinra in Still's disease originates from clinician-led studies

By providing the context in which anakinra was developed, Sobi hopes the limitations of the evidence base may be better understood. There have been no industry-led clinical trials of anakinra in Still's disease. The development of the evidence for the use of anakinra in Still's disease has been led by clinicians hypothesising its efficacy based on an understanding of the disease pathogenesis (i.e. the role of IL-1), and then documenting and publishing clinical experience in treating patients with anakinra. The collection of published clinical experience forms the evidence base for this submission.

1. Is the company looking to position anakinra as a second-line treatment after NSAIDs and corticosteroids (as in the 'per-label' pathway of the model)?

   Yes – Sobi's submission proposes that anakinra be used after non-steroidal anti-inflammatory drugs (NSAIDs) ± corticosteroids but before conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs, such as methotrexate). This positioning is aligned with the licensed indication for anakinra:

   > *"*[Anakinra] *is indicated in adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg 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* [NSAIDs] *or glucocorticoids.*
   >
   > [Anakinra] *can be given as monotherapy or in combination with other anti-inflammatory drugs and* [csDMARDs]*."* Anakinra SmPC[3]

2. The proposed positioning of anakinra is for use as per its licensed indication, Is the company also looking for a recommendation regarding anakinra in the third-line setting, after csDMARDs?

   Sobi's proposed positioning for anakinra is in the second line (before csDMARDs). The 'post-csDMARD' pathway in the model reflect the current use of anakinra in the third-line setting in NHS practice, which Sobi does not consider the most appropriate use of anakinra for sJIA or AOSD.

3. The 'per-label' model pathway does not include DMARDs so that treatment with both anakinra and tocilizumab is offered after NSAIDs and corticosteroids. Please comment on whether this pathway would likely be realised in clinical practice as tocilizumab is currently commissioned by NHS England only after DMARDs.

   In current practice, patients are permitted to receive treatment with a bDMARD (i.e. anakinra or tocilizumab) after failing either one (sJIA patients) or two (AOSD patients) csDMARD(s). This expectation is based on the corresponding NHS Clinical Commissioning Policies for AOSD and JIA, and verified with clinical expert opinion provided to Sobi.

   Use of tocilizumab in current NHS practice based on the JIA policy is based also on the NICE recommendation of tocilizumab in sJIA (NICE TA238).[*] Tocilizumab is not licensed for use in AOSD, and so no corresponding NICE

[*] The NICE recommendation for tocilizumab states: *"Tocilizumab is recommended for the treatment of* [sJIA] *in children and young people aged 2 years and older whose disease has responded inadequately to* [NSAIDs]*, systemic corticosteroids and methotrexate if the manufacturer makes tocilizumab available with the discount agreed as part of the patient access scheme. Tocilizumab is not recommended for the treatment of* [sJIA] *in children and young people aged 2 years and older whose disease continues to respond to methotrexate or who have not been treated with methotrexate."*

guidance exists in this population. Therefore, all use of tocilizumab in AOSD is (by definition) 'off label' in NHS practice.

When preparing the submission, Sobi engaged with clinical experts concerning how the treatment pathway would change were anakinra used after NSAIDs + corticosteroids. Clinical advice provided to Sobi was that it is highly unlikely that treatment with a csDMARD (such as methotrexate) would be introduced following failure on a bDMARD (such as anakinra) – especially noting that anakinra is itself a DMARD. The licensed indications for both anakinra and tocilizumab do not preclude their use in a second-line (i.e. pre-csDMARD) setting. A minor revision to the current NHS policies for JIA and AOSD would therefore be required to align with the final NICE guidance, should anakinra be recommended in line with its licensed indication.

4. Please explain what evidence was used to assume clinical equivalence between anakinra and tocilizumab in the model.

    a. Is there any further evidence about the relative efficacy and side effect profiles of anakinra and tocilizumab?

    As discussed in the NHS Clinical Commissioning Policy for AOSD, there is only one available RCT in this population (Nordstrom *et al.*, 2012) which compares anakinra and csDMARDs. For sJIA, the NHS Clinical Commissioning Policy for JIA does not discuss the evidence base at great length, but notes that there are no comparative studies for tocilizumab and anakinra. There are no head-to-head RCTs comparing tocilizumab with anakinra in either an sJIA or AOSD population. However, the absence of head-to-head trials is not unusual in this field.

    It is important to reiterate that tocilizumab is not licensed for patients with AOSD, and so the available data concerning the efficacy and safety of tocilizumab predominantly comprises of studies in exclusively sJIA populations. There are some studies concerning the use of tocilizumab in AOSD populations, but these are mainly case series. For context, tocilizumab was first licensed for use by the EMA approximately 7 years after the initial date of anakinra's marketing authorisation.

    In the clarification call held between NICE and Sobi on 29 January, reference was made to a study by Riancho-Zarrabeitia *et al.*, (2015) comparing tocilizumab and anakinra in AOSD.[4] This is a comparative, though non-randomised, study of both treatments in a mixed population of patients according to treatment history. This study was not included within Sobi's systematic review as it is an abstract from the 2015 EULAR meeting (i.e. no full publication is available).

While only the abstract is available, Sobi notes that there are several limitations to this study. Prior treatments were not balanced between the groups (steroids, conventional immunosuppressants, and biologics). This means it is unclear if any comparisons between the groups are appropriate within the context of this appraisal, given that the groups represent different stages in the treatment pathway. In addition, the median disease duration was notably different between the groups, again reflecting different stages of the treatment pathway. Finally, a clinician's choice to use either anakinra or tocilizumab may be based on a number of factors – e.g. risk of MAS (as was noted in the Kearsley-Fleet *et al.* study which was discussed in Sobi's submission).[5]

In the absence of robust comparative study data, clinical expert opinion was instead sought to establish the relative efficacy of anakinra and tocilizumab. Advice provided to both Sobi and the ERG was that anakinra and tocilizumab are considered to have similar efficacy in Still's disease. However, the decision to use one product over the other is usually based on a number of considerations (e.g. pharmacokinetics, route of administration, presentation of symptoms etc.).

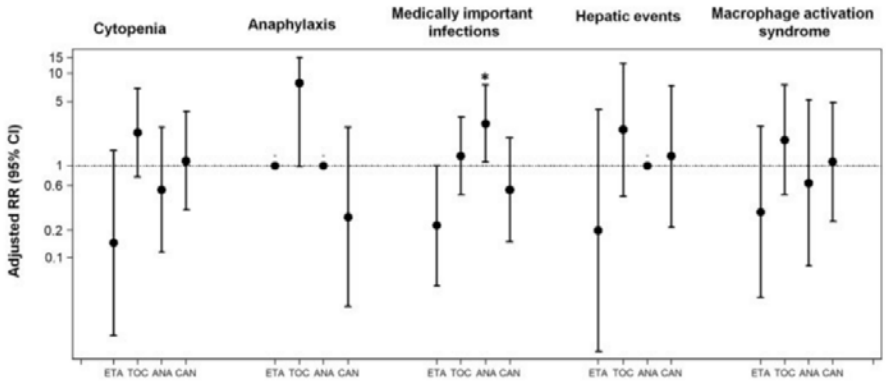
With regards to relative safety, a recent study by Klein *et al.*, (2019) provides some information comparing outcomes for patients treated with anakinra and tocilizumab (as well as canakinumab and etanercept – treatments that are both used in Germany).[6] Importantly, this study is based on an analysis of registry data, and so should be interpreted with caution. Figure 1 is an excerpt from this study which shows adjusted relative risks for each biologic compared with the other three biologics. The adverse events included within this were determined by the study authors to be of special interest (which is discussed in further detail within the full publication).

The findings of this analysis showed (after adjustment for patient characteristics) that anakinra was associated with a statistically-significant increase in the risk of medically important infections. Tocilizumab was associated with a numerical increase in the risk of cytopenia, anaphylaxis, hepatic events, and MAS (though none of these differences were shown to be statistically significant).

Importantly, the relative risk values are based on a comparison to the other three treatments and not a comparison of anakinra versus tocilizumab. Based on interpretation of the confidence intervals in Figure 1, there is no conclusive evidence for a statistically significant difference in adverse events between anakinra and tocilizumab treated patients. However, there are numerical differences in the adjusted risk ratios. In addition, as this is an analysis of registry data, any findings

should be interpreted with caution (given that it is unclear why specific treatments were selected for use in certain patients etc.).

Figure 1: Selected adverse events of special interest comparison of relative risk



Sobi highlighted within its submission all known evidence concerning the efficacy and safety of anakinra, including all possible comparative evidence to tocilizumab. Since Sobi's original submission, the study by Klein *et al.* was published (in December 2019), for which summary findings are provided above. However, other than this study, Sobi is unaware of any additional evidence that may provide additional information on the relative efficacy and safety of both treatments.

b. Could any further evidence be produced, for example a matching-adjusted indirect comparison (MAIC)?

A matching-adjusted indirect comparison (MAIC) is a statistical technique intended to 're-balance' patient characteristics in order to improve estimates of relative efficacy and/ or safety compared with a naïve (i.e. unadjusted) comparison. However, such methods do not adjust for differences in study design (e.g. differences in outcome measures, duration of follow-up, comparator therapies etc.) and rely upon a comparison of patients for which data are reported (i.e. at baseline).

A previously-published network meta-analysis (NMA) by Tarp *et al.*, (2016) is available, and was referenced within Sobi's original submission.[7] The analysis by Tarp *et al.* includes one trial for tocilizumab (TENDER) and one trial for anakinra (ANAJIS).[8,9] In TENDER, 'clinically inactive disease' which was achieved by 32% of the n=110 patients enrolled in the open-label extension phase (from 12 to 52 weeks). In ANAJIS, of the n=16 patients that reached month 12 of the open-label extension phase; n=5 had 'inactive disease' (31%).

An important limitation of the available data is that the patient characteristics of the population that were assessed for inactive

disease is unknown for both studies (as this is not the same population of patients enrolled at baseline). This means that it is not possible to undertake a population-adjusted comparison of the outcome of inactive disease (the outcome of most relevance to current NHS practice).

While it may be possible to undertake a population-adjusted comparison of outcomes based on an intention-to-treat analysis (such as ACR Pedi30 or adverse events), such comparisons also rely on the availability of patient-level data for at least one of the studies. Sobi does not have access to patient-level data from the TENDER trial (which was funded by Hoffmann–La Roche). Sobi also does not have access to the ANAJIS patient-level data. Financial support for this study was provided by Amgen (the original holders of the marketing authorisation for anakinra), though Amgen had *"no role in the analysis and reporting phase of the study"*.

5. Please explain why removing csDMARDs from the pathway (in the per-label pathway) leads to an increase in the proportion of patients having prolonged remission compared with the post-csDMARDs pathway and comment on whether this is clinically plausible.

    a. Would it be expected that disease that does not respond to csDMARDs or biologics when used sequentially, would respond to biologics if used in place of csDMARDs in the treatment pathway? If so, please provide evidence for the clinical plausibility of this.

    Removing an ineffective treatment from the pathway increases the proportion of patients given effective therapy earlier, which increases the chance of remission. The two issues raised in this question will be discussed separately:

    - The use of csDMARDs in Still's disease
    - The "window of opportunity" hypothesis in Still's disease

    While discussing the outcome of remission, it is important to note that the definition of remission is variable across different studies (as acknowledged within Sobi's submission). In practice, remission is generally referred to as an extended time period (normally of at least 6 months) wherein there is an absence of disease-related symptoms and systemic manifestations (e.g. raised inflammatory markers).[10,11] However, in older studies "remission" is sometimes used to describe short-term outcomes.

    <u>The use of csDMARDs in Still's disease</u>

    The efficacy of methotrexate is well established in adult rheumatology with remarkable success in improving clinical outcomes in RA. On this basis, Still's disease was historically treated with methotrexate with the

expectation of similar efficacy (before it was understood to be an autoinflammatory rather than autoimmune disease). Its continued use in Still's disease reflects this tradition.

This hypothesis has been tested and the balance of clinical evidence does not support the efficacy of methotrexate in Still's disease. For the purpose of describing an overview of the clinical evidence base, Sobi has presented summary findings from a number of notable articles that discuss the role of methotrexate in Still's disease (presented below). Sobi highlights that this is not based on a systematic review of the literature.

(Please note: in reviewing clinical evidence for the efficacy of methotrexate in Still's disease, the reader should be aware of the tendency in earlier literature to document all JIA subtypes, rather than testing sJIA specifically).

Halle and Prieur (Clin Exp Rheumatol 1991)[12]

Thirty children with JIA, including ten patients with a systemic onset, refractory to slow-acting antirheumatic drugs (SAARDs) (hydroxychloroquine, chloroquine, penicillamine, the gold complexes and sulphasalazine) were treated with oral methotrexate (0.2 increasing to 0.8mg/kg/week) for 6-30 months.

Results that follow are for the ten participants in the systemic onset subgroup:

- Extraarticular symptoms improved subjectively in seven out of ten participants, with four subsequently relapsing
- Fever, present in 7 patients, improved in four and later reappeared in two participants
- Duration of morning stiffness increased, and number of active joints showed a non-significant trend to decrease
- ESR did not decrease
- Oral corticosteroids could not be stopped in any patients in the systemic-onset subgroup and NSAIDs had to be increased

The authors concluded that there existed a differential effect of methotrexate therapy according to subtype, with the systemic subtype less responsive to methotrexate than the antinuclear antibodies (ANA)-positive form and the polyarticular onset.

Speckmaier et al. (Clin Exp Rheumatol 1989)[13]

Twelve children with severe systemic juvenile chronic arthritis all requiring high dose corticosteroids were treated with methotrexate (8.5 mg/m^2) for six months.

- Marked clinical improvement was seen in four children (reduction in number of active joints, improvement in systemic features and haematological parameters), allowing a reduction in steroids in two participants
- In contrast, the disease activity deteriorated in two children and steroids were increased in a further three children.

The authors concluded that a third of children with severe systemic juvenile arthritis improved in six months in response to methotrexate.

Woo (Arthr & Rheum, 2000)[14]

This study was conducted in recognition of the underrepresentation of the systemic and extended oligoarthritis subgroups in the recent studies of methotrexate efficacy in various forms of juvenile polyarthritis.

n=45 and n=43 patients meeting the ILAR criteria for sJIA and extended oligoarticular arthritis respectively were enrolled in a double-blind placebo-controlled cross-over trial of methotrexate given at 15-20mg/m^2.

Results described here will be limited to those of the sJIA group:

- Only two of five core variables (physician's and parent's global assessment of disease activity) improved significantly†
- The systemic features of the disease were not significantly different between methotrexate and placebo treatment
- There was no significant difference between methotrexate and placebo in the joint range of motion for participants who had complete records of joint range for both treatment periods
- Combining both subgroups showed no significant difference between placebo and methotrexate in the number of active joints and there was no difference in treatment effect between subgroups
- CRP and ESR decreased significantly from baseline in both subgroups, however when compared to placebo, the sJIA

† The core variables refer to the variables and criteria for improvement proposed by Giannini *et al*.[15]

subgroup showed no significant reduction in these inflammatory markers

- None were able to reduce steroid use by more than 5mg/day
- Six patients withdrew from the study because of unremitting disease, with only two of these during the placebo period

Nordström (J Rheumatol, 2012)[16]

As described in Sobi's submission, this study was conducted in 22 patients with AOSD taking prednisolone ≥10 mg/day. Patients were randomised to receive either anakinra (n=12) or csDMARD (n=10), in addition to corticosteroids.

In the csDMARD group, n=6 patients received methotrexate, n=3 received azathioprine, and n=1 received leflunomide.

The primary endpoint was remission according to specific criteria at 8 weeks [afebrile (≤ 37°C body temperature, measured twice from armpit), in the absence of NSAIDs 24 hours prior to measurement, decrease of CRP and ferritin to reference limits] and normal swollen (SJC) and tender joint counts (TJC).

The results described below relate to the csDMARD group:

- In remission at Weeks 4, 8, and 24 were 3/10, 5/10, and 2/10 patients treated with csDMARD + corticosteroids
- No patients treated with csDMARD were able to discontinue oral corticosteroids
- In the open-label extension (OLE) phase, n=8 of the csDMARD patient continued until Week 52
    - Only n=3 patients originally on csDMARD (2 on methotrexate and 1 on azathioprine) remained on the same medication at Week 52
    - Among the remaining n=5 patients, 2 had switched to methotrexate and anakinra, 1 to leflunomide and anakinra, 1 to anakinra monotherapy, and 1 to infliximab
    - During the OLE half of the patients randomised to csDMARD had a disease flare
    - Numerically higher responder rate was observed in the anakinra group, at week 52, 6 patients (50%) were in remission, as compared to 3 patients (30%) of the csDMARD group

Please note: remission in this study was defined as early as after 4 weeks of treatment. Modern studies in Still's disease define remission after a minimum of at least 6 months of treatment.[10,11]

The "window of opportunity" hypothesis in Still's disease

Approximately half of patients have a chronic persistent arthritis requiring extended therapy, sometimes into adulthood. In these patients, growth failure, radiographically evident joint injury, and long-term disability have historically been very common.[17] Noting differential clinical outcomes when IL-1 blockade is initiated later in the disease course, Nigrovic, 2014 proposed a biphasic model of sJIA.[17] In this model, early sJIA is driven by innate immune mechanisms, while chronic arthritis is mediated, at least in part, by autoreactive T cells. They therefore proposed that a "window of opportunity" would exist in which the progression of disease pathophysiology might be altered to avoid chronic arthritis.

This hypothesis was tested in a single centre in the Netherlands (initially reported by Vastert *et al.*, 2014 and later by ter Haar *et al.*, 2019).[18,19] Between 2008 and 2017, the investigators enrolled 51 patients with new-onset sJIA to be treated in a treat-to-target strategy and subsequent drug-tapering strategy. Patients with fever unresponsive to 7 days of NSAID therapy were initiated on anakinra at 2mg/kg/day. If fever was still present after 3 days this was escalated to 4mg/kg/day. If clinically inactive disease was not obtained, anakinra was switched to an alternative therapy with or without glucocorticoids. Once clinically inactive disease was attained, a tapering strategy was initiated, targeting maintenance of drug free remission. 42 patients were followed up for a median of 5.8 years. At 1 year, 76% had clinically inactive disease and 52% had clinically inactive disease off medication. At 5 years follow-up, 95% of included patients had clinically inactive disease and 72% had inactive disease off medication.

This study validated the "window of opportunity" hypothesis by showing rapid and sustained inactive disease in the majority of sJIA patients and reduced glucocorticoid use.

In addition to the study conducted in the Netherlands, Pardeo *et al.*, (2019) recently documented findings of early treatment with anakinra in sJIA in the Italian setting.[20] In this study, the investigators assessed n=57 patients treated with anakinra to establish whether the response to anakinra was related to baseline variables. n=30 (52.6%) of the patients received anakinra within 2 months from disease onset. At 6 months after beginning of anakinra treatment, 28/30 patients (93.3%) who started anakinra within 2 months from disease onset and 12/27

(44.4%) who started anakinra after 2 months from disease onset reached clinical inactive disease off glucocorticoids (p=0.0001). Patients who started anakinra after the first 2 months from disease onset had a significantly higher risk of non-response (odds ratio [OR] 8.06, 95% confidence intervals: 2.03-32.0).

This study provides further evidence of the "window of opportunity" hypothesis, illustrating the clinical plausibility of improved patient outcomes gained by enabling earlier IL-1 inhibition.

The descriptions provided above concerning the sequential use of csDMARDs (such as methotrexate) and bDMARD and the "window of opportunity" in Still's disease are separate, yet related points. The use of ineffective treatment with csDMARDs reduces the "window of opportunity" through delayed initiation of anakinra, as patients are expected to derive the most benefit with anakinra via its inhibition of IL-1 early in the disease process.

6. The ERG highlighted that within the model, treatment switching is set at a fixed probability per weekly cycle for patients who have not achieved remission. Please provide scenario analyses where this probability is varied.

In the model submitted by Sobi, treatment switching (and/or "adding") in the model is informed by a fixed (i.e. time-invariant) probability per weekly cycle. This assumption was also made in the previous NICE assessment of tocilizumab in sJIA (TA238), and it is this previous appraisal from which the values used for initial bDMARDs within the model were taken.

There are limited data to inform treatment discontinuation for patients with Still's disease, and so the assumption of a static probability was made for simplicity. In reality, the proportion of patients expected to discontinue treatment at each point in time may differ, based on a combination of the following:

- Patients initiating a treatment may have a different probability of discontinuing treatment compared to those that have been receiving treatment for a longer time – for example, patients would be expected to remain on treatment until an assessment of response is established
- Patients that have experienced disease recurrence (i.e. are no longer in remission) are expected to be treated in order to re-induce remission. If considered an immediate failure, patients may promptly discontinue treatment
- Patients that have experienced difficulty in managing symptoms, as well as those that have a history of previous complications (e.g. MAS), may be less likely to discontinue treatment compared with those that have experienced relatively mild symptoms

Given that the model adopts a Markovian approach to inform transitions between health states, it is not possible to identify this precise mix of patients at any given point in time. Therefore, any implementation of time-varying probabilities for discontinuation is highly uncertain, and should be interpreted with caution. Sobi does however appreciate that scenario analysis exploring time-varying probability of treatment discontinuation may be helpful to consider, and so has undertaken an exploratory analysis for this within the submitted economic model.

To account for a time-varying probability of discontinuation, Sobi has updated the model to include two different sets of transition matrices. The model will consider probabilities from one set of matrices up until a given model cycle, after which transitions are informed from the other set of matrices. In the second set of transition matrices, all probabilities are set to be the same as the first set of matrices, except for the probability of discontinuation (and by extension, the probability of remaining in a given health state, as this is calculated as one minus the sum of all other probabilities). For discontinuation, the model now allows for the user to specify a probability multiplier to explore either an increased or decreased risk of treatment discontinuation after a given point in time.

Due to the numbers of calculations required to estimation health state occupancy within the model, the switch between the matrices may be varied at any model cycle up until 1 year. This structural limitation was made to ensure the model can still be run within a reasonable timeframe, yet could be overridden by simply replicating the formulae on the 'Transitions' sheet further down the sheet, and amending the data validation on the input cell on the 'ClarQ' sheet.

Sobi notes that this analysis should be considered exploratory, as an immediate change in the probability of discontinuation at a given point in time is unlikely to accurately reflect clinical practice.

Implementation of a time-varying probability of discontinuation within a cohort-level model is highly complex, and were sufficient data available to inform such a model parameter, an alternative model structure (e.g. a multi-state modelling or discrete event simulation approach) may have been possible to consider. Tunnel states are also not possible to consider within the model, as the model would theoretically need to be able to capture patients entering and leaving different tunnel states at every model cycle (in order to capture the possible routes through the treatment cascade, including remission and recurrence).

Using the proposed approach, Sobi has opted to implement one time point at which the probability of discontinuation is changed. Theoretically, the model could be extended to include a separate set of matrices for each model cycle. However, it is unclear how probabilities to inform these matrices could be feasibly established. Therefore, while Sobi accepts the approach is limited,

Sobi considers specification of further model complexity to be unsubstantiated with available evidence and so restricting the analysis as described above is expected to be the most informative approach for decision making.

Sobi has provided results based on the following scenarios using the time-varying discontinuation approach:

- Increase discontinuation for all treatments by 20% after 6 months
- Increase discontinuation for only bDMARDs by 20% after 6 months
- Increase discontinuation for all treatments by 20% after 12 months
- Increase discontinuation for only bDMARDs by 20% after 12 months
- Decrease discontinuation for all treatments by 20% after 6 months
- Decrease discontinuation for only bDMARDs by 20% after 6 months
- Decrease discontinuation for all treatments by 20% after 12 months
- Decrease discontinuation for only bDMARDs by 20% after 12 months

However, should the ERG wish to explore alternative scenarios, the model allows for the specification of the time point and multipliers on the “ClarQ” sheet. The results of the sensitivity analysis (compared with the base-case analysis) are provided in Table 1.

Table 1: Scenario analyses (time-varying discontinuation)

Arm	Total			Incremental			INMB (£), vs.	
	Costs (£)	QALYs	LYs	Costs (£)	QALYs	LYs	1)	2)
Base-case analysis								
1) No anakinra	258,107	11.304	28.202					
2) Post-csDMARD	224,343	11.657	28.509	-33,764	0.353	0.307	40,817	
3) Per-label	201,317	11.970	28.774	-23,026	0.313	0.265	70,102	29,285
Scenario #1 – Increase discontinuation for all treatments by 20% at 6 months								
1) No anakinra	268,365	11.213	28.120					
2) Post-csDMARD	236,869	11.549	28.415	-31,496	0.336	0.295	38,223	
3) Per-label	212,856	11.872	28.690	-24,013	0.322	0.275	68,681	30,458
Scenario #2 – Increase discontinuation for only biologic DMARDs by 20% at 6 months								
1) No anakinra	265,949	11.230	28.136					
2) Post-csDMARD	234,678	11.563	28.427	-31,271	0.333	0.291	37,936	
3) Per-label	211,033	11.883	28.700	-23,645	0.320	0.273	67,974	30,038
Scenario #3 – Increase discontinuation for all treatments by 20% at 12 months								
1) No anakinra	266,883	11.229	28.133					
2) Post-csDMARD	235,445	11.564	28.427	-31,438	0.335	0.294	38,146	
3) Per-label	211,892	11.882	28.699	-23,554	0.318	0.271	68,050	29,904
Scenario #4 – Increase discontinuation for only biologic DMARDs by 20% at 12 months								
1) No anakinra	264,679	11.244	28.147					
2) Post-csDMARD	233,452	11.577	28.438	-31,227	0.333	0.291	37,879	
3) Per-label	210,224	11.892	28.707	-23,227	0.315	0.269	67,409	29,530
Scenario #5 – Decrease discontinuation for all treatments by 20% at 6 months								
1) No anakinra	244,916	11.418	28.302					
2) Post-csDMARD	208,982	11.784	28.619	-35,935	0.366	0.317	43,256	
3) Per-label	187,919	12.080	28.867	-21,063	0.296	0.248	70,244	26,989
Scenario #6 – Decrease discontinuation for only biologic DMARDs by 20% at 6 months								
1) No anakinra	248,086	11.397	28.284					
2) Post-csDMARD	211,700	11.768	28.606	-36,386	0.371	0.322	43,812	
3) Per-label	190,117	12.068	28.857	-21,583	0.300	0.251	71,390	27,577
Scenario #7 – Decrease discontinuation for all treatments by 20% at 12 months								
1) No anakinra	246,777	11.398	28.286					
2) Post-csDMARD	210,672	11.767	28.605	-36,104	0.368	0.319	43,473	
3) Per-label	189,030	12.069	28.858	-21,643	0.302	0.253	71,156	27,682
Scenario #8 – Decrease discontinuation for only biologic DMARDs by 20% at 12 months								
1) No anakinra	249,660	11.380	28.270					
2) Post-csDMARD	213,136	11.753	28.593	-36,524	0.373	0.324	43,988	
3) Per-label	191,034	12.058	28.849	-22,102	0.305	0.256	72,192	28,205

Key: csDMARD, conventional-synthetic disease-modifying anti-rheumatic drug; ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; LY, life year; QALY, quality-adjusted life year.

Note: These results take into account the assumed commercially-sensitive simple patient access scheme discount for tocilizumab ([redacted]). INMB calculated assuming a willingness-to-pay threshold of £20,000 per QALY gained.

The scenario analysis yielding the largest total QALYs (and smallest total costs) for each strategy is Scenario #5 (where the probability of discontinuation was

decreased for all treatments by 20% at 6 months). This scenario reflects the analysis wherein treatment is continued for the longest possible time period, during which the probability to achieve remission across all strategies (and thus avoid unresolved disease) is maximised. This scenario yields the lowest INMB for 'per-label' versus 'post-csDMARD'.

However, the lowest INMB for 'per-label' versus 'no anakinra' is for Scenario #4 (where the probability of discontinuation was increased for only bDMARDs by 20% at 12 months). This scenario greatly affects the possibility of achieving remission with bDMARDs, while leaving all other settings the same. By reducing the duration over which patients may achieve remission with bDMARDs, this scenario reduces the QALY gain for the 'per-label' scenario, resulting in a lower INMB estimate.

The scenario with the largest total costs (and smallest total QALYs) for each strategy is Scenario #1 (where the probability of discontinuation was increased for all treatments by 20% at 6 months). In this scenario, all treatments are discontinued more quickly, and so a larger proportion of patients will have unresolved disease, increased medical resource costs, and poorer health-related quality of life. The estimate of the INMB for 'per-label' versus 'post-csDMARD' is the largest of all scenarios (due to greater cost savings through avoided unresolved disease).

The largest INMB for 'per-label' versus 'no anakinra' is shown in Scenario #8 (where the probability of discontinuation was decreased for only biologic DMARDs by 20% at 12 months). This scenario is associated with the largest differential in terms of capacity to induce remission between these states of the world.

Sobi highlights again that these results should be considered as exploratory, and so Sobi's preference remains for the use of a statistic probability in the absence of any other data to inform time-varying discontinuation. In general, however, the conclusion of the model was unchanged through these exploratory sensitivity analyses.

7. The ERG considers it implausible that the probability of achieving remission with csDMARDs for people with chronic disease is 0. Please provide scenario analyses where this probability is varied.

Clinical expert advice provided to Sobi indicated that it is not possible to induce remission through the use of csDMARDs in patients with chronic disease course. Further information concerning the efficacy of csDMARDs in Still's disease is provided in response to Question 5.

While contradictory to clinical opinion provided to Sobi, the model has been edited to allow for the specification of a non-zero probability for achieving remission with csDMARDs. The results of this scenario analysis are presented in Table 2, where the probability of achieving remission with csDMARDs has

been set equal to the value applied for patients with monocyclic disease course. The 'per-label' results are identical to the base-case analysis (given that in this state of the world, csDMARDs are not used). However, for the other two states of the world, the total costs are reduced and the total QALYs are increased (due to an increase in the proportion of patients that achieve remission, and thus avoid unresolved disease).

Table 2: Scenario analyses (remission with csDMARDs)

Arm	Total			Incremental			INMB (£), vs.	
	Costs (£)	QALYs	LYs	Costs (£)	QALYs	LYs	1)	2)
Base-case analysis								
1) No anakinra	258,107	11.304	28.202					
2) Post-csDMARD	224,343	11.657	28.509	-33,764	0.353	0.307	40,817	
3) Per-label	201,317	11.970	28.774	-23,026	0.313	0.265	70,102	29,285
Scenario #9 – Probability of remission for chronic course patients same as monocyclic patients								
1) No anakinra	255,574	11.326	28.222					
2) Post-csDMARD	222,021	11.675	28.526	-33,553	0.349	0.303	40,533	
3) Per-label	201,317	11.970	28.774	-20,704	0.295	0.249	67,144	26,611

Key: csDMARD, conventional-synthetic disease-modifying anti-rheumatic drug; ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; LY, life year; QALY, quality-adjusted life year.

Note: These results take into account the assumed commercially-sensitive simple patient access scheme discount for tocilizumab ([redacted]). INMB calculated assuming a willingness-to-pay threshold of £20,000 per QALY gained.

8. Please provide scenario analyses where the time horizon is increased above 30 years.

In the previous NICE TA238 of tocilizumab in sJIA, the model time horizon was capped at 16 years in the company's submission, which the ERG restricted to 11 years in its preferred base-case analysis (i.e. the only differences in costs/effects captured by the model were those incurred/accrued during childhood and adolescence). A diagnosis of sJIA is expected to continue into adulthood. As such, Sobi sought to provide a model with a time horizon that was sufficiently long to capture important differences in costs and effects, regardless of when patients are classified as adults.

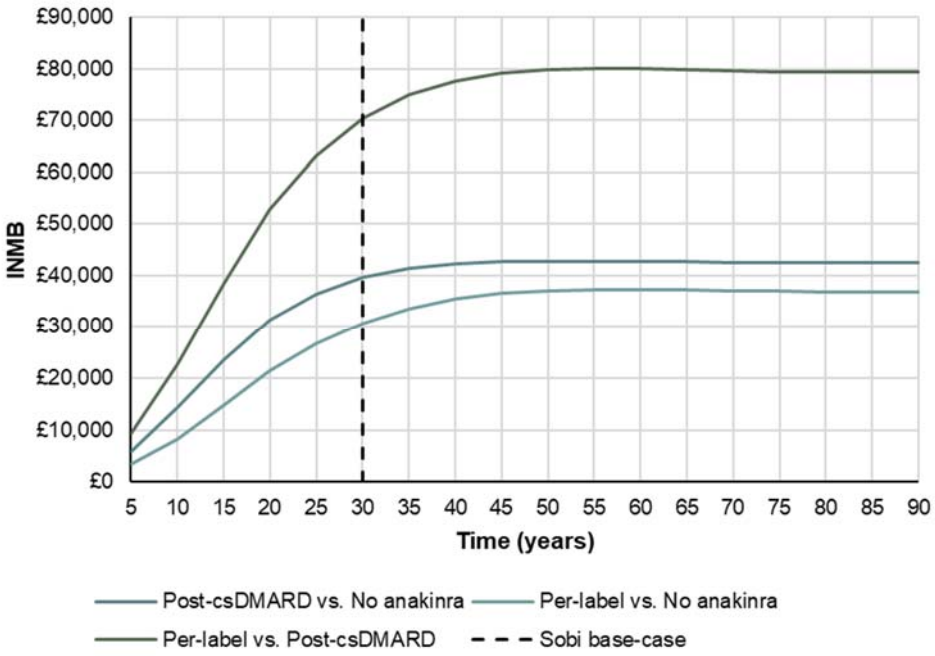
However, owing to the need to construct a model that captures the full treatment pathway (accounting for three possible 'states of the world' and alternative subgroups/ disease courses), there was a need to trade-off the computational burden of the model calculations, with the period over which important costs and effects were expected to be present. Consequently, the model time horizon was set to 30 years.

The choice of 30 years was made only in the interest of ensuring model run time was as short as possible, while also ensuring the majority of important differences in costs and effects were captured by the model. Nevertheless, Sobi understands that a longer time horizon is necessary to capture the full differences in costs and effects.

To provide scenario analyses with a longer time horizon, Sobi has edited the economic model to extend the model calculations up until a time horizon of 90 years. By the time the average age of the sJIA reaches 87 years, the estimated cumulative hazard of death has exceeded 1 (based on life table mortality data, which were adjusted to account for the weekly model cycle length), and as such all patients are modelled to have died within a 90-year time horizon, regardless of starting age.

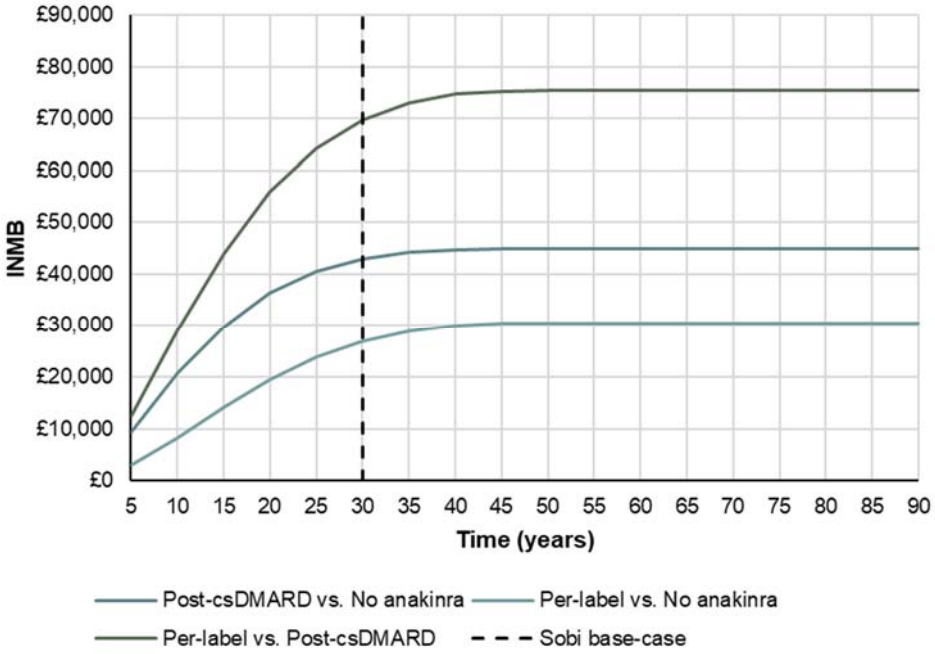
Using the base-case model settings and assumptions per Sobi's original submission, the relationship between the increment net monetary benefit (INMB) and the model time horizon may be established. Results for the sJIA and AOSD populations are presented in Figure 2 and Figure 3, respectively.

Figure 2: Relationship between INMB and time horizon, sJIA population (company base-case settings)



Key: csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; INMB, incremental net monetary benefit; sJIA, systemic juvenile idiopathic arthritis.

Figure 3: Relationship between INMB and time horizon, AOSD population (company base-case settings)



Key: AOSD, adult-onset Still's disease; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; INMB, incremental net monetary benefit.

As can be seen from the plots, there is relatively little to gain from extending the model time horizon from around 50 years in the sJIA population, or from around 40 years in the AOSD population. The plots demonstrate that the model results based on a time horizon of 30 years (per Sobi's original submission) are arguably conservative, as some additional costs and effects were omitted after this time, which led to improved estimates of cost effectiveness. However, the overall conclusion remains unchanged, and by 30 years the majority of the differences in costs and effects are established (as may be inferred through the relatively small changes in the curves after 30 years).

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Anakinra for treating Still's disease [ID1463]

ERG comments on the company's responses to NICE's additional clarification questions

February 2020

File name	Version	Contains confidential information	Date
2020-02-12_ID1463 anakinra additional clarification letter - Sobi response	v1-0	Yes	12/02/20

Introduction

Sobi thanks NICE and the ERG for the opportunity to provide clarification concerning the submission and supporting economic model. Following the informal discussion concerning the clarification questions on 29 January, Sobi respectfully wishes to clarify three points which may supplement understanding and assist review.

1. Still's disease (systemic juvenile idiopathic arthritis [sJIA] and adult-onset Still's disease [AOSD]) is an autoinflammatory disease; rheumatoid arthritis (RA) and other juvenile idiopathic arthritis (JIA) subtypes are autoimmune diseases.

Still's disease is understood to be a polygenic *autoinflammatory* disease – a disease of the innate immune system driven predominantly by interleukin-1 (IL-1) and IL-6. In this regard it is entirely distinct from RA, an *autoimmune* disease driven by pathology in the adaptive immune system driven predominantly by tumour necrosis factor (TNF) and IL-6.

Anakinra was first licensed for use in RA by the European Medicines Agency (EMA) in March 2002, and its use in rheumatology spans nearly two decades. RA is a chronic autoimmune disease which benefits from an array of new treatments targeting specific cytokines relevant in autoimmune pathogenesis. Use of anakinra in RA in the UK is extremely limited, aligned with NICE Guideline 100 and with the modern understanding of the limited role of IL-1 in autoimmune disease.

A summary of the key differences in autoinflammatory and autoimmune disease is provided below:

Disease	Autoinflammatory	Autoimmune
Immunological basis	Innate (non-specific) immune dysfunction	Adaptive (specific) immune dysfunction
Predominant cytokines increased	IL-1, IL-6	TNF, IL-6

2. Systemic JIA distinct in pathogenesis from JIA and AOSD distinct from RA

Following increased understanding of disease pathogenesis, the International League of Associations for Rheumatology (ILAR) classification of juvenile arthritis was updated in 2019 to the Paediatric Rheumatology International Trials Organisation (PRINTO) classification.[1] In this updated classification, the systemic features of sJIA were attributed to the disease's underlying autoinflammatory pathogenesis and accounted for the difference in response to inhibitors of IL-1/ IL-6.

The new PRINTO classification also removed the requirement for arthritis to diagnose sJIA, acknowledging the paradox of a classification of "arthritis" with systemic features only and no arthritis. (*"There was consensus to keep the term systemic JIA, even though some patients may not have arthritis, to be consistent with the current accepted terminology. Similarly, there was consensus to keep systemic JIA among the JIA disorders rather than grouping it with autoinflammatory*

diseases"). Rather than arthritis, the dominant features of sJIA include fever, rash, lymphadenopathies, marked systemic inflammation and a risk of developing macrophage activation syndrome (MAS).

Lopalco *et al.*, (2015) provides a helpful description of the differences between RA and AOSD.[2] As described above, RA is an autoimmune disorder that predominantly affects joints. TNF-α, IL-1β, and IL-6, are all involved in the pathogenesis of RA. For the autoinflammatory disorder AOSD, the main cytokine increased is IL-1β.

3. Clinical evidence for anakinra in Still's disease originates from clinician-led studies

By providing the context in which anakinra was developed, Sobi hopes the limitations of the evidence base may be better understood. There have been no industry-led clinical trials of anakinra in Still's disease. The development of the evidence for the use of anakinra in Still's disease has been led by clinicians hypothesising its efficacy based on an understanding of the disease pathogenesis (i.e. the role of IL-1), and then documenting and publishing clinical experience in treating patients with anakinra. The collection of published clinical experience forms the evidence base for this submission.

1. Is the company looking to position anakinra as a second-line treatment i.e. after NSAIDs and corticosteroids (as in the 'per-label' pathway of the model)?

   Yes – Sobi's submission proposes that anakinra be used after non-steroidal anti-inflammatory drugs (NSAIDs) ± corticosteroids but before conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs, such as methotrexate). This positioning is aligned with the licensed indication for anakinra:

   > *"*[Anakinra] *is indicated in adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg 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* [NSAIDs] *or glucocorticoids.*
   >
   > [Anakinra] *can be given as monotherapy or in combination with other anti-inflammatory drugs and* [csDMARDs]*."* Anakinra SmPC[3]

ERG comments (Q1)

The clarification provided by the company on their proposed positioning of anakinra will help focus NICE Appraisal Committee (AC) discussions.

2. The proposed positioning of anakinra is for use as per its licensed indication, Is the company also looking for a recommendation regarding anakinra in the third-line setting, after csDMARDs?

   Sobi's proposed positioning for anakinra is in the second line (before csDMARDs). The 'post-csDMARD' pathway in the model reflect the current use of anakinra in the third-line setting in NHS practice, which Sobi does not consider the most appropriate use of anakinra for sJIA or AOSD.

ERG comments (Q2)

The clarification provided by the company on their proposed positioning of anakinra will help focus NICE AC discussions.

3. The 'per-label' model pathway does not include DMARDs so that treatment with both anakinra and tocilizumab is offered after NSAIDs and corticosteroids. Please comment on whether this pathway would likely be realised in clinical practice as tocilizumab is currently commissioned by NHS England only after DMARDs.

   In current practice, patients are permitted to receive treatment with a bDMARD (i.e. anakinra or tocilizumab) after failing either one (sJIA patients) or two (AOSD patients) csDMARD(s). This expectation is based on the corresponding NHS Clinical Commissioning Policies for AOSD and JIA, and verified with clinical expert opinion provided to Sobi.

Use of tocilizumab in current NHS practice based on the JIA policy is based also on the NICE recommendation of tocilizumab in sJIA (NICE TA238).* Tocilizumab is not licensed for use in AOSD, and so no corresponding NICE guidance exists in this population. Therefore, all use of tocilizumab in AOSD is (by definition) 'off label' in NHS practice.

When preparing the submission, Sobi engaged with clinical experts concerning how the treatment pathway would change were anakinra used after NSAIDs + corticosteroids. Clinical advice provided to Sobi was that it is highly unlikely that treatment with a csDMARD (such as methotrexate) would be introduced following failure on a bDMARD (such as anakinra) – especially noting that anakinra is itself a DMARD. The licensed indications for both anakinra and tocilizumab do not preclude their use in a second-line (i.e. pre-csDMARD) setting. A minor revision to the current NHS policies for JIA and AOSD would therefore be required to align with the final NICE guidance, should anakinra be recommended in line with its licensed indication.

ERG comments (Q3)

The clarification provided by the company on their proposed positioning of anakinra, especially relative to tocilizumab, will help focus NICE AC discussions.

4. Please explain what evidence was used to assume clinical equivalence between anakinra and tocilizumab in the model.

    a. Is there any further evidence about the relative efficacy and side effect profiles of anakinra and tocilizumab?

    As discussed in the NHS Clinical Commissioning Policy for AOSD, there is only one available RCT in this population (Nordstrom *et al.*, 2012) which compares anakinra and csDMARDs. For sJIA, the NHS Clinical Commissioning Policy for JIA does not discuss the evidence base at great length, but notes that there are no comparative studies for tocilizumab and anakinra. There are no head-to-head RCTs comparing tocilizumab with anakinra in either an sJIA or AOSD population. However, the absence of head-to-head trials is not unusual in this field.

    It is important to reiterate that tocilizumab is not licensed for patients with AOSD, and so the available data concerning the efficacy and

* The NICE recommendation for tocilizumab states: *"Tocilizumab is recommended for the treatment of* [sJIA] *in children and young people aged 2 years and older whose disease has responded inadequately to* [NSAIDs]*, systemic corticosteroids and methotrexate if the manufacturer makes tocilizumab available with the discount agreed as part of the patient access scheme. Tocilizumab is not recommended for the treatment of* [sJIA] *in children and young people aged 2 years and older whose disease continues to respond to methotrexate or who have not been treated with methotrexate."*

safety of tocilizumab predominantly comprises of studies in exclusively sJIA populations. There are some studies concerning the use of tocilizumab in AOSD populations, but these are mainly case series. For context, tocilizumab was first licensed for use by the EMA approximately 7 years after the initial date of anakinra's marketing authorisation.

In the clarification call held between NICE and Sobi on 29 January, reference was made to a study by Riancho-Zarrabeitia *et al.*, (2015) comparing tocilizumab and anakinra in AOSD.[4] This is a comparative, though non-randomised, study of both treatments in a mixed population of patients according to treatment history. This study was not included within Sobi's systematic review as it is an abstract from the 2015 EULAR meeting (i.e. no full publication is available).

While only the abstract is available, Sobi notes that there are several limitations to this study. Prior treatments were not balanced between the groups (steroids, conventional immunosuppressants, and biologics). This means it is unclear if any comparisons between the groups are appropriate within the context of this appraisal, given that the groups represent different stages in the treatment pathway. In addition, the median disease duration was notably different between the groups, again reflecting different stages of the treatment pathway. Finally, a clinician's choice to use either anakinra or tocilizumab may be based on a number of factors – e.g. risk of MAS (as was noted in the Kearsley-Fleet *et al.* study which was discussed in Sobi's submission).[5]

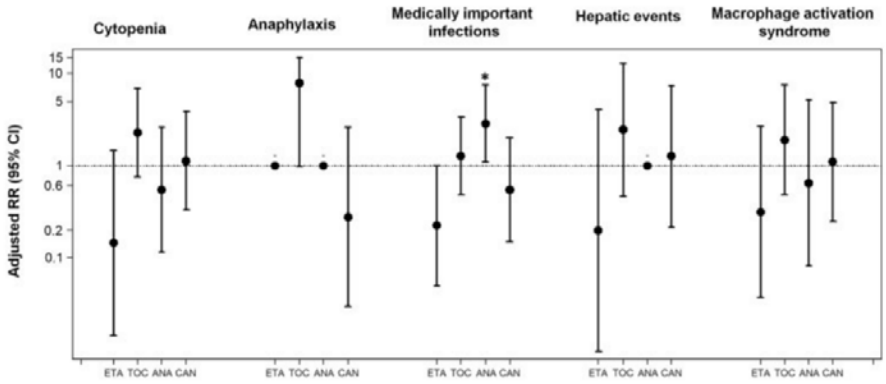
In the absence of robust comparative study data, clinical expert opinion was instead sought to establish the relative efficacy of anakinra and tocilizumab. Advice provided to both Sobi and the ERG was that anakinra and tocilizumab are considered to have similar efficacy in Still's disease. However, the decision to use one product over the other is usually based on a number of considerations (e.g. pharmacokinetics, route of administration, presentation of symptoms etc.).

With regards to relative safety, a recent study by Klein *et al.*, (2019) provides some information comparing outcomes for patients treated with anakinra and tocilizumab (as well as canakinumab and etanercept – treatments that are both used in Germany).[6] Importantly, this study is based on an analysis of registry data, and so should be interpreted with caution. Figure 1 is an excerpt from this study which shows adjusted relative risks for each biologic compared with the other three biologics. The adverse events included within this were determined by the study authors to be of special interest (which is discussed in further detail within the full publication).

The findings of this analysis showed (after adjustment for patient characteristics) that anakinra was associated with a statistically-significant increase in the risk of medically important infections. Tocilizumab was associated with a numerical increase in the risk of cytopenia, anaphylaxis, hepatic events, and MAS (though none of these differences were shown to be statistically significant).

Importantly, the relative risk values are based on a comparison to the other three treatments and not a comparison of anakinra versus tocilizumab. Based on interpretation of the confidence intervals in Figure 1, there is no conclusive evidence for a statistically significant difference in adverse events between anakinra and tocilizumab treated patients. However, there are numerical differences in the adjusted risk ratios. In addition, as this is an analysis of registry data, any findings should be interpreted with caution (given that it is unclear why specific treatments were selected for use in certain patients etc.).

Figure 1: Selected adverse events of special interest comparison of relative risk



Sobi highlighted within its submission all known evidence concerning the efficacy and safety of anakinra, including all possible comparative evidence to tocilizumab. Since Sobi's original submission, the study by Klein *et al.* was published (in December 2019), for which summary findings are provided above. However, other than this study, Sobi is unaware of any additional evidence that may provide additional information on the relative efficacy and safety of both treatments.

ERG comments (Q4 and Q4a)

The company's update on available evidence highlights the lack of robust evidence available for the comparison of anakinra versus tocilizumab in terms of efficacy and safety.

b. Could any further evidence be produced, for example a matching-adjusted indirect comparison (MAIC)?

A matching-adjusted indirect comparison (MAIC) is a statistical technique intended to 're-balance' patient characteristics in order to improve estimates of relative efficacy and/ or safety compared with a naïve (i.e. unadjusted) comparison. However, such methods do not adjust for differences in study design (e.g. differences in outcome measures, duration of follow-up, comparator therapies etc.) and rely upon a comparison of patients for which data are reported (i.e. at baseline).

A previously-published network meta-analysis (NMA) by Tarp *et al.*, (2016) is available, and was referenced within Sobi's original submission.[7] The analysis by Tarp *et al.* includes one trial for tocilizumab (TENDER) and one trial for anakinra (ANAJIS).[8,9] In TENDER, 'clinically inactive disease' which was achieved by 32% of the n=110 patients enrolled in the open-label extension phase (from 12 to 52 weeks). In ANAJIS, of the n=16 patients that reached month 12 of the open-label extension phase; n=5 had 'inactive disease' (31%).

An important limitation of the available data is that the patient characteristics of the population that were assessed for inactive disease is unknown for both studies (as this is not the same population of patients enrolled at baseline). This means that it is not possible to undertake a population-adjusted comparison of the outcome of inactive disease (the outcome of most relevance to current NHS practice).

While it may be possible to undertake a population-adjusted comparison of outcomes based on an intention-to-treat analysis (such as ACR Pedi30 or adverse events), such comparisons also rely on the availability of patient-level data for at least one of the studies. Sobi does not have access to patient-level data from the TENDER trial (which was funded by Hoffmann–La Roche). Sobi also does not have access to the ANAJIS patient-level data. Financial support for this study was provided by Amgen (the original holders of the marketing authorisation for anakinra), though Amgen had *"no role in the analysis and reporting phase of the study"*.

ERG comments (Q4b)

The ERG considers that, in light of the limitations of the available evidence base, the results of any further statistical analyses are unlikely to be robust.

5. Please explain why removing csDMARDs from the pathway (in the per-label pathway) leads to an increase in the proportion of patients having prolonged

remission compared with the post-csDMARDs pathway and comment on whether this is clinically plausible.

a. Would it be expected that disease that does not respond to csDMARDs or biologics when used sequentially, would respond to biologics if used in place of csDMARDs in the treatment pathway? If so, please provide evidence for the clinical plausibility of this.

Removing an ineffective treatment from the pathway increases the proportion of patients given effective therapy earlier, which increases the chance of remission. The two issues raised in this question will be discussed separately:

- The use of csDMARDs in Still's disease
- The "window of opportunity" hypothesis in Still's disease

While discussing the outcome of remission, it is important to note that the definition of remission is variable across different studies (as acknowledged within Sobi's submission). In practice, remission is generally referred to as an extended time period (normally of at least 6 months) wherein there is an absence of disease-related symptoms and systemic manifestations (e.g. raised inflammatory markers).[10,11] However, in older studies "remission" is sometimes used to describe short-term outcomes.

<u>The use of csDMARDs in Still's disease</u>

The efficacy of methotrexate is well established in adult rheumatology with remarkable success in improving clinical outcomes in RA. On this basis, Still's disease was historically treated with methotrexate with the expectation of similar efficacy (before it was understood to be an autoinflammatory rather than autoimmune disease). Its continued use in Still's disease reflects this tradition.

This hypothesis has been tested and the balance of clinical evidence does not support the efficacy of methotrexate in Still's disease. For the purpose of describing an overview of the clinical evidence base, Sobi has presented summary findings from a number of notable articles that discuss the role of methotrexate in Still's disease (presented below). Sobi highlights that this is not based on a systematic review of the literature.

(Please note: in reviewing clinical evidence for the efficacy of methotrexate in Still's disease, the reader should be aware of the tendency in earlier literature to document all JIA subtypes, rather than testing sJIA specifically).

Halle and Prieur (Clin Exp Rheumatol 1991)[12]

Thirty children with JIA, including ten patients with a systemic onset, refractory to slow-acting antirheumatic drugs (SAARDs) (hydroxychloroquine, chloroquine, penicillamine, the gold complexes and sulphasalazine) were treated with oral methotrexate (0.2 increasing to 0.8mg/kg/week) for 6-30 months.

Results that follow are for the ten participants in the systemic onset subgroup:

- Extraarticular symptoms improved subjectively in seven out of ten participants, with four subsequently relapsing
- Fever, present in 7 patients, improved in four and later reappeared in two participants
- Duration of morning stiffness increased, and number of active joints showed a non-significant trend to decrease
- ESR did not decrease
- Oral corticosteroids could not be stopped in any patients in the systemic-onset subgroup and NSAIDs had to be increased

The authors concluded that there existed a differential effect of methotrexate therapy according to subtype, with the systemic subtype less responsive to methotrexate than the antinuclear antibodies (ANA)-positive form and the polyarticular onset.

Speckmaier et al. (Clin Exp Rheumatol 1989)[13]

Twelve children with severe systemic juvenile chronic arthritis all requiring high dose corticosteroids were treated with methotrexate (8.5 mg/m^2) for six months.

- Marked clinical improvement was seen in four children (reduction in number of active joints, improvement in systemic features and haematological parameters), allowing a reduction in steroids in two participants
- In contrast, the disease activity deteriorated in two children and steroids were increased in a further three children.

The authors concluded that a third of children with severe systemic juvenile arthritis improved in six months in response to methotrexate.

Woo (Arthr & Rheum, 2000)[14]

This study was conducted in recognition of the underrepresentation of the systemic and extended oligoarthritis subgroups in the recent studies of methotrexate efficacy in various forms of juvenile polyarthritis.

n=45 and n=43 patients meeting the ILAR criteria for sJIA and extended oligoarticular arthritis respectively were enrolled in a double-blind placebo-controlled cross-over trial of methotrexate given at 15-20mg/m^2.

Results described here will be limited to those of the sJIA group:

- Only two of five core variables (physician's and parent's global assessment of disease activity) improved significantly†
- The systemic features of the disease were not significantly different between methotrexate and placebo treatment
- There was no significant difference between methotrexate and placebo in the joint range of motion for participants who had complete records of joint range for both treatment periods
- Combining both subgroups showed no significant difference between placebo and methotrexate in the number of active joints and there was no difference in treatment effect between subgroups
- CRP and ESR decreased significantly from baseline in both subgroups, however when compared to placebo, the sJIA subgroup showed no significant reduction in these inflammatory markers
- None were able to reduce steroid use by more than 5mg/day
- Six patients withdrew from the study because of unremitting disease, with only two of these during the placebo period

Nordström (J Rheumatol, 2012)[16]

As described in Sobi's submission, this study was conducted in 22 patients with AOSD taking prednisolone ≥10 mg/day. Patients were randomised to receive either anakinra (n=12) or csDMARD (n=10), in addition to corticosteroids.

In the csDMARD group, n=6 patients received methotrexate, n=3 received azathioprine, and n=1 received leflunomide.

The primary endpoint was remission according to specific criteria at 8 weeks [afebrile (≤ 37°C body temperature, measured twice from armpit), in the absence of NSAIDs 24 hours prior to measurement, decrease of CRP and ferritin to reference limits] and normal swollen (SJC) and tender joint counts (TJC).

The results described below relate to the csDMARD group:

† The core variables refer to the variables and criteria for improvement proposed by Giannini *et al*.[15]

- In remission at Weeks 4, 8, and 24 were 3/10, 5/10, and 2/10 patients treated with csDMARD + corticosteroids
- No patients treated with csDMARD were able to discontinue oral corticosteroids
- In the open-label extension (OLE) phase, n=8 of the csDMARD patient continued until Week 52
    - Only n=3 patients originally on csDMARD (2 on methotrexate and 1 on azathioprine) remained on the same medication at Week 52
    - Among the remaining n=5 patients, 2 had switched to methotrexate and anakinra, 1 to leflunomide and anakinra, 1 to anakinra monotherapy, and 1 to infliximab
    - During the OLE half of the patients randomised to csDMARD had a disease flare
    - Numerically higher responder rate was observed in the anakinra group, at week 52, 6 patients (50%) were in remission, as compared to 3 patients (30%) of the csDMARD group

Please note: remission in this study was defined as early as after 4 weeks of treatment. Modern studies in Still's disease define remission after a minimum of at least 6 months of treatment.[10,11]

The "window of opportunity" hypothesis in Still's disease

Approximately half of patients have a chronic persistent arthritis requiring extended therapy, sometimes into adulthood. In these patients, growth failure, radiographically evident joint injury, and long-term disability have historically been very common.[17] Noting differential clinical outcomes when IL-1 blockade is initiated later in the disease course, Nigrovic, 2014 proposed a biphasic model of sJIA.[17] In this model, early sJIA is driven by innate immune mechanisms, while chronic arthritis is mediated, at least in part, by autoreactive T cells. They therefore proposed that a "window of opportunity" would exist in which the progression of disease pathophysiology might be altered to avoid chronic arthritis.

This hypothesis was tested in a single centre in the Netherlands (initially reported by Vastert *et al.*, 2014 and later by ter Haar *et al.*, 2019).[18,19] Between 2008 and 2017, the investigators enrolled 51 patients with new-onset sJIA to be treated in a treat-to-target strategy and subsequent drug-tapering strategy. Patients with fever unresponsive to 7 days of NSAID therapy were initiated on anakinra at

2mg/kg/day. If fever was still present after 3 days this was escalated to 4mg/kg/day. If clinically inactive disease was not obtained, anakinra was switched to an alternative therapy with or without glucocorticoids. Once clinically inactive disease was attained, a tapering strategy was initiated, targeting maintenance of drug free remission. 42 patients were followed up for a median of 5.8 years. At 1 year, 76% had clinically inactive disease and 52% had clinically inactive disease off medication. At 5 years follow-up, 95% of included patients had clinically inactive disease and 72% had inactive disease off medication.

This study validated the “window of opportunity” hypothesis by showing rapid and sustained inactive disease in the majority of sJIA patients and reduced glucocorticoid use.

In addition to the study conducted in the Netherlands, Pardeo *et al.*, (2019) recently documented findings of early treatment with anakinra in sJIA in the Italian setting.[20] In this study, the investigators assessed n=57 patients treated with anakinra to establish whether the response to anakinra was related to baseline variables. n=30 (52.6%) of the patients received anakinra within 2 months from disease onset. At 6 months after beginning of anakinra treatment, 28/30 patients (93.3%) who started anakinra within 2 months from disease onset and 12/27 (44.4%) who started anakinra after 2 months from disease onset reached clinical inactive disease off glucocorticoids (p=0.0001). Patients who started anakinra after the first 2 months from disease onset had a significantly higher risk of non-response (odds ratio [OR] 8.06, 95% confidence intervals: 2.03-32.0).

This study provides further evidence of the “window of opportunity” hypothesis, illustrating the clinical plausibility of improved patient outcomes gained by enabling earlier IL-1 inhibition.

The descriptions provided above concerning the sequential use of csDMARDs (such as methotrexate) and bDMARD and the “window of opportunity” in Still’s disease are separate, yet related points. The use of ineffective treatment with csDMARDs reduces the “window of opportunity” through delayed initiation of anakinra, as patients are expected to derive the most benefit with anakinra via its inhibition of IL-1 early in the disease process.

ERG comments (Q5 &Q5a)

In response to NICE's question, the company has provided their rationale for positioning anakinra before, rather than after, csDMARDs. The company's argument is that (i) csDMARDs are not effective and (ii) treatment with bDMARDs is more effective if used before, rather than after, csDMARDs.

(i) <u>The company case that csDMARDs are not effective</u>

The ERG considers that the evidence presented by the company does not support their assertion that csDMARDs are not effective, rather, it demonstrates that csDMARDs are effective for some patients.

In the CS, and in this clarification response, the company has provided evidence from the Nordström study to demonstrate the effectiveness of csDMARDs after failure of treatment with NSAIDs. Over and above concerns relating to the small size of the Nordström study population (10 patients received csDMARDs and 12 patients received bDMARDs), there are two major issues that make results from the Nordstrom study unfit for this purpose. First, the Nordström study compared the effectiveness of csDMARDs versus bDMARDs in patients who were refractory to csDMARDs. As the population was refractory to csDMARDs, the evidence provided by this study does not inform the effectiveness of csDMARDs, or that of bDMARDs, as a first treatment following failure of NSAIDs. Second, 30% of patients in the csDMARDS arm of the Nördstom study were in remission at 12 months; this does not support the company position that csDMARDs are ineffective.

(ii) <u>bDMARDs are more effective in a second-line setting</u>

The company has considered two possible treatment strategies:

a) NSAIDS -> csDMARDs -> bDMARDs (company post-csDMARD scenario)

b) NSAIDS -> bDMARDs (company per-label scenario)

However, the company has not provided robust comparative evidence to support either positioning of bDMARDs.

In their economic model, the company assumed that remission rates for patients treated with bDMARDs differed depending on where bDMARDs were positioned in the treatment pathway. The assumption was that patients who received bDMARDs after csDMARDs had lower remission rates than patients who received bDMARDs after NSAIDs. However, the ERG considers that the evidence used to support this assumption was derived from a flawed and misleading analysis of published remission rates.

When modelling treatment strategy (a), the company used remission rates derived from the Nordström study. Results from the Nordström study showed that the remission rate at 24 weeks was 50%. This result was used to calculate the model weekly probability of remission (2.85%). When populating treatment strategy (b),

the company used a remission rate result from the Horneff study (44.4% at 12 weeks) to estimate a model weekly remission rate of 4.41%. This approach to estimating weekly remission rates ignores the fact that the Nordström study reported the same remission rate at 4 weeks and at 24 weeks, and a higher remission rate at 8 weeks (58%). It is unclear why the company chose the 24-week result as the basis for their weekly remission rate estimate.

Number and proportion of patients achieving remission

Weeks	Nordström study					Horneff study	
	Anakinra (N=12)		csDMARD (N=10)		Weekly rate ratio	Anakinra (n=9)	
	n (%)	Weekly rate	n (%)	Weekly rate		n	Weekly rate
4	6 (50.0%)	15.91%	3 (30.0%)	8.53%	1.87	-	-
8	7 (58.3%)	10.37%	5 (50.0%)	8.30%	1.25	-	-
12	-	-	-	-	-	4 (44.4%)	4.41%
24	6 (50.0%)	2.85%	2 (20.0%)	0.93%	3.08	-	-

Further, it is not valid to compare a weekly remission rate based on a 24-week result from one study (Nordström study) with a weekly remission rate based on a 12-week result from another study (Horneff study). It is also misleading to suggest that, compared with effectiveness when bDMARDs are used in treatment strategy (a), the Horneff study results support a higher remission rate when bDMARDs are used as part of treatment strategy (b).

Given that there is no published evidence to demonstrate differential effectiveness of bDMARDs depending on their position in the treatment pathway, the company model should not have been populated with values suggesting differential effectiveness.

6. The ERG highlighted that within the model, treatment switching is set at a fixed probability per weekly cycle for patients who have not achieved remission. Please provide scenario analyses where this probability is varied.

   In the model submitted by Sobi, treatment switching (and/or "adding") in the model is informed by a fixed (i.e. time-invariant) probability per weekly cycle. This assumption was also made in the previous NICE assessment of tocilizumab in sJIA (TA238), and it is this previous appraisal from which the values used for initial bDMARDs within the model were taken.

   There are limited data to inform treatment discontinuation for patients with Still's disease, and so the assumption of a static probability was made for simplicity. In reality, the proportion of patients expected to discontinue treatment at each point in time may differ, based on a combination of the following:

   - Patients initiating a treatment may have a different probability of discontinuing treatment compared to those that have been receiving

treatment for a longer time – for example, patients would be expected to remain on treatment until an assessment of response is established

- Patients that have experienced disease recurrence (i.e. are no longer in remission) are expected to be treated in order to re-induce remission. If considered an immediate failure, patients may promptly discontinue treatment
- Patients that have experienced difficulty in managing symptoms, as well as those that have a history of previous complications (e.g. MAS), may be less likely to discontinue treatment compared with those that have experienced relatively mild symptoms

Given that the model adopts a Markovian approach to inform transitions between health states, it is not possible to identify this precise mix of patients at any given point in time. Therefore, any implementation of time-varying probabilities for discontinuation is highly uncertain, and should be interpreted with caution. Sobi does however appreciate that scenario analysis exploring time-varying probability of treatment discontinuation may be helpful to consider, and so has undertaken an exploratory analysis for this within the submitted economic model.

To account for a time-varying probability of discontinuation, Sobi has updated the model to include two different sets of transition matrices. The model will consider probabilities from one set of matrices up until a given model cycle, after which transitions are informed from the other set of matrices. In the second set of transition matrices, all probabilities are set to be the same as the first set of matrices, except for the probability of discontinuation (and by extension, the probability of remaining in a given health state, as this is calculated as one minus the sum of all other probabilities). For discontinuation, the model now allows for the user to specify a probability multiplier to explore either an increased or decreased risk of treatment discontinuation after a given point in time.

Due to the numbers of calculations required to estimation health state occupancy within the model, the switch between the matrices may be varied at any model cycle up until 1 year. This structural limitation was made to ensure the model can still be run within a reasonable timeframe, yet could be overridden by simply replicating the formulae on the ‘Transitions’ sheet further down the sheet, and amending the data validation on the input cell on the ‘ClarQ’ sheet.

Sobi notes that this analysis should be considered exploratory, as an immediate change in the probability of discontinuation at a given point in time is unlikely to accurately reflect clinical practice.

Implementation of a time-varying probability of discontinuation within a cohort-level model is highly complex, and were sufficient data available to inform such

a model parameter, an alternative model structure (e.g. a multi-state modelling or discrete event simulation approach) may have been possible to consider. Tunnel states are also not possible to consider within the model, as the model would theoretically need to be able to capture patients entering and leaving different tunnel states at every model cycle (in order to capture the possible routes through the treatment cascade, including remission and recurrence).

Using the proposed approach, Sobi has opted to implement one time point at which the probability of discontinuation is changed. Theoretically, the model could be extended to include a separate set of matrices for each model cycle. However, it is unclear how probabilities to inform these matrices could be feasibly established. Therefore, while Sobi accepts the approach is limited, Sobi considers specification of further model complexity to be unsubstantiated with available evidence and so restricting the analysis as described above is expected to be the most informative approach for decision making.

Sobi has provided results based on the following scenarios using the time-varying discontinuation approach:

- Increase discontinuation for all treatments by 20% after 6 months
- Increase discontinuation for only bDMARDs by 20% after 6 months
- Increase discontinuation for all treatments by 20% after 12 months
- Increase discontinuation for only bDMARDs by 20% after 12 months
- Decrease discontinuation for all treatments by 20% after 6 months
- Decrease discontinuation for only bDMARDs by 20% after 6 months
- Decrease discontinuation for all treatments by 20% after 12 months
- Decrease discontinuation for only bDMARDs by 20% after 12 months

However, should the ERG wish to explore alternative scenarios, the model allows for the specification of the time point and multipliers on the “ClarQ” sheet. The results of the sensitivity analysis (compared with the base-case analysis) are provided in Table 1.

Table 1: Scenario analyses (time-varying discontinuation)

Arm	Total			Incremental			INMB (£), vs.	
	Costs (£)	QALYs	LYs	Costs (£)	QALYs	LYs	1)	2)
Base-case analysis								
1) No anakinra	258,107	11.304	28.202					
2) Post-csDMARD	224,343	11.657	28.509	-33,764	0.353	0.307	40,817	
3) Per-label	201,317	11.970	28.774	-23,026	0.313	0.265	70,102	29,285
Scenario #1 – Increase discontinuation for all treatments by 20% at 6 months								
1) No anakinra	268,365	11.213	28.120					
2) Post-csDMARD	236,869	11.549	28.415	-31,496	0.336	0.295	38,223	
3) Per-label	212,856	11.872	28.690	-24,013	0.322	0.275	68,681	30,458
Scenario #2 – Increase discontinuation for only biologic DMARDs by 20% at 6 months								
1) No anakinra	265,949	11.230	28.136					
2) Post-csDMARD	234,678	11.563	28.427	-31,271	0.333	0.291	37,936	
3) Per-label	211,033	11.883	28.700	-23,645	0.320	0.273	67,974	30,038
Scenario #3 – Increase discontinuation for all treatments by 20% at 12 months								
1) No anakinra	266,883	11.229	28.133					
2) Post-csDMARD	235,445	11.564	28.427	-31,438	0.335	0.294	38,146	
3) Per-label	211,892	11.882	28.699	-23,554	0.318	0.271	68,050	29,904
Scenario #4 – Increase discontinuation for only biologic DMARDs by 20% at 12 months								
1) No anakinra	264,679	11.244	28.147					
2) Post-csDMARD	233,452	11.577	28.438	-31,227	0.333	0.291	37,879	
3) Per-label	210,224	11.892	28.707	-23,227	0.315	0.269	67,409	29,530
Scenario #5 – Decrease discontinuation for all treatments by 20% at 6 months								
1) No anakinra	244,916	11.418	28.302					
2) Post-csDMARD	208,982	11.784	28.619	-35,935	0.366	0.317	43,256	
3) Per-label	187,919	12.080	28.867	-21,063	0.296	0.248	70,244	26,989
Scenario #6 – Decrease discontinuation for only biologic DMARDs by 20% at 6 months								
1) No anakinra	248,086	11.397	28.284					
2) Post-csDMARD	211,700	11.768	28.606	-36,386	0.371	0.322	43,812	
3) Per-label	190,117	12.068	28.857	-21,583	0.300	0.251	71,390	27,577
Scenario #7 – Decrease discontinuation for all treatments by 20% at 12 months								
1) No anakinra	246,777	11.398	28.286					
2) Post-csDMARD	210,672	11.767	28.605	-36,104	0.368	0.319	43,473	
3) Per-label	189,030	12.069	28.858	-21,643	0.302	0.253	71,156	27,682
Scenario #8 – Decrease discontinuation for only biologic DMARDs by 20% at 12 months								
1) No anakinra	249,660	11.380	28.270					
2) Post-csDMARD	213,136	11.753	28.593	-36,524	0.373	0.324	43,988	
3) Per-label	191,034	12.058	28.849	-22,102	0.305	0.256	72,192	28,205

Key: csDMARD, conventional-synthetic disease-modifying anti-rheumatic drug; ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; LY, life year; QALY, quality-adjusted life year.

Note: These results take into account the assumed commercially-sensitive simple patient access scheme discount for tocilizumab ([redacted]). INMB calculated assuming a willingness-to-pay threshold of £20,000 per QALY gained.

The scenario analysis yielding the largest total QALYs (and smallest total costs) for each strategy is Scenario #5 (where the probability of discontinuation was

decreased for all treatments by 20% at 6 months). This scenario reflects the analysis wherein treatment is continued for the longest possible time period, during which the probability to achieve remission across all strategies (and thus avoid unresolved disease) is maximised. This scenario yields the lowest INMB for 'per-label' versus 'post-csDMARD'.

However, the lowest INMB for 'per-label' versus 'no anakinra' is for Scenario #4 (where the probability of discontinuation was increased for only bDMARDs by 20% at 12 months). This scenario greatly affects the possibility of achieving remission with bDMARDs, while leaving all other settings the same. By reducing the duration over which patients may achieve remission with bDMARDs, this scenario reduces the QALY gain for the 'per-label' scenario, resulting in a lower INMB estimate.

The scenario with the largest total costs (and smallest total QALYs) for each strategy is Scenario #1 (where the probability of discontinuation was increased for all treatments by 20% at 6 months). In this scenario, all treatments are discontinued more quickly, and so a larger proportion of patients will have unresolved disease, increased medical resource costs, and poorer health-related quality of life. The estimate of the INMB for 'per-label' versus 'post-csDMARD' is the largest of all scenarios (due to greater cost savings through avoided unresolved disease).

The largest INMB for 'per-label' versus 'no anakinra' is shown in Scenario #8 (where the probability of discontinuation was decreased for only biologic DMARDs by 20% at 12 months). This scenario is associated with the largest differential in terms of capacity to induce remission between these states of the world.

Sobi highlights again that these results should be considered as exploratory, and so Sobi's preference remains for the use of a statistic probability in the absence of any other data to inform time-varying discontinuation. In general, however, the conclusion of the model was unchanged through these exploratory sensitivity analyses.

ERG comments (Q6)

The ERG agrees with the company that presented analyses should only be considered as exploratory. The company has presented no evidence to demonstrate that any scenario, including the company base case, is more realistic than any other scenario.

7. The ERG considers it implausible that the probability of achieving remission with csDMARDs for people with chronic disease is 0. Please provide scenario analyses where this probability is varied.

Clinical expert advice provided to Sobi indicated that it is not possible to induce remission through the use of csDMARDs in patients with chronic disease course. Further information concerning the efficacy of csDMARDs in Still's disease is provided in response to Question 5.

While contradictory to clinical opinion provided to Sobi, the model has been edited to allow for the specification of a non-zero probability for achieving remission with csDMARDs. The results of this scenario analysis are presented in Table 2, where the probability of achieving remission with csDMARDs has been set equal to the value applied for patients with monocyclic disease course. The 'per-label' results are identical to the base-case analysis (given that in this state of the world, csDMARDs are not used). However, for the other two states of the world, the total costs are reduced and the total QALYs are increased (due to an increase in the proportion of patients that achieve remission, and thus avoid unresolved disease).

Table 2: Scenario analyses (remission with csDMARDs)

Arm	Total			Incremental			INMB (£), vs.	
	Costs (£)	QALYs	LYs	Costs (£)	QALYs	LYs	1)	2)
Base-case analysis								
1) No anakinra	258,107	11.304	28.202					
2) Post-csDMARD	224,343	11.657	28.509	-33,764	0.353	0.307	40,817	
3) Per-label	201,317	11.970	28.774	-23,026	0.313	0.265	70,102	29,285
Scenario #9 – Probability of remission for chronic course patients same as monocyclic patients								
1) No anakinra	255,574	11.326	28.222					
2) Post-csDMARD	222,021	11.675	28.526	-33,553	0.349	0.303	40,533	
3) Per-label	201,317	11.970	28.774	-20,704	0.295	0.249	67,144	26,611

Key: csDMARD, conventional-synthetic disease-modifying anti-rheumatic drug; ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; LY, life year; QALY, quality-adjusted life year.

Note: These results take into account the assumed commercially-sensitive simple patient access scheme discount for tocilizumab ([redacted]). INMB calculated assuming a willingness-to-pay threshold of £20,000 per QALY gained.

ERG comments (Q7)

The remission rates for people receiving csDMARDs that have been used in the company analyses are based on results from the Nordström study. As explained in the ERG response to Q5, the Nordström study recruited patients who were refractory to csDMARDs and hence results from that study cannot be used to demonstrate the effectiveness of csDMARDs, or bDMARDs, as second line treatments. As such, the analyses presented by the company in response to Q7 are populated by misleading data.

8. Please provide scenario analyses where the time horizon is increased above 30 years.

In the previous NICE TA238 of tocilizumab in sJIA, the model time horizon was capped at 16 years in the company's submission, which the ERG restricted to 11 years in its preferred base-case analysis (i.e. the only differences in costs/effects captured by the model were those incurred/accrued during childhood and adolescence). A diagnosis of sJIA is expected to continue into adulthood. As such, Sobi sought to provide a model with a time horizon that was sufficiently long to capture important differences in costs and effects, regardless of when patients are classified as adults.

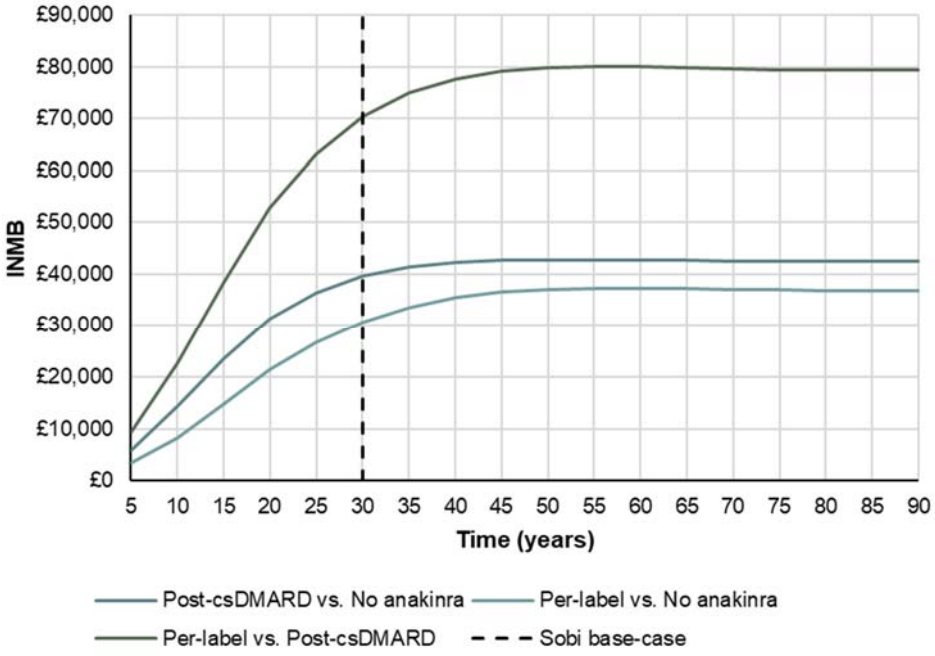
However, owing to the need to construct a model that captures the full treatment pathway (accounting for three possible 'states of the world' and alternative subgroups/ disease courses), there was a need to trade-off the computational burden of the model calculations, with the period over which important costs and effects were expected to be present. Consequently, the model time horizon was set to 30 years.

The choice of 30 years was made only in the interest of ensuring model run time was as short as possible, while also ensuring the majority of important differences in costs and effects were captured by the model. Nevertheless, Sobi understands that a longer time horizon is necessary to capture the full differences in costs and effects.

To provide scenario analyses with a longer time horizon, Sobi has edited the economic model to extend the model calculations up until a time horizon of 90 years. By the time the average age of the sJIA reaches 87 years, the estimated cumulative hazard of death has exceeded 1 (based on life table mortality data, which were adjusted to account for the weekly model cycle length), and as such all patients are modelled to have died within a 90-year time horizon, regardless of starting age.

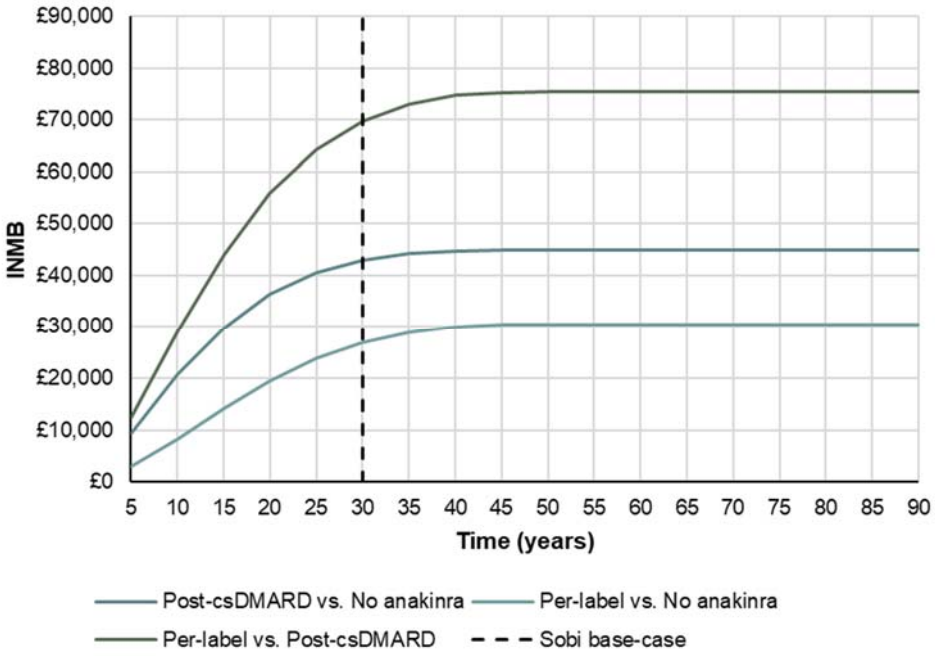
Using the base-case model settings and assumptions per Sobi's original submission, the relationship between the increment net monetary benefit (INMB) and the model time horizon may be established. Results for the sJIA and AOSD populations are presented in Figure 2 and Figure 3, respectively.

Figure 2: Relationship between INMB and time horizon, sJIA population (company base-case settings)



Key: csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; INMB, incremental net monetary benefit; sJIA, systemic juvenile idiopathic arthritis.

Figure 3: Relationship between INMB and time horizon, AOSD population (company base-case settings)



Key: AOSD, adult-onset Still's disease; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; INMB, incremental net monetary benefit.

As can be seen from the plots, there is relatively little to gain from extending the model time horizon from around 50 years in the sJIA population, or from around

40 years in the AOSD population. The plots demonstrate that the model results based on a time horizon of 30 years (per Sobi's original submission) are arguably conservative, as some additional costs and effects were omitted after this time, which led to improved estimates of cost effectiveness. However, the overall conclusion remains unchanged, and by 30 years the majority of the differences in costs and effects are established (as may be inferred through the relatively small changes in the curves after 30 years).

ERG comments (Q8)

The ERG agrees with the company view that a time horizon of 30 years is sufficiently long to reflect differences in costs or outcomes between the technologies being compared.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Anakinra for treating active Stills disease [ID1463]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Rare Autoinflammatory Conditions Community – UK (RACC-UK)
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	**Rare Autoinflammatory Conditions Community - UK (RACC-UK)** RACC - UK is the UK's patient-run, patient charity for patients and families suffering from **#Rare** Autoinflammatory conditions. We are a completely self-funded organisation, led by volunteer patients, parents, and experienced Medical Professionals, in the fields of Rheumatology, Immunology and Nephrology. We also have several closed private Facebook discussion groups with over 400 members from the UK suffering from **#Rare** Autoinflammatory conditions. **In addition, RACC - UK, are RIPAG members of the European Reference Network, Rare Primary Immunodeficiency, Autoinflammatory and Autoimmune (RITA) diseases. Also, we are involved in the EURORDIS Drug Force Task, DITA (2019-2020)** **We are registered stakeholders for NHS Clinical Reference Groups relevant to Autoinflammatory conditions.** **Background** Patients in the UK with Autoinflammatory conditions have often endured a long delay to diagnosis which impacts on long-term health and quality of life. Autoinflammatory conditions are **#Rare** genetic diseases which often leave patients feeling vulnerable and isolated with little support.
4b. Do you have any direct or indirect links with, or funding	NO

from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	Mainly through asking questions in our social media forums and our website forum. We also liaised with international patient organisations that may have contact with UK patients who may not have found us. Where some patients wanted to remain anonymous and for their information to be shared privately, they were able to email us with specific information they felt was relevant to this appraisal.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	*Manifestations:* • Splenomegaly • Lymphadenopathy • Swollen Glands, groin, neck and under arm • Painful areas, tender to touch • Anaemia • Causing tiredness and breathlessness. Usually combined with high inflammatory levels and low neutrophils. • Extremely high/ raised CRP levels (inflammation), symptomatic of auto inflammatory activities, leading to chronic inflammation of internal organs, bones/ joints, muscles etc... • Recurrent Pyrexia

	• Frequent use of paracetamol is required. • Sometimes during a fever, the bedding must be stripped and washed due to sweating. • Hepatomegaly (enlarged liver) • Abdominal adhesions and Irritable Bowel with stomach pains, sharp stabbing pains, cramps, constipation, diarrhoea, nausea and sickness • Has often resulted in hospital admissions throughout their life. Some patients have reported they have required surgery. • Recurrent severe infections requiring use of antibiotics. (Middle Ear, Chest (often increased use of inhalers as well as antibiotics), Throat, Nose, UTI, Skin • Frequent Issues/ Disabilities and how affected: • Joint Swelling (knees, ankles, wrists, fingers, elbows, shoulders). Due to joint swelling, personal care tasks often restricted. Patients rely on friends or family nearby for support with: • Bathing- Brushing Hair, Cleaning Teeth, getting in and out of the bath. • Cooking and preparing meals can be very difficult. Friends and family sometimes prepare meals. • Ironing – often impossible • Cleaning the house – often impossible • Food shopping - is either done online, with a friend or friends/ family will collect it • Rashes on arms and legs can be very severe, hot and itchy. • Fatigue can be a symptom as well because of other symptoms, necessitating prolonged bed

rest, making self-care difficult.

- Ulcers, genital and mouth can be extremely painful making it difficult to eat, and often impossible to get comfortable
- With these symptoms, mobility is restricted, requiring bed rest due to severe fatigue, pain and discomfort. Patients also try and avoid dirty and crowded environments due to risk of infections.

Mobility Aids Used:

1. Wheelchair
2. Electric Scooter for home and being in the village
3. Crutches
4. Bath/ Shower seat
5. Handrails in bath/ shower
6. Wrist and arm supports
7. Hot water dispenser rather than a kettle
8. Electric can opener rather than manual
9. Bed Pillow Support Frame
10. Bed table
11. Lightweight Pans
12. Some patients require lever taps in kitchen and bathroom, as well as a step into the bath

- *"On a good day, using a pencil/ pen is ok but I cannot use them for an extended period due to pain, and will require rests in between use. I can use a keyboard or mouse when fingers, elbows, wrists*

	are wrists are swollen but typing maybe much slower. Sometimes I will need to rest from using a mouse if my wrists and elbows are swollen due to throbbing pain and discomfort." • *"When elbows or shoulder are swollen, I cannot bend to reach the top of the pocket of a coat or jacket whilst wearing it. I can't fasten zips or reach top buttons either. When elbows are swollen, I can raise arms above head however I cannot bend elbows to touch my head. I cannot hold them above my head for long without them aching or throbbing. When shoulders are seized up, I cannot move arms above my head due to severe throbbing and discomfort. This probably affects me most days. Friends and family do help to dress and undress at times."* • *"Meeting with known people such as friends or family in a public place is not a problem as long as I have all of my relevant pain relief with me; this stops me feeling anxious about being in so much pain and discomfort when I am out. Meeting medical professionals for appointments, especially if they are new causes me to feel anxious as I know I have to explain my condition and I always worry that I will forget to discuss important information or concerns. When possible, I will get a friend or family member to accompany me to my appointment. Sometimes going somewhere that I am not familiar with does cause anxiety because of fear of being ill, and/or managing the physical problems I am dealing with at the time. I get frustrated and sometimes angry when I can't do things for myself. I find it difficult to ask others for help as I feel like a burden. When angry, I often shout at friends or family members that are close to me and thus it affects my relationships with them. I also verbally lash out at friends when I feel isolated as I feel that they are not being supportive or understanding. Although this may not be the case, my relationships again are affected by how I feel about my health."* • *"Debilitating and depressing - I have lost my career and most of my hobbies. I can't work or do most of the things I used to. I can't exercise or socialise."* • *"Knee and/or ankle swelling. I often use crutches or a manual wheelchair when I cannot walk at all due to severe pain, inflammation and muscle tension.*

	• *Frequent Infections - especially chest and throat make it difficult to be active at all due to tiredness and/or breathlessness and/or concurrent symptoms such as nausea and /or diarrhoea. When affected, being mobile is very difficult as I get out of breath even after a few steps.* • *Anaemia – leaves me tired and breathless, meaning I often need to stop many time's and rest within 100m.* • *Irritable bowel/ adhesions - can leave me in excruciating pain, doubled over in posture and requires frequent pain relief. This usually requires a lot of bed rest.* • *Knee and ankle swelling – Sometimes I cannot manage any steps, on other occasions I use one crutch and a hand rail to go up and down two steps* • *Infections – I may be too unwell to use steps at all, but sometimes I can, although may need to stop after 2 steps to catch my breath and take my inhaler due to tiredness and breathlessness.* • *Anaemia- I sometimes may need to stop after 2 steps to catch my breath and due to tiredness.* • *Where possible, I avoid going places with steps and I use a lift. I also live on a ground floor flat with no steps to access via communal areas.* • *Arms or shoulders- in addition to the above, I often cannot use handrails to get me up and down the stairs due to pain and inflammation.* • *During a flare of knees and ankles, I cannot move from one seat to another right next to it without the help from someone else due to inflammation and pain.* • *During a flare I cannot stand without the help of another person and be pain free in my knees, ankles, lower back and hips.* • *Sitting- During a flare, I cannot sit without the help of another person and be pain free in my knees, ankles, lower back, hips, arms, shoulders.*

	• *When elbows or shoulder are swollen, I cannot bend to reach the top of the pocket of a coat or jacket whilst wearing it. I can't fasten zips or reach top buttons either.* • *When elbows are swollen, I can raise arms above head however I cannot bend elbows to touch my head. I cannot hold them above my head for long without them aching or throbbing.* • *When shoulders are seized up, I cannot move arms above my head due to severe inflammation. This probably affect me most days.* • *When hands, wrists, shoulders are swollen, gripping and lifting such items as a half- litre carton is difficult due to inflammation, restricted movement and pain."* • Some patients have also commented on that they feel isolated living with this condition and since being able to link up with other patients via the charity or other online forums, they haven't felt as alone. Some patients would like to have opportunities to meet patients face to face away from a hospital environment. Carers have reported that they sometimes feel at a loss to know what to do to help as the fatigue and pain can be terrible. They would have to cook and clean for the patient, as well as deal with their grief, depression and frustration. Carers may also take time off work to attend appointments with patients and therefore can experience a financial strain.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Patients often go through a trial and error of various diagnosis and treatments before they are accurately diagnosed and able to receive sufficient treatment. For example, Patients may be tested for routine Autoimmune conditions such as Rheumatoid Arthritis, Crohn's Disease with Colitis. Patients will often try treatments such as Methotrexate, Leflunomide, NSAIDS before receiving Anakinra. Patients wish for an earlier diagnosis and wish that Anakinra was made available to them much sooner.

	"Initially I really struggled; I am severely needle phobic so a treatment involving injections daily is my worst case scenario. For blood tests I take Diazepam just to get me in the waiting room! The first month or so of daily injections involved lots of fainting; slowly I'm adjusting to this. I can now do them by myself, and sit on a chair rather than part lying down – smashing it! Sometimes I struggle pushing the syringe down in me and need help from someone, I do have quite shaky hands however I wonder if this is difficult for people whose dexterity is reduced".
8. Is there an unmet need for patients with this condition?	Although patients have reported a significant improvement in their quality of life, some still experience symptoms. Sometimes that may mean the dosage of treatment needs to be increased. Whilst patients are aware that Anakinra is not a cure for the condition, some patients do wish to be less symptomatic. The other difficulty is that every patient is different so what may work for one patient, may not work for the other.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The majority of patients are satisfied or more than satisfied with Anakinra and have seen an improvement in their quality of life. They understand that Anakinra is not a cure though. Some patients have also reported that they have decreased their use of NSAIDS and opioids since starting Anakinra. *"Since starting Anakinra it has been a huge upheaval to re-learn certain mental patterns and coping mechanisms that I had put in place. Learning to listen to my body, rather than believing my body is "out to get me and trap me in misery" has been a big journey. Partner / family and I are so happy the treatment is available with the NHS; it definitely feels an essential treatment to me"* This patient reported that they accessed Mental Health support services to help them overcome their fears and manage their lifestyle differently to before, undergoing Cognitive Behavioural Therapy. They reported that they felt access to such services was more accessible once they had a diagnosis and started their treatment. *"Improved quality of life. Reduction of need for benefits [Financial / State] support. Reduction of reliance on painkillers"* This patient was able to return to work, and is now living a better quality of life in retirement.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Access to getting the medication to be delivered at home only rather than travelling to collect their next stock which requires travel cool bags / portable fridges. *"The biggest impact since starting Anakinra has been the need to refrigerate them. Slightly unimportantly 6 months' worth takes up a lot of fridge space! We've considered an extra fridge but there's a cost to the electricity (we've just bought a fixer-upper, money's tight!)."* 1) Patients would prefer the drug via an epipen type injection rather than the current subcutaneous needle and syringe. The current subcutaneous injection is painful, with a long needle. This puts some patients with needle phobias at a disadvantage and causes patients anxiety when injecting. 2) *"The biggest change has been that normally when I was feeling healthy I would go camping or on camping/hiking trips, I really like to be as rural as possible for as much time as possible. Obviously this isn't possible, so we can't holiday like we used to, and instead need to camp in our van, with an electric hook up facility. It feels silly to complain though when the improvement to my quality of life has been so huge."* 3) Acceptance, support and understanding from family and friends for needing to self-inject, particularly where the patient has experienced adult onset of symptoms.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Due to the complexity of the conditions, a diagnosis often takes a long time. Therefore many children may not receive the treatment until later childhood. Parents have reported that they are anxious about a late diagnosis as they don't know what damage has been caused before treatment. Some patients, with a range of ages, may not receive the treatment until other options have been exhausted, such as NSAIDS or DMARDS. This may also depend on who is overseeing patient care, their understanding of Autoinflammatory conditions and the knowledge of treatments available. Some patients have reported that where they are seen in a specialist centre, they feel that access to the drug is easier. Patients with adult onset symptoms are usually treated with Anakinra, however, the dosage will vary among patients due to the severity of the condition. Despite being symptomatic of such conditions, where there is no clear diagnosis, patients are not able to access the drug. Some patients may be given the drug as a trial; however, we do not hold such data.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Where we have patients with several different Autoinflammatory conditions, it is difficult to understand and explain why some patients are eligible for Anakinra while some are not. Eligibility does seem to start with which condition a patient has been diagnosed with rather than which symptoms they present. This can be particularly difficult where a patient may not have disease causing gene mutations but is clearly symptomatic. There also seems to be a disparity between patients and where they live as to whether or not they can access the drug sooner than others. Some patients have reported that they have been given alternative treatments to try as access to Anakinra was not possible. We share the drug consultation policy document

	with patients to help them understand when they may be able to access Anakinra.
Other issues	
13. Are there any other issues that you would like the committee to consider?	Often CRP and SAA tests are used to determine if the disease is still ongoing. Many chronic patients find that their CRP normalises. However, patients are encouraged to keep a diary of symptoms, recording both the severity and frequency. This enables Healthcare Professionals to see the 'bigger picture' and not be solely reliant on blood results to assess a Patients Quality Of Life.
Key messages	

15. In up to 5 bullet points, please summarise the key messages of your submission:

- Anakinra may improve the quality of life of patients while reducing the reliance on NSAIDs that causes stomach damage and painkillers such as opioids
- Anakinra may improve the quality of life of the families and carers of these patients
- The accessibility and delivery of the drug varies from patients and regions within the UK.
- The style of injection could be improved to a more efficient and accessible device.
- Patients may face extra costs to cater for their stock of the drug; buying additional fridges and an increase in electricity. This also hinders patients being able to travel.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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- ✓ ☐ **Please tick this box** if you would like to receive information about other NICE topics.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Anakinra for treating Still's disease [ID1463]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- Your response should not be longer than 13 pages.

About you	
1. Your name	Eslam Al-Abadi
2. Name of organisation	Birmingham Women's and Children's Hospital NHS Foundation Trust

3. Job title or position	Consultant Paediatric Rheumatologist
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	1. Induce remission of disease in the first few weeks following presentation. 2. Achieve and maintain a steroid free remission. 3. Achieve and maintain a drug free remission.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Resolution of symptoms and signs as well as normalisation of inflammatory markers are the trends that are observed by clinicians. Equally important are the patient reported outcome measures that reflect daily function and quality of life. A 30% improvement compared to baseline is usually accepted in clinical research as significant improvement. However, this is not usually clinically accepted as there would be a significant ongoing disease activity. Treat to target approach is now the accepted approach and the aim is disease remission or, in some circumstances, minimal disease activity without the use of steroids.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. The current treatment pathway of using methotrexate as first line treatment lacks any evidence to support it. There are also different phenotypes with some predominantly systemic, some with evidence of Macrophage activation and some with a strong arthritic component. Methotrexate is not a suitable first line treatment and physicians would be best placed to decide what would be the most suitable initial treatment approach. Therefore, there is a need to expand the options available for first line treatment that are most suitable for the patients phenotype.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	This is dependent on the disease phenotype Some (circa 10%) have a mild presentation that improves with non-steroidal anti-inflammatory drugs. For more severe disease steroids are given and followed by methotrexate. If steroids free remission can't be achieved or there is no response then treatment is escalated to use Tocilizumab. Finally, Anakinra is introduced if further treatment is still required. Unfortunately, this is not in keeping with the published evidence.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	The guidelines used are those that are agreed by NHS England: • Clinical Commissioning Policy: Anakinra/tocilizumab for the treatment of Adult-Onset Still's Disease refractory to second-line therapy (adults) https://www.england.nhs.uk/wp-content/uploads/2018/07/1609-anakinra-and-tocilizumab-for-aosd.pdf • Clinical Commissioning Policy Statement: Biologic Therapies for the treatment of Juvenile Idiopathic Arthritis (JIA) o https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/10/e03pd-bio-therapies-jia-oct15.pdf o https://www.england.nhs.uk/wp-content/uploads/2018/07/Biologic-therapies-for-the-treatment-of-juvenile-idiopathic-arthritis-Appendix-A.pdf
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway to access available interventions is clear in NHSE pathways. However, there are discussions amongst professionals to change the treatment approach from a stepping up towards achieving remission to a stepping down following a rapid achievement of remission. At the heart of that is the use early use of the most appropriate treatment depending on patient phenotype.

• What impact would the technology have on the current pathway of care?	The technology is already part of the pathway. The impact would be achieved if its position in the pathway was moved, along with Tocilizumab, to a first line intervention.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The current way of using the intervention in NHS clinical practice is dictated by the existing pathway and does not reflect the evidence base. Please see previous question for the proposed position of the intervention in the pathway.
• How does healthcare resource use differ between the technology and current care?	Not significantly. Eventually, patients will receive the intervention. Unfortunately, they would have disease and steroid related morbidity by the time they have accessed it.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	In specialist clinics and in secondary care where an agreement is in place with a specialist clinic.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The intervention is already in practice. Moving the position is the pathway would not require additional investment.
12. Do you expect the technology to provide clinically	Yes.

meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	Theoretically yes. No long term data exist to show that effect because its not been available for long enough and the disease is not usually fatal in the earlier phases.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	More effective in patients with predominant systemic features and hyperinflammation at presentation. The intervention is not a first line choice if there is a strong arthritic component with minimal systemic features.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare	The intervention is already in practice. Altering its position does not have any additional resource implications in my view.

professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes, rules can be set for when the treatment should be started and stopped. These rules are already existing and therefore do not require any additional testing.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the	The use of the technology as a first line treatment will reduce steroid side effects with a significant impact of the quality of life. I am not an expert in how QALY is calculated and don't know if this aspect will be captured in the calculations.

quality-adjusted life year (QALY) calculation?	
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	By using the Anakinra earlier in the patient pathway we have a chance to influence the outcome during a window of opportunity when the disease is predominantly driven by the IL-1 pathway. This has now been demonstrated in a few trials. It has the potential tol result in a considerable step change in outcomes and has the potential to make a significant and substantial impact on health-related benefits. The published trials have demonstrated: i. an earlier remission, ii. less or no steroid use and iii. higher numbers of drug free survival.
• Is the technology a 'step-change' in the management of the condition?	Using Anakinra earlier in the treatment pathway would represent a step change in the management of the condition.
• Does the use of the technology address any particular unmet need of the patient population?	Using Anakinra earlier in the treatment pathway with its potential to achieve early remission and reduction of disease and steroid morbidity is a significant unmet need in this population.

18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effect profile is similar, and in some aspects milder, compared to other interventions in the pathway. It is significantly favourable compared to steroids and methotrexate. Initial injection site reaction is experience by some but resolves after the first few weeks with regular use of anti-histamines.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	No. Clinical trials are focussing on the early use of Anakinra while current clinical practice in the UK is limited by the funding pathway and access to Anakinra is late when the the disease pathophysiology has become more complex.
• If not, how could the results be extrapolated to the UK setting?	Anakinra, as well as Tocilizumab, should be available to be use at the same time as Methotrexate. The access to drugs should be in parallel and not sequential.
• What, in your view, are the most important outcomes, and were they measured in the trials?	The following are most important and have been measured in trials: 1. Resolution of symptoms 2. Normalisation of inflammatory markers (1&2 are incorporated in the definition of clinically inactive disease) 3. Reduction of steroid burden

	4. Patient assessment of disease activity and overall wellbeing
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	So far, I am not aware of any additional side effects that have become apparent that are not reported in trials or cautioned in the summery of product characteristics
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	I am not familiar with the search strategy of your systematic review and therefore can not comment.
21. Are you aware of any new evidence for tocilizumab since the publication of NICE	There has been no new evidence for the use of Tocilizumab in AOSD that would significantly alter the NICE TA238. However, there is evidence to support that AOSD and sJIA are a continuum of one disease manifesting at different ages. There has been on open label trial of early vs late use of Tocilizumab in children with sJIA that demonstrated a clear superiority of early vs late use of Tocilizumab 10.1007/s00296-016-3595-z

technology appraisal guidance TA238?	
22. How do data on real-world experience compare with the trial data?	Real world experience obtained from registries reflect practice that predates the latest trials results and has Anakinra and Tocilizumab used later rather than earlier and therefore is not a like for like comparison.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
24. Would you say that the efficacy of anakinra, tocilizumab and canakinumab	These outcomes have not been compared in clinical research. My personal opinion is: a. achieving and maintaining remission: Most likely similar.

for treating both systemic juvenile idiopathic arthritis (sJIA) and adult-onset Still's disease (AOSD) in practice are similar in terms of: a. achieving and maintaining remission b. adverse events c. treatment discontinuation rates?	b. adverse events: Overall similar. Tocilizumab blocks CRP and fever pathways, even due to infection. Therefore, patients seen in primary care or local out of hours services risk being severely unwell and not be recognised. There should be a lower limit to the use of antibiotics. This is not something a generalist would be expected to be familiar with and has the potential to be fatal if not recognised early. c. treatment discontinuation rates? Most likely similar. NB There is no pathway to access canakinumab within NHSE for this population. Anyone using it is has been in a trial, had an individual funding request accepted or obtained it via compassionate use from the drug company. Therefore, the numbers are small in the England and there is no single point of accessing data on its use.
25. What are the clinical reasons why either tocilizumab or anakinra would be chosen over the other?	There is no published evidence to support the use of one over the other. In my experience and through discussions with colleagues I consider there to be trends: 1. Predominant systemic features, with minimal or no arthritis, and a hyperinflammtory clinical picture: Anakinra is likely to be an initial choice 2. Predominant polyarthritis with milder systemic features: Tocilizumab is likely to be an initial choice. 3. Mix of mild-moderate systemic features and milder arthritis: either could be initial choice. In any of the above, if there is no or suboptimal response, the clinician is likely to, in no particular order, either: 1. Swap from one to the other; or 2. Add in a csDMARD

	3. Re-introduce corticosteroids
26. Of people with sJIA receiving tocilizumab, what percentage would you estimate would receive it: a. subcutaneously b. intravenously?	Such data does not exist. Partly because the subcutaneous injections became available later and only recently in children. There was a drive towards offering patients the choice which then was accelerated and became a necessity due to COVID and the need to reduce hospital attendances for these patients. Therefore, I suspect that currently the vast majority are given subcutaneously. However, many colleagues are reporting loss of disease control on switching to the subcutaneous injection and the need for either more frequent dosing or switching back to the intravenous infusions.
27. Would all people with AOSD receiving tocilizumab receive it subcutaneously?	Unless there is a patient specific reason why not to or a contraindication, I would presume that to be the case.
28. Are there people with sJIA who still have sJIA in adulthood? Are these people treated in the same way as children with sJIA or as adults with AOSD?	The disease is a continuum across the age groups and the treatments in both groups are the same. The difference might be in the more common use of Tocilizumab subcutaneously rather than intravenously in adult populations, although this trend is also evolving in paediatric practice as well in the past year.

Key messages
29. In up to 5 bullet points, please summarise the key messages of your statement. • Early achievement of disease inactivity followed by drug free remission is possible. • This can be achieved by early use of highly targeted treatments like Anakinra and Tocilizumab. • There is no evidence to support the use of methotrexate in systemic juvenile idiopathic arthritis and adult-onset Still's disease • In addition to poor disease control, there is a significant side morbidity and poor quality of life associated to the prolonged use of steroids and methotrexate. • The cost implications to the early use of Anakinra and Tocilizumab will exist elsewhere in the health economy if methotrexate and steroids were used as first lien.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Anakinra for treating Still's disease [ID1463]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Lisa Dunkley**
2. Name of organisation	**Sheffield Teaching Hospitals/ British Society Rheumatology rep to RCP Young Adult & Adolescent Steering Group**

3. Job title or position	**Consultant Rheumatololgist**
4. Are you (please tick all that apply):	X☐ an employee or representative of a healthcare professional organisation that represents clinicians? X☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it X☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To switch off inflammation (drug induced remission) and thereby prevent progression to irreversible joint damage, systemic amyloid & chronic long-term disability & ill health as a result. Keep patients well enough to remain in paid employment; prevent need for secondary interventions such as joint arthroplasty, long term renal replacement therapy or cardiac support in secondary amyloid.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Improvement of serological markers (Ferritin, CRP/ ESR, serum amyloid) of at least 25% and/or accompanied by improvement of clinical features (fever, rash, arthritis, fatigue, quality of life, physician and patient global VAS). Where arthritis a prominent feature at baseline – an improvement in joint scores (none validated in AOSD) but extrapolation from Systemic Onset Juvenile Idiopathic Arthritis (SOJIA) might reasonably use cJADAS (clinical Juvenile Arthritis Disease Activity Score) & require improvement in all components of score (active joint count/ physician VAS/ patient VAS). NHSe guidance uses DAS score (extrapolated from Rheumatoid Arthritis) but in my opinion as a physician treating both RA/ JIA and AOSD, DAS is an inadequate and inaccurate tool for this.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Currently patients have to fail NSAIDs/ steroids/ 2 conventional DMARDs (per NHSe guidance 2018) in order to qualify for treatment with Anakinra or Tocilizumab. This differs from patients <16 with SOJIA who qualify for biologic therapy (TOCI 1st line unless concurrent macrophage activation syndrome (MAS); Anakinra 2nd line or for MAS) after failure of 1 conventional DMARD. Meaning adolescents & adults with the same condition have a more protracted treatment pathway than children, potentially leading to poorer health outcomes.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	NSAIDs/ steroids/ conventional DMARDs/ Biologics (Anakinra/ Tocilizumab) as per NHSe 2018
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NHS England 2018 https://www.england.nhs.uk/wp-content/uploads/2018/07/1609-anakinra-and-tocilizumab-for-aosd.pdf
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	AOSD is still relatively rare compared with other conditions we treat (RA, psoriatic arthritis, connective tissue disease etc) – so I suspect an average consultant rheumatologist will have no more than 2 to 3 patients at any one time. So hands-on experience outside a paediatric/ grown-up JIA setting is quite patchy. I work in an adolescent rheumatology service & closely with my colleagues in paediatric rheumatology, so have greater experience than some in looking after SOJIA, and by default then often get referred newly presenting patients with AOSD. My point here is that yes, I think there is variation in treating these patients. The NHSe policy of 2018 helped. My experience is within England.
• What impact would the technology have on the current pathway of care?	The real question here seems to be the timing of Anakinra use, rather than whether it has a role or not (at all) in AOSD. For many patients, positioning Anakinra after cDMARDs (1 rather than 2) might be reasonable. However, the very important issue is that if a patient is sick, failing to respond to steroids, and/or has any features of macrophage activation, a clinician needs to be able to use their own judgement as to whether in those acute circumstances, Anakinra should be available to induce remission rapidly, with a view to later maintenance therapy with MTX/ low dose steroids etc. This would better model other inflammatory conditions where induction of remission utilises potent drugs at presentation, eg cyclophosphamide in acute vasculitis.
11. Will the technology be used (or is it already used) in	It is already used

the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care Rheumatology
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Nil
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase	In the case of concurrent MAS = yes

length of life more than current care?	
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	No

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	I'm not sure
17. Do you consider the technology to be innovative in	

its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Potentially – it depends on the final positioning of the drug in the treatment pathway.
• Does the use of the technology address any particular unmet need of the patient population?	
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side-effects minimal and comparable/ better than cDMARDs/ long term steroids
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Generally, yes.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Please see my comment above about joint scores (DAS 28) not being an appropriate score in AOSD QoL important and not included in all trials. Also global patient/ physician VAS important.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to my knowledge
20. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for tocilizumab since the publication of NICE technology appraisal guidance TA238?	No
22. How do data on real-world experience compare with the trial data?	
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	There are more favourable treatment pathways for those <16 yrs than for those >16. So a newly presenting 16 year old would have less ready access to anakinra for Still's disease, than a 15 year old peer. Patients with active inflammatory arthritis in other conditions (RA/ PsA) are not required to have systemic steroids as part of their treatment before they can qualify for biologic therapy. The arthritis in AOSD has equal potential to cause erosive disease and joint damage, so this inequity should not exist.

23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
24. Would you say that the efficacy of anakinra, tocilizumab and canakinumab for treating both systemic juvenile idiopathic arthritis (sJIA) and adult-onset Still's disease (AOSD) in practice are similar in terms of: a. achieving and maintaining remission b. adverse events c. treatment discontinuation rates?	I would consider Anakinra and Tocilizumab to have equal efficacy in inducing and maintaining remission overall in a population of patients with AOSD. I have no personal experience using Canakinumab, although am aware my colleagues in paediatric rheumatology do use it on occasion. At individual patient level, often one works better than the other – so the ability to sequentially switch remains important. It is also possible for a patient to require Anakinra for MAS/ systemic predominant disease at presentation, and at a later date move into a more chronic arthritis phase where Tocilizimab may be the more appropriate long-term drug. Adverse events – relatively low in both drugs and I would perceive no difference between them. Treatment discontinuation rates = similar.

25. What are the clinical reasons why either tocilizumab or anakinra would be chosen over the other?	As above, Anakinra for systemic presentation/ MAS (with or without joint disease). Toci for more arthritis predominant.
26. Of people with sJIA receiving tocilizumab, what percentage would you estimate would receive it: a. subcutaneously b. intravenously?	75% subcut 25% iv This reflects local practice. Historically more iv was used in paediatrics, so these local data may not be representative UK wide.
27. Would all people with AOSD receiving tocilizumab receive it subcutaneously?	I would estimate 80% sc and 20% iv. There are always patients that prefer to come and have drugs administered to them, rather than self-inject. Personal preference. There are some where sc TOCI does not seem to be as effective as iv (we don't always have an explanation for this – apart perhaps from adherence which is a huge issue in treating young adults (who preferentially are affected by AOSD)). And then there are deliberate clinician choices to facilitate ongoing review/ medication adherence in young adults who are often very sick.
28. Are there people with sJIA who still have sJIA in	Yes. In our service, we transfer them from paediatric services into our young adult service around the age of 16. Even as adults >25 years they remain under the care of a specialist team with expertise in treating

adulthood? Are these people treated in the same way as children with sJIA or as adults with AOSD?	JIA. In other rheumatology services they will be looked after in general rheumatology clinics. In our service we would continue to treat as SOJIA. In other services I suspect they might get re-labelled as AOSD. I would argue this re-labelling is not the right approach.

Key messages

29. In up to 5 bullet points, please summarise the key messages of your statement.

- Anakinra is a well tolerated & established drug in the treatment of adult and paediatric Still's disease
- The position of its place in treatment pathway needs to be decided but it must be available at presentation for those patients presenting with (impending) MAS = 10% SOJIA & 20% AOSD patients
- There is inequity treating this disease in children vs. (young) adults
- Current outcome measures may not be suitable (disease activity scores/ joint counts)
- It's use needs to be available at the discretion of treating clinicians for acute/ life-threatening presentations in AOSD (incl. MAS)

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient expert statement

Anakinra for treating Still's disease [ID1463]

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Amanda Jones**
2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	Rare Autoinflammatory Conditions Community – UK (RACC-UK)
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	I was diagnosed with Still's Disease at the time which then started being referred to as sJIA. My main symptoms were that of arthritis and I had ongoing joint damage and issues into adulthood. I was essentially treated as though I had RA, but in 2018 I had a sore throat and all over body pain, rashes, fevers/rigors, full body oedema (6kg of it), skin stretched to splitting point and I became incredibly unwell-was admitted to Acute Respiratory Care Unit, unable to move or swallow with a CRP of 603. I became unable to move at all and couldn't even lift my hand to my face. The only part of me that did not hurt was my teeth. Paracetamol, morphine, tramadol and codeine did not make the pain bearable. My rash was confused with an allergic reaction to antibiotics as I was being treated as having sepsis. It

	was a very scary time. I was incredibly unwell for quite some time, and it wasn't until the correct medication was found that I began to feel better.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	I was already being treated for RA and was on NSAIDS and various biologics (having been on a whole range over the years, including hydroxychloroquine, COX II inhibitors, methotrexate, naproxen, and 4 or 5 different biologics. Before that most recent flare, I was on Cimzia. I was then 'trialled' on various treatments, with huge doses of methyl prednisolone being administered to try and get my condition under some sort of control. I had IgG therapy, I am currently on prednisolone, sulfasalazine, methotrexate and Anakinra. Anakinra worked almost straight away for me, with regards to the systemic inflammation, and I was moved onto Tocilizumab, but the systemic inflammation returned for me.
10. Is there an unmet need for patients with this condition?	I am still not very well controlled with this condition and although Anakinra has saved my life, and given me back some of my quality of life, I still have to be controlled with quite a lot of other medication due to the complexity of the condition.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Anakinra saved my life. Without this drug, I was unable to function. On the rare occasions that I have had to stop the drug, within two days I am admitted to hospital and become unable to function at all. I personally like the needle and syringe, as I find that the metoject style injection makes me flinch and also cause bruises, which would be an issue and make my abdomen sore.

Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	I often have a delicate abdomen and often get gastroenteritis type infections, at which time I find it very difficult to self-administer this drug. As a result of hip replacements and infections, I have little muscle mass on my hips so find that I cannot inject there and have to only use my abdomen, which can get a little sore as I also administer methotrexate there. I am also unable to self-administer my drug if I am flaring. I also find it difficult accessing this drug, as it is currently being funded via my hospital. This route means that I have to make a trip to the hospital monthly to collect this drug, and also it means that it does not show up on my usual list of medications when I see my GP. I also find it quite frustrating that very few doctors are familiar with the drug and I always have to explain it to them. The drug does impact travel and planning, especially as it is taken daily, so any potential overnight stay needs to be carefully considered and cool bags and fridges accessed.
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients can take a long time to be diagnosed and also some patients may not have the correct diagnosis, potentially not making this drug available to them.
Equality	
14. Are there any potential equality issues that should be	**I have only been able to access Anakinra due to my rheumatologist fighting for it for me and the hospital agreeing to fund it to prevent my continual hospital admission.**

taken into account when considering this condition and the technology?	
Other issues	
15. Are there any other issues that you would like the committee to consider?	
Key messages	

16. In up to 5 bullet points, please summarise the key messages of your statement:

- Anakinra saved my life and enables me to function
- Anakinra has decreased my systemic inflammation and also enabled me to stop the use of opiods.
- The frequency the drug is taken and the need to refrigerate it requires quite a lot of planning on the part of us as patients.
- Accessing the drug was a huge worry for me, as it was needed to keep me alive, but it was not clear if it would be available to me/funded
-

Thank you for your time.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Rachel Rimmer**
2. Are you (please tick all that apply):	☐ a patient with the condition? ☐ a carer of a patient with the condition? ✓ ☐ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	Rare Autoinflammatory Conditions Community – UK (RACC-UK)
4. Did your nominating organisation submit a submission?	✓ ☐ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	✓ ☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	✓ ☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☐ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	
10. Is there an unmet need for patients with this condition?	
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	
Patient population	
13. Are there any groups of patients who might benefit	

more or less from the technology than others? If so, please describe them and explain why.	
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
15. Are there any other issues that you would like the committee to consider?	
Key messages	
16. In up to 5 bullet points, please summarise the key messages of your statement: • •	

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-
-

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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

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Date completed: 18 December 2019

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

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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

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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

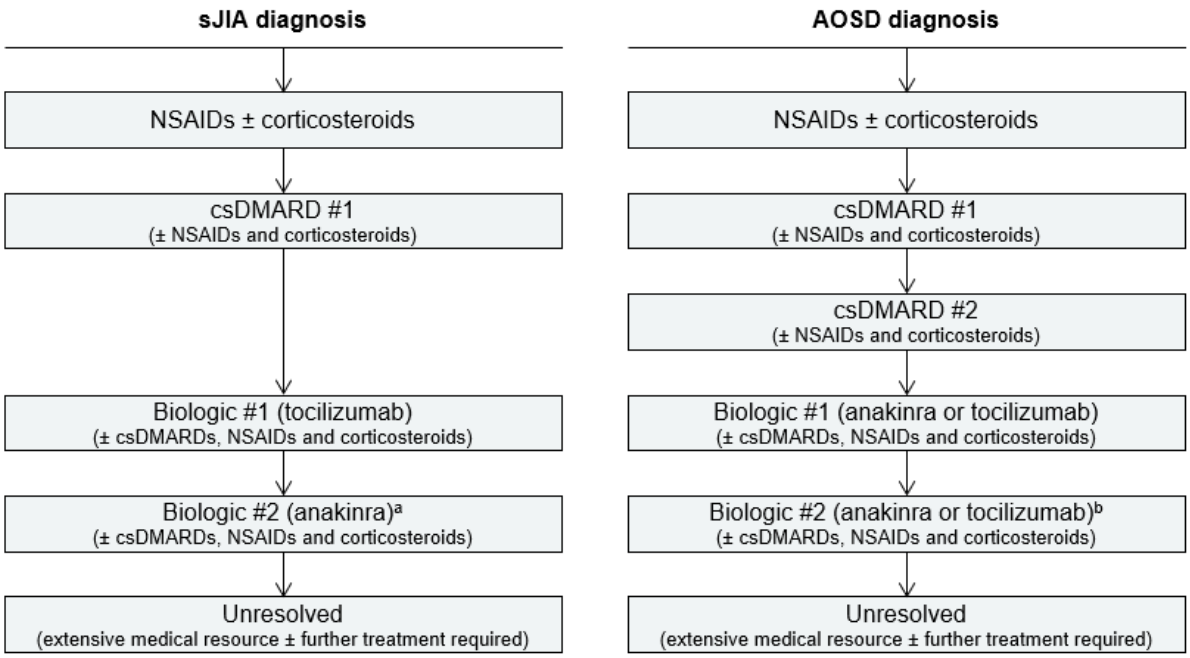
Treatment aims
The aim of treatment is to achieve remission of symptoms by controlling pain, fever and inflammation and to minimise joint damage.

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

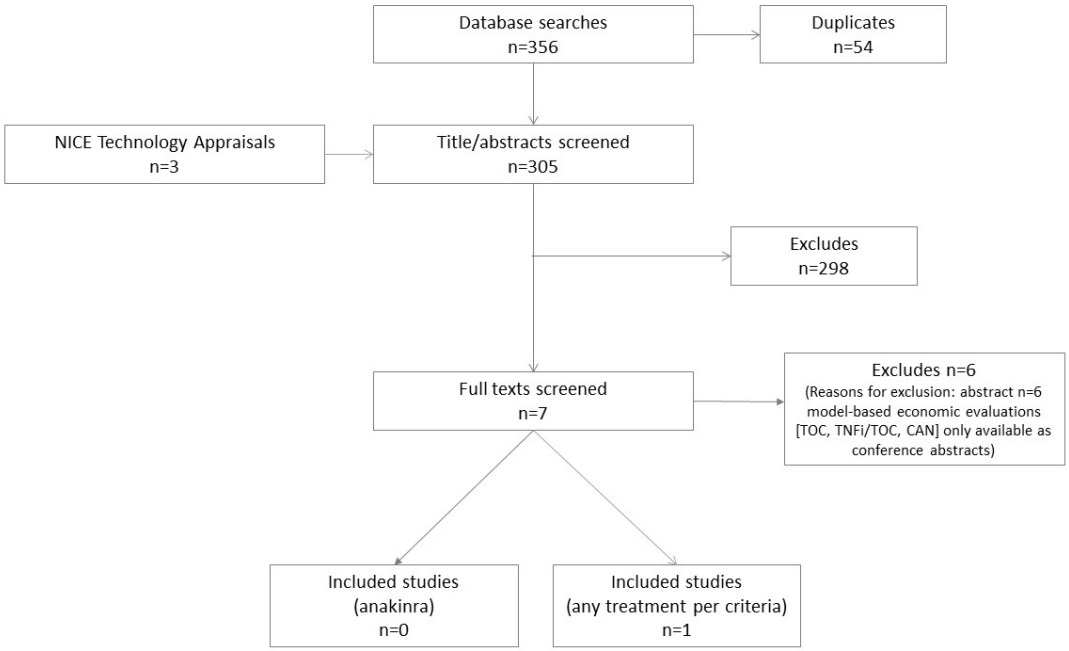
The objective of the literature search carried out by the company was to identify previously published cost effectiveness studies of anakinra for the treatment of Still's disease (defined as SJIA and/or AOSD).

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.

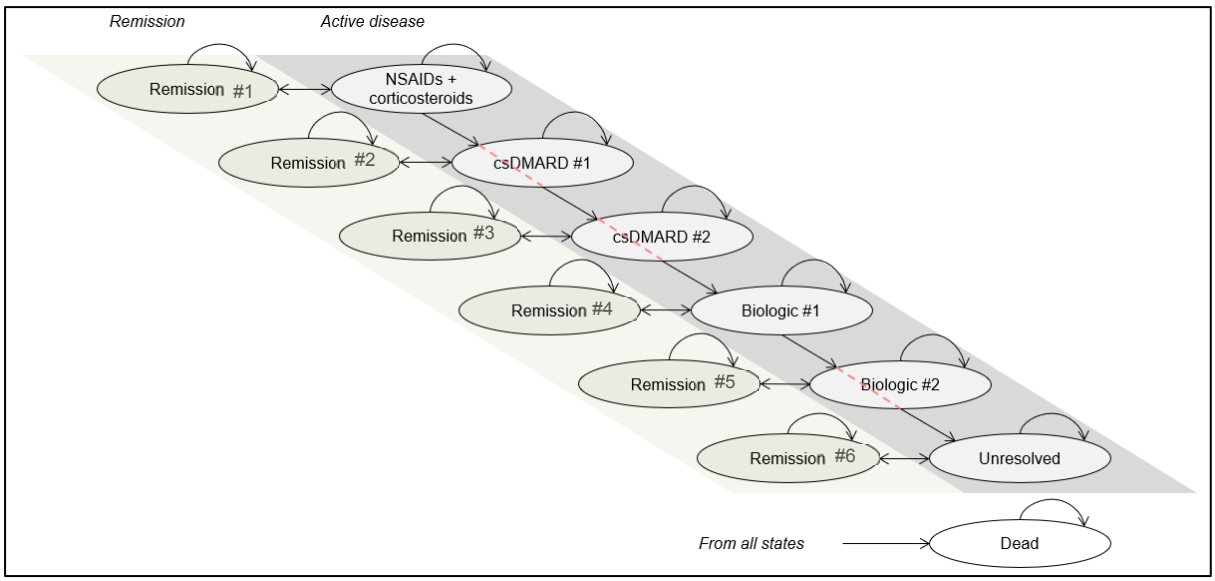


Figure 3 Structure of the company model

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

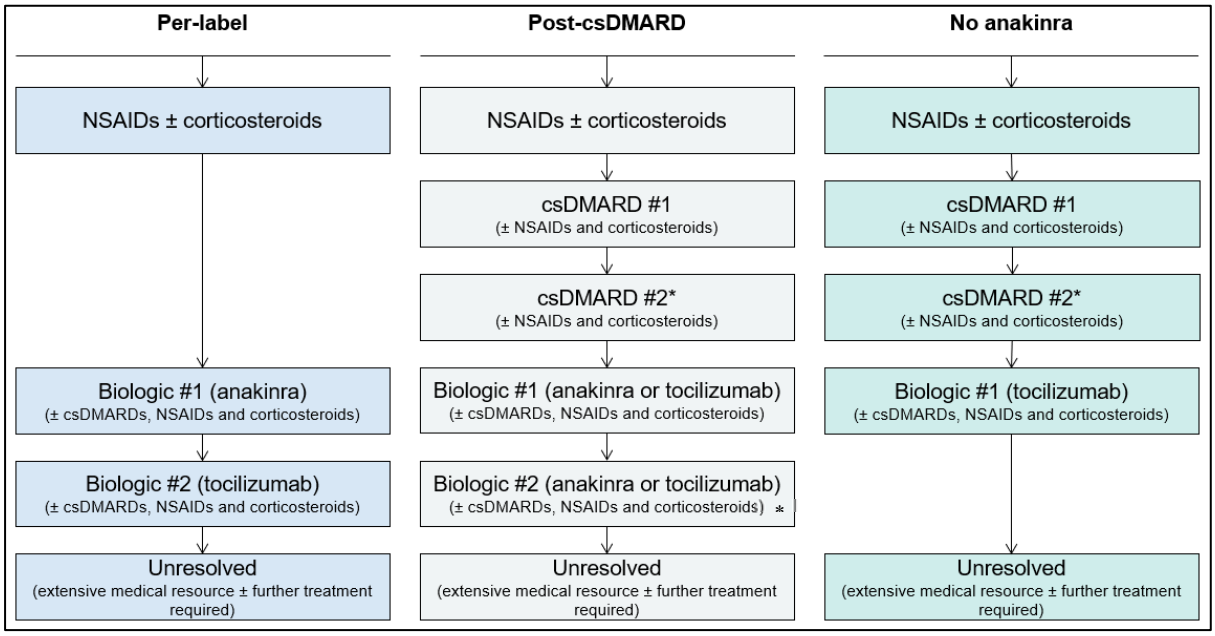


Figure 4 Company model permitted treatment-related health states

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.

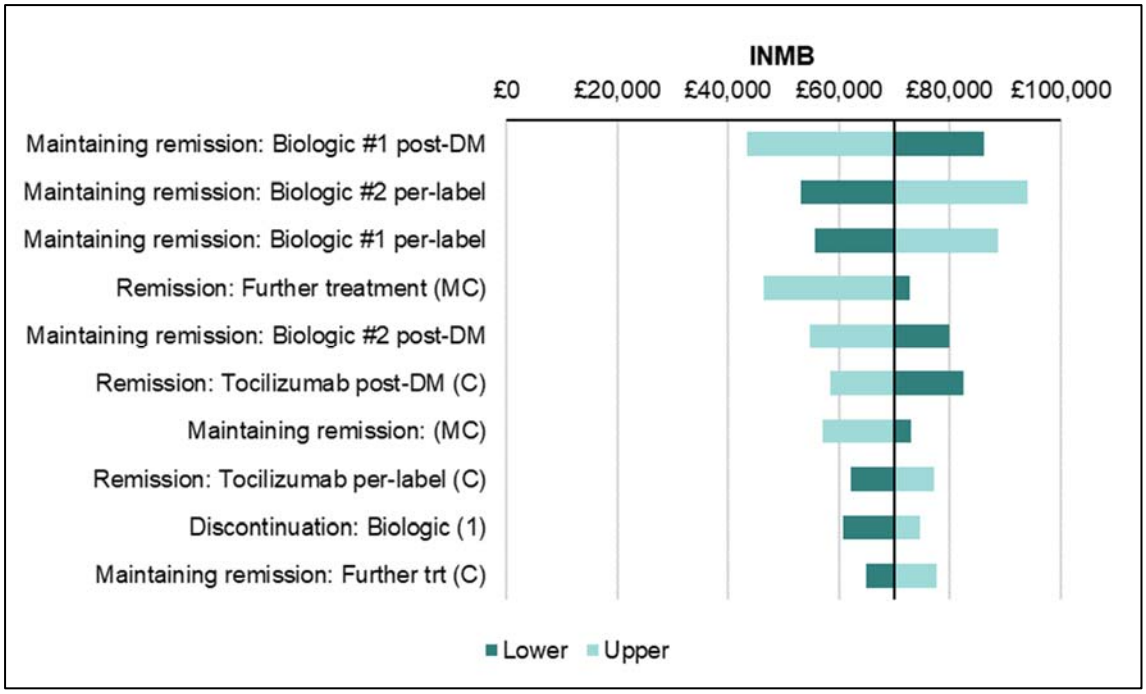


Figure 5 Tornado diagram – per-label arm versus no-anakinra arm

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

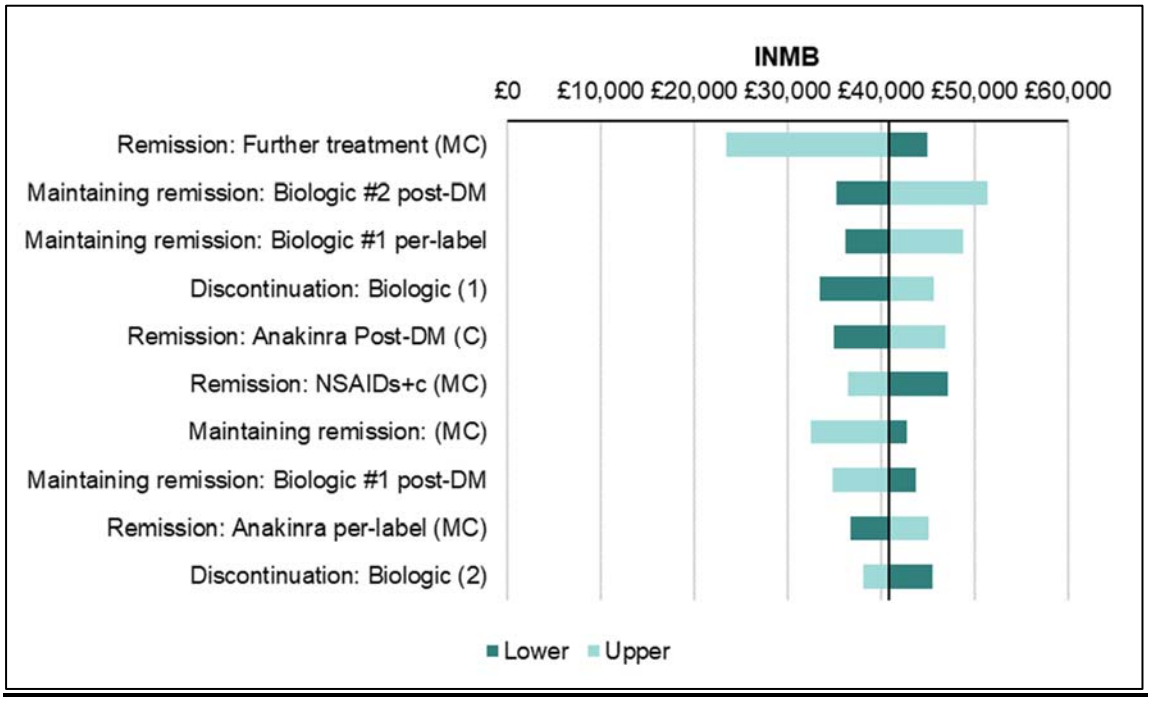


Figure 6 Tornado diagram – post-csDMARD arm versus no-anakinra arm

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

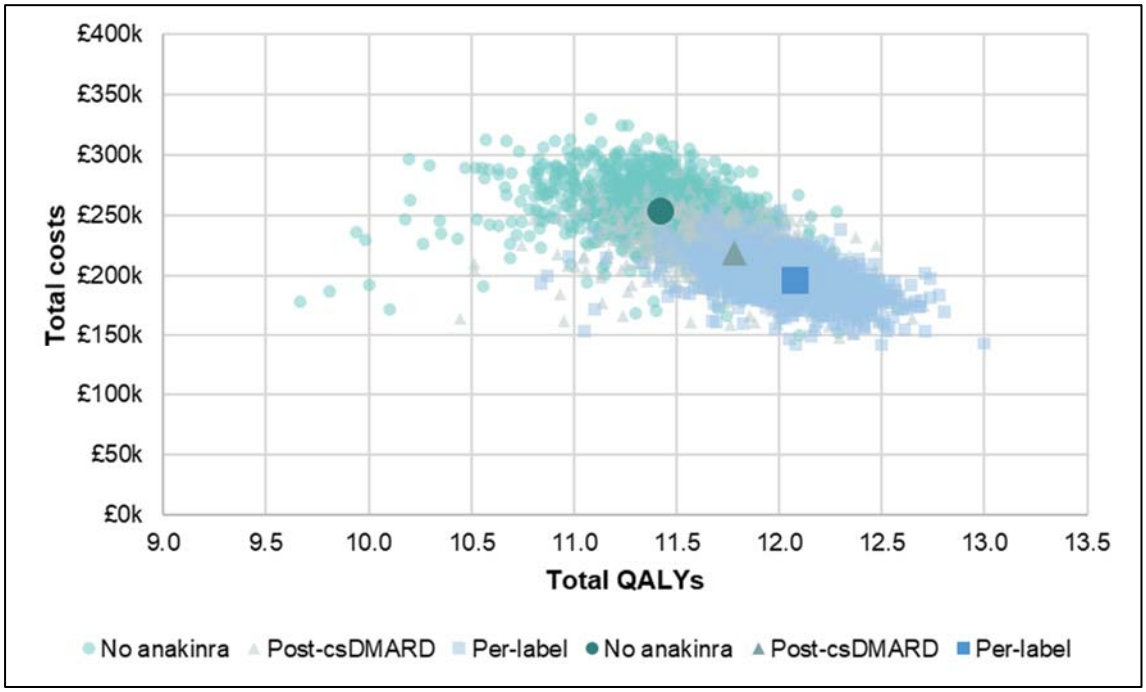


Figure 7 Probabilistic sensitivity analysis scatterplot

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).

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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

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check

Anakinra for treating Still's disease [ID1463]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by **5pm on Monday 13 January 2020.** using the below comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Errors in understanding and communication of features of the economic model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 12 of the report, the ERG states: *"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."* This is partially correct, as resource use and costs for the model health states were informed via clinical advice provided to Sobi. However, importantly the approach to obtain clinical advice was based upon presentation of the original TA238 data for these health states, and clinicians were asked if any edits should be made (given that TA238 was published in 2012). The statement in the ERG's report currently implies TA238 were disregarded entirely in favour of clinical advice from first principles, which is incorrect (appreciating that the CS did not explicitly describe the approach taken).	Sobi requests the ERG revises this text to the following: *"Data reported in TA238 were used to represent the HRQoL in the model. Resource use and costs for the model health states were based on a combination of data reported in TA238 and clinical advice to the company."*	By correcting this error, a more accurate description of the approach taken to quantify costs and resource use may be inferred by the reader. Without this correction, it may be mistakenly inferred that potentially-relevant evidence from TA238 was overlooked by Sobi.	This is not a factual inaccuracy but a matter of opinion. The ERG is explicit which values were taken from TA238 and which were taken from clinical advice to the company.
On page 14 of the report, the ERG states: *"a patient can remain on an ineffective*	Sobi requests these statements be amended to the following: Page 14	It is entirely plausible for a patient to continue a treatment while not achieving clinical remission, provided they are considered to be deriving	This is not a factual inaccuracy. 'Ineffective' in the sense of the clinical model means failure to move a person into remission.

treatment for the whole model time horizon" Here, the use of the phrase "ineffective" is incorrect and therefore misleading. The ERG is correct to highlight that within the submitted model structure, patients could remain on a treatment for the whole model time horizon without achieving remission, but this is not equivalent to the treatment being entirely "ineffective". Later in the ERG's report, it is stated: *"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 not having an effect 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 had no effect, 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, ineffective, bDMARD treatment. The ERG considers that this is unrealistic."* ERG report, page 64 It is factually inaccurate to suggest that use of a drug that has not led to remission is equivalent to that drug "not	*"a patient can remain on a treatment for the whole model time horizon without achieving remission, though this is expected to reflect current practice"* Page 64 *"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 does not lead to 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 led to 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 which has not led to remission."* The latter part of this statement noted that the ERG considered this to be unrealistic. In light of the information provided in this response, Sobi asks the ERG to reconsider whether it still deems this to be unrealistic.	benefit in terms of symptom control. The statement made by the ERG does not accurately reflect the nature of long-term continued treatment for patients not in remission. Within the context of treatment with anakinra, it may be (for example) that treatment is continued for extended periods of time without achieving remission if the treating clinician suspects the patient is at an elevated risk of developing macrophage activation syndrome (MAS) - particularly if the patient has previous history of MAS. By correcting the potentially misleading use of "ineffective", the clarity of the statement made by the ERG is improved.	Whilst the person may get some benefit from the treatment model effectiveness relates to movement in to remission. For clarity, the ERG has amended the text on page 64 to say: *"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."*

having an effect".			
On page 14 of the report, the ERG states: *"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"* While technically possible, this is very unlikely – for example, with probabilities of achieving remission = 2.85% (anakinra used after csDMARDs), and relapse = 0.54%, the probability of this loop happening <u>once</u> can be calculated as: 2.85% × 0.54% × 2.85% = 0.00044% As such, Sobi considers it appropriate to state for context that the probability of this happening is very small (i.e. a fraction of a percent).	Sobi requests this statement be amended to the following: *"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. However, the probability of this happening is very small."*	The probability of this happening within the model is very small, and similar criticisms could be applied to a number of other Markovian state-transition models constructed for rare diseases. Editing this point made by the ERG appropriately reflects a series of technically-possible transitions within the model, yet qualifies that the probability of this happening is very small.	This is not a factual inaccuracy. The loop can happen and was used to exemplify an implausible model structure.
On page 14 of the ERG's report, it is stated: *"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"*	Sobi requests this statement be removed in its entirety.	The statement provided by the ERG is incorrect, and is listed as a limitation of the structure of the model that "allows clinically implausible situations to arise". This feature of the model aims to capture the additional costs incurred within the remission health states, and importantly does not represent the situation described by the ERG.	This is not a factual inaccuracy. As stated by the company in the submission and in their FAC response, all patients in the remission health state are assigned half the cost of the health state that resulted in remission because some patients remain on treatment

This is factually inaccurate. Within the CS, it is stated: *"To incorporate the possibility that several patients may remain on treatment or undergo dose tapering after remission, it is assumed that within each remission health state a proportion of patients still incur the costs associated with the health state from which they achieved remission. … In the base case this proportion is set to 50% for the remission health states following use of either anakinra or tocilizumab, and 0% for all other health states."* Document B, page 154 The value of 50% represents the approximate proportion of costs incurred within the remission health state, <u>not</u> the proportion of patients expected to continue treatment with the same dose/ regimen prior to achieving remission indefinitely. This setting is aligned with the cohort-level structure Sobi deemed necessary to adopt when modelling the treatment pathway of patients with Still's disease in light of the limited evidence base. This assumption was also stress-tested in sensitivity analysis, by setting the value to 0% and 100%.		As described in the CS, patients in remission may continue treatment for a specified time period or lower their dose, and so this model setting is intended to reflect reality which is that a proportion of the average costs incurred prior to remission are carried through into remission. Patients that relapse could have stopped treatment completely, have lowered their dose, or have continued on the same dose prior to remission. Nevertheless, clinical advice provided to Sobi was that if a treatment had been previously effective in achieving remission, it would be used again in most cases.	and some have tapered treatment. As all patients incur this cost in the model (a cost which includes costs of bDMARDs) it means that all patients in the model are assumed to still be on bDMARDs at the time of any relapse from the remission state. Therefore, some patients who relapse and are tried again on bDMARDs will, as the ERG report has described, return to treatment with the same bDMARD they were prescribed at the time of relapse.
On page 14 of the report, the ERG states: *"overestimation of costs in the unresolved state"*	Sobi requests this statement be removed in its entirety.	The statement made by the ERG is incorrect, based on a misunderstanding of the TA238 CS. The original table (within the previous CS for TA238) labels this cost as	The ERG misinterpreted the data in TA238 and agrees a factual inaccuracy has been made. The statement and section will be deleted as

This is incorrect. Here, the ERG is referring to the annual costs of patients in an unresolved disease state, which based on Sobi's model is estimated to be in the region of £13,000-15,000 (ERG report, page 65). The ERG refers to an inflated "annual" cost of £3,973 based on Table 65 of the TA238 CS. In Table 65 (of the TA238 CS), the "total" cost is listed as £3,640.51, however this applies to the cycle length used in this previous appraisal (12 weeks). This may be inferred by looking at the first resource use item: <u>Inpatient stay</u> • Cost per day: £428.32 • Days in hospital per year: 24.5 • % of patients requiring hospital stay: 90% • £428.32 × 24.5 × 90% = £9,444.46 This cost (for hospitalisations only) is over £9,400 per year, and so it can be seen that the total figure in Table 65 refers to a 12-week model cycle.		"total", yet this is the total cost per model cycle (and the cycle length in this previous submission was 12 weeks). Scaling up the ERG's estimated cost of £3,978 (by multiplying by the ratio 52/12) yields a value of over £17,000 per annum – greater than, but in the same region as, the total cost used by Sobi of £13,000-£15,000.	suggested.
On page 14 of the report, the ERG states: *"cost of treating patients with SJIA with anakinra"* This refers to the acquisition costs for paediatric patients treated with anakinra. The ERG implies later in its	Sobi requests this statement be removed in its entirety.	The statement made by the ERG is incorrect, based on a misunderstanding of the application of drug costs within the economic model. Sobi expects that for patients who do not require an entire syringe of anakinra, the remaining product is wasted, and so this was specifically	The ERG accepts that vial sharing did not occur and so has removed this statement and section from the ERG report.

report that wastage costs were not included within the model calculations: *"The anakinra dose for children is based on their weight. The company has costed treatment assuming that there will be no wastage, i.e., as if a portion of the pre-filled syringe can be saved and used as part of a subsequent administration. In the SmPC for anakinra it is stated that the pre-filled syringe is for single use only and any unused content should be discarded. The cost of treatment with anakinra for all patients should, therefore, be the cost of one pre-filled syringe per day whilst on treatment."* ERG report, page 66 This is factually inaccurate – wastage was captured by rounding the dose needed up to the nearest whole vial. This may be inferred through inspection of the "Costs" sheet of the model, in cell range O227 wherein the ROUNDUP function is used to ensure the total cost per administration is based on integer quantities of pre-filled syringes.		factored into the model calculations. Sobi acknowledges that this model setting was not explicitly stated within the CS, but provides this explanation for clarity. Product dosage was presented in Document B, whereas product usage informed the costing of drugs to inform the model (including wastage). Sobi apologises for the lack of clarity surrounding the application of costing within the model, but hopes this explanation aids understanding.	
On page 14 of the report, the ERG states: *"underestimation of the effectiveness of prior treatments in the post-csDMARD strategy"* Here, the ERG refers to Sobi's	Sobi requests both of these statements be removed in their entirety	The statement made by the ERG is incorrect – Sobi has intentionally specified that the probability of achieving remission for patients with chronic disease course receiving csDMARDs +/- steroids is zero. However, this does not mean that	This is not a factual inaccuracy. 'Ineffective' in the model means failure to achieve remission. Clinical advice to the ERG was that it was implausible that no patients would achieve remission with csDMARDs

structural decision to assign a probability of achieving remission with csDMARDs of zero for patients with chronic disease course. Later in the report, the ERG notes that *"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."* ERG report, page 66 Sobi does not have access to a record of the discussion(s) held between the ERG and the clinical experts who provided advice to the ERG. However, the term "completely ineffective" is misleading as the outcome of a treatment with a drug is not binary (ineffective or remission). Patients are currently treated effectively with csDMARDs in practice (in line with NHS policy) with the understanding that many patients will require bDMARD treatment to achieve remission. Patients with chronic disease course are expected to receive csDMARDs in practice as disease course (monocyclic or chronic) is not possible to ascertain prospectively. Clinical advice provided to Sobi indicated that patients with a chronic disease course would not achieve remission with csDMARDs (+/-		these patients would derive zero benefit from receiving these treatments (e.g. use of csDMARDs may allow steroid tapering, management of symptoms, etc.).	alone.

steroids) alone, yet they may accrue benefits in terms of symptom management and other aspects of the disease distinct from remission.			
On page 14, the ERG report states: *"canakinumab should have been a treatment option in the third-line setting and for patients with unresolved disease"* Later in the report, the ERG further clarifies this point: *"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. The ERG notes that the final scope issued by NICE includes canakinumab as a comparator in the third-line setting, therefore, treatment with canakinumab should have been considered by the company."* ERG report, page 67 Elsewhere within the ERG's report, it is stated: *"Clinical advice to the ERG is that canakinumab is not routinely used in the NHS to treat patients with SJIA or AOSD."* ERG report, page 19 As stated in Sobi's submission, canakinumab <u>may</u> be used if refractory	Sobi requests the following modifications are made to the ERG's statement concerning canakinumab use: Page 14 *"based on the final scope, canakinumab should have been a treatment option in the third-line setting and for patients with unresolved disease; yet clinical advice provided to the ERG noted that canakinumab is not used routinely in the NHS to treat patients with SJIA or AOSD"* Page 67: *"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, and clinical advice provided to the company suggested it is not routinely used. The ERG notes that the final scope issued by NICE includes*	Canakinumab is <u>not</u> used in the third-line treatment setting in NHS practice, nor is it routinely used for patients who have exhausted all other treatment options. This is aligned with clinical opinion provided to both Sobi and the ERG. Sobi acknowledges that the final scope issued by NICE lists canakinumab as a potential comparator. The ERG is correct to highlight that in order to review an economic model that is fully aligned with this scope, a comparison to third-line canakinumab is needed. However, the context in which these statements are provided by the ERG may imply that canakinumab is currently used in practice. Sobi did consider including a comparison to canakinumab within the model, but opted not to provide this within its submission given that based on the unanimous clinical advice provided, it was abundantly clear that canakinumab is not relevant when considering current NHS practice.	This is not a factual inaccuracy. Third line setting in the model implicitly means treatment for patients who have entered the unresolved disease having exhausted all other treatment options other than BMT and canakinumab (as stated in p 192 of the CS). It is only in this state that patients can receive canakinumab and doing so is consistent with clinical advice to the ERG and the company.

to other recommended treatments, including anakinra and tocilizumab. This is also mirrored by clinical advice provided to the ERG: *"Clinical advice to the ERG is that canakinumab would be considered once all other treatment options had been exhausted."* ERG report, page 67. The ERG's rationale for suggesting canakinumab should be included within the model as a third-line option is based entirely on the NICE final scope, which is misaligned with current treatment practice. Sobi's rationale for not including canakinumab as a third-line option is based on NHS policies and clinical advice provided to Sobi concerning current practice. The ERG's suggestion that canakinumab should have been included as a third-line comparator (and for patients with unresolved disease) is directly contradictory with clinical advice provided to both Sobi and the ERG, but is aligned with the final NICE scope. Failure to clearly state these two facts within the text is misleading, and implies omission of treatments relevant to current practice within the submitted model.	*canakinumab as a comparator in the third-line setting, therefore, treatment with canakinumab should have been considered by the company."*		
On page 14 of the ERG's report, it is stated: *"model time horizon was not sufficiently*	Sobi requests the ERG amend this statement to briefly explain Sobi's rationale for adopting a shorter-than-	Edit made to the ERG's text to align with the description provided by Sobi in the CS. The added text is lifted from	This is not a factual inaccuracy. The ERG stated (ERG report p 67) the reasons why the time

long to allow all costs and benefits to be captured" Sobi appreciates that a lifetime horizon for this patient population is longer than 30 years (given that most patients are expected to die from non-disease related causes if managed effectively). However, a 30-year time horizon was selected such that the majority of the difference in costs and effects between treatment strategies may be captured. This was described in the CS: *"In the base-case analysis a 30-year horizon was selected as a suitable balance between computational burden and reflecting differences in costs and outcomes."* Document A, page 120 The ERG's text could be misleading, as omission of Sobi's explanation for its choice of model time horizon implies that Sobi considered 30 years was long enough to "allow all costs and benefits to be captured".	ideal time horizon: *"model time horizon was not sufficiently long to allow all costs and benefits to be captured (but considered by the company to be long enough to reflect all important differences in costs or outcomes between the technologies being compared)"*	a later section of the ERG's report (Section 3.6, page 29) for consistency.	horizon was not long enough and does not accept that the model would have been made too complex by extending the time horizon.
On page 15, the ERG report states: *"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."*	Sobi proposes that the ERG revisit these statements and adapt them based on the explanations provided concerning factual inaccuracies (in the rows above). Specific edits are not provided by Sobi, as Sobi acknowledges that the statements made are based on the ERG's opinion.	Sobi requests that the ERG revisits these statements specifically in light of the explanations provided as part of this FAC response.	This is not a factual inaccuracy but a matter of opinion. The ERG considers that the model structure contains flaws that in combination with the weak evidence base means that the model results are not informative. Whether some of the assumptions are conservative is immaterial if the

Also, on page 73, the ERG states: *"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."* Sobi understands that the model is subject to unavoidable uncertainty (primarily due to the limited clinical evidence base), but disagrees that the results of the model are "uninformative and potentially misleading"; especially in light of some of the factual inaccuracies highlighted. Sobi requests that the ERG revisits its statement concerning the model's structure in light of the explanations provided. In addition, the ERG's suggestion that the results "would, at best, be uninformative and, at worst, misleading" fails to acknowledge the numerous conservative assumptions made by Sobi within the model, which were described in the CS: *"There are several aspects of the submitted model that may underestimate the benefit that anakinra provides, primarily due* [to] *data availability. For example, long-term health and side effects for all other*			evidence base is weak and the model is structurally flawed.

treatments (such as stunted growth for corticosteroids) were not explicitly modelled, and other long-run consequences of poor disease control (such as the development of osteoarthritis) were also omitted from the analysis. While not captured within the economic analysis, the increased risk of such negative health effects are nonetheless real consequences of poor disease control, for which the use of anakinra is expected to reduce the number of patients affected." Document B, page 182			
On page 73 of the report, the ERG states: *"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."* The model was developed based on the structure used to inform the previous NICE assessment of tocilizumab for sJIA (TA238) – the only economic evaluation identified by Sobi's systematic review. When developing the model, adjustments were made based on changes in disease management over time (i.e. focusing on achieving remission, as opposed to improvement in ACR Pedi scores), and limitations highlighted as	Sobi asks the ERG to reconsider its position with respect to the usefulness of the submitted model for decision making, based on the information provided in the CS and this FAC response. Specific edits are not provided by Sobi, as Sobi acknowledges that the statements made are based on the ERG's opinion.	Sobi has requested the ERG revisit this statement specifically in light of the explanations provided as part of this FAC response.	This is not a factual inaccuracy but a matter of opinion. The ERG commended the company in the ERG report (p 64) and does so again here for producing a model that tried to address the decision problem. However, the evidence base is weak and the model structure flawed which is why the ERG suggested that a cost minimisation analysis may be a more appropriate method to assess anakinra.

part of this appraisal (e.g. using a rounded number of weeks as the model cycle length, ensuring the health states are mutually-exclusive etc.). In addition, aspects not captured within the TA238 model but deemed important by clinical experts (e.g. MAS) were also included. Mirroring Sobi's comments provided in the responses written above, the evidence base for anakinra in Still's disease is unavoidably limited. Still's disease affects less than 0.005% of the UK population*, and future clinical trials of anakinra within this population to address uncertainties are unlikely to be possible (as seen with the terminated anaSTILLS trial). Consequently, a number of assumptions were necessary to make when developing the model. Sobi considers it extremely important to note that the understanding of Still's disease is ever-developing. Since the introduction of anakinra in 2002 in the EU for the treatment of rheumatoid arthritis, there has been substantial improvements in understanding the differences between autoimmune and autoinflammatory diseases, as well as the role of IL-1 inhibition. Nevertheless, many aspects of Still's disease are still not understood, and few studies have to date been carried out. As an example of recent developments, in December 2019, Klein *et al.*			

published long-term safety data concerning biologics for sJIA with regard to adverse events of special interest was assessed. This study found that MAS occurred in all cohorts with a higher frequency in patients with canakinumab (3.2/100 patient years [PY]) and tocilizumab (2.5/100 PY) vs anakinra (0.83/100 PY).[1] Sobi strongly disagrees that the submitted model cannot be used to inform decisions on the cost effectiveness of anakinra. In addition to several of the criticisms highlighted by the ERG which Sobi notes are factually inaccurate, the submitted model provides a synthesised summary of all available (and suitable) economic and clinical evidence concerning the use of anakinra and its comparators for the treatment of Still's disease. In addition, the model allows for a number of structural assumptions to be explored and tested, which the ERG has opted not to consider.			

*0.005% based on the ratio of 1,800 estimated patients in England, and the population of England ~56 million.

[1]Klein *et al.* Long-term surveillance of biologic therapies in systemic-onset juvenile idiopathic arthritis: data from the German BIKER registry. Rheumatology (2019); 0:1–12.

Issue 2 Errors in interpretation and criticism of the evidence base and treatment pathway

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 9 of the report, the ERG	In order to more accurately reflect the	The evidence base for anakinra in	This is not a factual error, but an

states: *"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."* Sobi does not consider the trial evidence provided to be irrelevant or the results from these studies to be unreliable. The terms "(not/ ir-) relevant" and "(not/ un-) reliable" are also used in the following pages of the ERG's report within this same context: • Section 1.4, page 11 • Section 1.6, page 12 • Section 1.8.2, pages 13-14 • Section 3, page 25 • Section 3.1, page 26 • Section 3.5, page 29 • Section 4.2.1, page 36 • Section 4.5, page 43 • Section 5.4.2, page 63 • Section 5.4.3, page 64	nature of the evidence base available for anakinra, and its applicability to the decision problem, Sobi suggests this text be amended in accordance with the following: *"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 notes that the available RCT evidence considers comparisons of anakinra to csDMARDs in patients with sJIA or AOSD – most of whom had previously been treated with csDMARDs. Consequently, evidence from these studies does not cover the full 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 uncertain."* Elsewhere within the ERG's report, Sobi requests the ERG to reconsider its use of the terms "(not/ ir-) relevant" and "(not/ un-) reliable" as per the above suggestion. Sobi understands the evidence is uncertain, and does not cover the full scope issued by NICE, but highlights that the ERG's choice of vocabulary does not point to the evidence being unreliable. Sobi suggests changing "irrelevant" to "fully	Still's disease is unavoidably uncertain. However, the terms "not relevant" and "unreliable" have specific connotations which Sobi does not consider to apply here. • "Not relevant" implies that the studies do not provide any information useful to the decision problem • "Unreliable" implies that the study conduct was potentially compromised and/or that the results could not be feasibly reproduced The studies were conducted in patients with Still's disease, and the comparator treatments are representative of the standard of care at the time the studies were conducted. As correctly highlighted by the ERG, the RCT evidence does not cover the full NICE scope, but this does not render the evidence irrelevant. This point is aligned with several statements provided by the ERG elsewhere within its report, such as: *"The ERG considers that the company has provided all the available (RCT and non-RCT) evidence that is relevant to the current appraisal."* and *"However, the company has presented relevant evidence from a published UK registry study"*.	opinion. In the report, the ERG explains why results from the included studies are not considered as relevant to the decision problem and the results were unreliable. The ERG considers results from studies with small sample sizes and short follow-up periods to be unreliable as there is a high likelihood that different results would be obtained if the trial were to be repeated. No change is required.

• Section 5.4.4, page 65	aligned with the NICE final scope", and that "unreliable" should be changed to "uncertain".	The evidence from these studies is inherently uncertain (owing to unavoidably small sample sizes and limited follow up), yet this does not mean the results are unreliable. Amendment of this text within the ERG's report is intended to appropriately reflect the ERG's criticisms of the evidence base by using more specific terminology.	
On page 21 of the report, the ERG states: *"The company correctly states (CS, p29 and Figure 1) that the NHS England Commissioning Policy 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)."* Clinical advice provided to Sobi (by two paediatric and two adult rheumatologists) was that in the NHS most patients are treated in line with the appropriate policy. Children with sJIA receive one DMARD before biologics (NHS England Policy E03X04) and adults with AOSD receive two DMARDS before biologics	Sobi requests that the ERG's report be amended to acknowledge the conflicting clinical opinion provided to the company and to the ERG: *"The company correctly states (CS, p29 and Figure 1) that the NHS England Commissioning Policy 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."*	Clinical advice provided to the company and to the ERG is contradictory in this instance, yet the ERG's report does not acknowledge this. By including this statement, this area of disagreement can be appropriately reflected in the ERG's report, and subsequently can be considered by the NICE technical team and Appraisal Committee.	Thank you. The text has been amended as advised.

(NHS England Policy 170056P). The clinical advice provided to the ERG is contradictory to the published NHS Clinical Commissioning Policy for AOSD, as well as the clinical advice provided to Sobi.			
In two statements within the ERG's report, the post-marketing experience of anakinra is referred to: *"The safety profile of anakinra in other diseases is well known and there is 15 years of post-marketing experience in a number of licensed indications, including rheumatoid arthritis"*, page 13 *"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 15 years of post-marketing experience in a number of licensed indications."*, page 42 In the CS it was stated that there is more than 15 years of post-marketing experience with anakinra. Anakinra was first granted a marketing authorisation by the European Medicines Agency (EMA) on 8 March, 2002; and by the Food and Drugs Agency (FDA) on November 14, 2001.	Sobi requests that the ERG's report be revised to align with the description provided within the CS concerning post-marketing experience with anakinra: *"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"*, page 13 *"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."*, page 42	This minor modification of the ERG's report is intended to clarify the source of the 15 years figure, and note that there is more than 15 years of experience (within the context of the EMA approval, there is close to 18 years of post-marketing experience at the time of writing).	Thank you. The text has been amended as advised.

On page 29 of the ERG's report, the available RCT evidence for anakinra is presented in Table 4. Within this table, the study by Nordstrom *et al.* is described as a study of anakinra versus placebo. This is incorrect – the comparator treatment in this study was csDMARDs (not placebo).	Sobi requests that the ERG revise Table 4 to clarify that the Nordstrom *et al.* study was csDMARD controlled, and not placebo controlled.	This proposed edit to the ERG's report is intended to clarify the comparator treatment used in the Nordstrom *et al.* study.	Thank you. Table 4 has been amended as advised.

Issue 3 Miscellaneous errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The measure of response in studies of sJIA is typically the ACR Pedi score. In the ERG's report, this is often referred to as the JIA ACR measure, which is incorrect. This is referred to in the list of abbreviations, as well as on pages 11, 27, 35, 40, and 68.	Sobi requests that the ERG revises its report to change "JIA ACR" to "ACR Pedi".	Correction of the measure used in the studies is intended to improve the clarity of reporting, and avoid potential confusion in the outcome measures collected. Furthermore, JIA refers to juvenile idiopathic arthritis for which sJIA is considered a subtype – clarifying that the measure is not sJIA- or JIA-specific is important for context.	Thank you. The text has been amended as advised.
On page 8, the ERG refers to the dosing of anakinra: *"It is available in pre-filled syringes and administered via subcutaneous injection with dose varying depending on body weight."* While true, the dose only depends on body weight for patients with a body weight of less than 50kg. For patients with a body weight of 50kg or more, the licensed dose of anakinra is fixed	Sobi requests that the ERG modifies its description of the dosing of anakinra to explicitly state the nature in which it is administered. For example: *"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*	Modification of the ERG's description of anakinra's dosing is intended to clarify which parts of the patient population would have a weight-based dose versus which patients would receive a fixed dose. The majority of patients would require a single, fixed dose of anakinra which is simple to administer.	Thank you. The text has been amended as advised.

at 100 mg per day by subcutaneous injection (i.e. one pre-filled syringe)	*100mg/day for patients weighing 50kg or more).*		

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

Anakinra for treating Still's disease

This document is the technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- topic background based on the company's submission
- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

1. Summary of the draft technical report

1.1 In summary, the technical team considered the following:

Issue 1 It is unlikely that the 'per-label' pathway would be realised in NHS clinical practice because tocilizumab is only recommended for use after immunosuppressants including methotrexate.

Issue 2 Canakinumab is not a relevant comparator for anakinra after conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) because it is not used in NHS clinical practice for treating systemic juvenile idiopathic arthritis (sJIA) and adult-onset Still's disease (AOSD).

Issue 3 More evidence is needed to show that anakinra and tocilizumab are equally effective.

Issue 4 There is insufficient evidence to suggest that the overall remission rate would be higher when csDMARDs are removed from the treatment pathway and biologics are used earlier in the treatment pathway.

Issue 5 It is important to reflect the administration costs of tocilizumab accurately in the cost-effectiveness analysis, according to current NHS clinical practice.

Issue 6 No evidence has been presented to support any of the scenario analyses about treatment discontinuation, including the company's base case, over the others.

Issue 7 The most plausible remission rate from treatment with csDMARDs is unknown for people with chronic disease, but is likely to be higher than 0.

1.2 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- The clinical trials only included small numbers of patients and had short follow-up periods.

- The comparators used in the trials do not reflect current practice in the NHS in England.

1.3 The technical team does not have a preferred incremental cost-effectiveness ratio (ICER) (see table 1) because the robustness of the cost-effectiveness model and the extent to which it reflects NHS clinical practice is unclear. The cost-effective estimates include the company's assumption of the commercial arrangement for tocilizumab. Estimates with the actual commercial arrangement for tocilizumab are confidential and cannot be reported here. However, in the company's base case, the 'per label' pathway would remain dominant if the commercial arrangement were included.

1.4 The technology is unlikely to be considered innovative (see table 3).

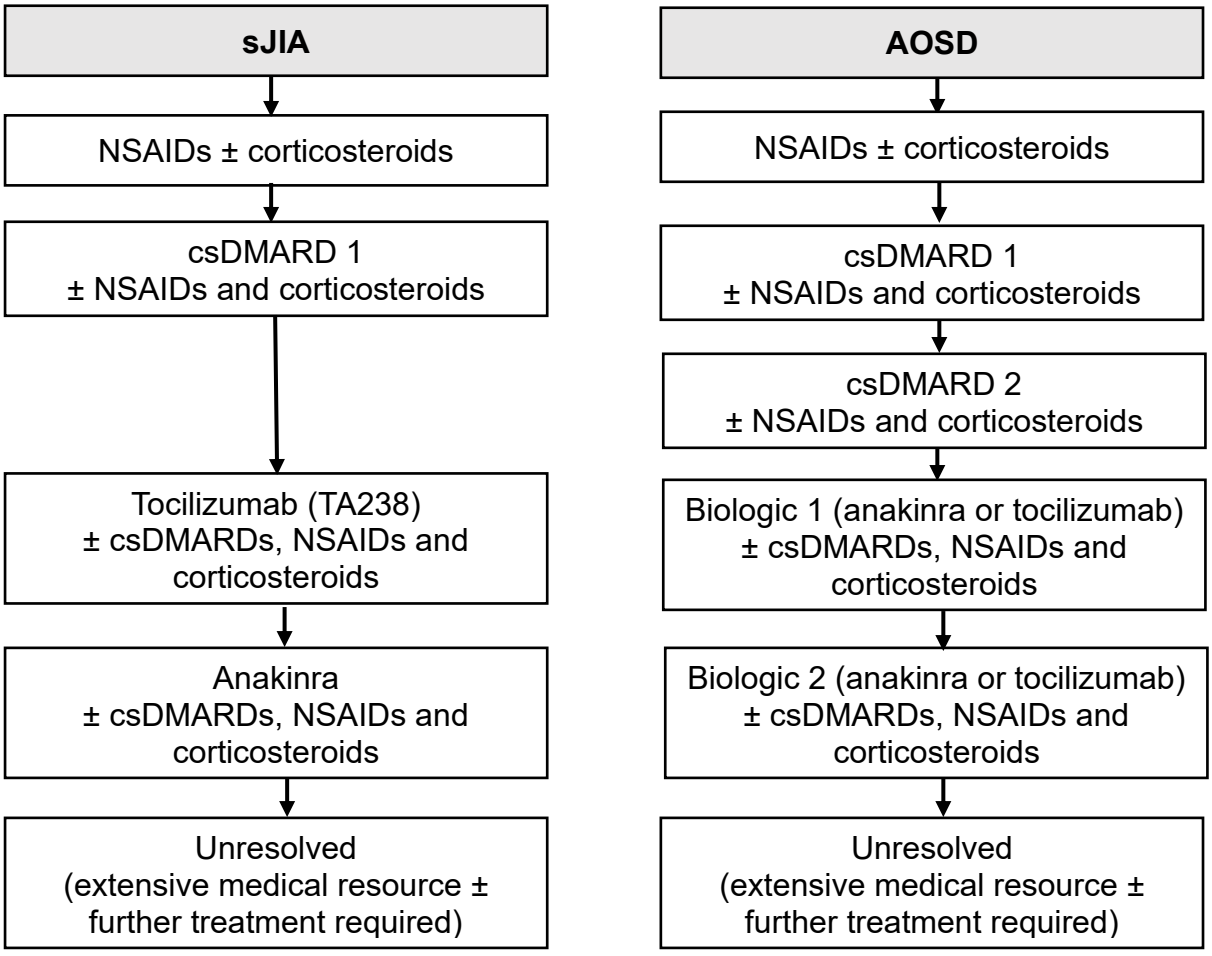
1.5 No equality issues were identified.

2. Topic background

2.1 Disease background

- Rare systemic inflammatory disorder
  - In children: systemic juvenile idiopathic arthritis (sJIA)
    - ◊ onset usually 3-5 years and resolves before adulthood for 50%
  - In adults: adult-onset Still's disease (AOSD)
    - ◊ primarily affects young adults
  - can either be monocyclic, where people only have 1 disease flare followed by lifelong remission, or chronic, where people have repeated disease flares or persistent disease
- Affects between 400 and 800 adults and around 1,000 children in England
- Symptoms vary between people but include fever, joint and muscle pain and swelling
- Generally a progressive disease leading to significant pain, joint destruction and functional decline

2.2 Treatment pathway



NSAID, non-steroidal anti-inflammatory drug; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug

- An NHS England clinical commissioning policy recommends anakinra for systemic juvenile idiopathic arthritis (sJIA) that does not respond to tocilizumab and for macrophage activation syndrome.
- An NHS England clinical commissioning policy recommends anakinra and tocilizumab for adult-onset Still's disease (AOSD) that is refractory to second-line therapy.
- Tocilizumab does not have a marketing authorisation for treating AOSD.
- In AOSD, clinical consensus suggests that tocilizumab may be chosen in preference to anakinra for patients where joint inflammation predominates and anakinra in preference to tocilizumab where systemic symptoms predominate.

2.3 Anakinra

Marketing authorisation (April 2018)	Indicated in adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg 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 given as monotherapy or in combination with other anti-inflammatory drugs and disease-modifying antirheumatic drugs (DMARDs).
Mechanism of action	Anakinra inhibits binding of interleukin-1α (IL-1α) and interleukin-1β (IL-1β) to interleukin-1 type I receptor (IL-1RI). Interleukin-1 (IL-1) is a pro-inflammatory cytokine mediating many cellular responses including those important in synovial inflammation.
Administration	Subcutaneous injection
Price	£183.61 for 7 injections [BNF online] Average cost of 1 year of treatment is £9,580.51 [company submission]

2.4 Clinical evidence

sJIA:

	Ilowite (2008)	**Quartier (2011) (ANAJIS)**	**Kearsley-Fleet (2019)**
Design	Two-part trial: - Randomised, blinded (1 month) - Open-label treatment (12 months)	Three-part trial: - Open-label run in (12 wks) - Randomised, double-blind (16 weeks) - Open-label extension (12 months)	Non-randomised UK registry
Population	Aged 2-17 with polyarticular-course JRA. Subgroup of	Aged 2-20 with sJIA for >6 months.	sJIA + starting either tocilizumab or anakinra from 01/01/10 with

	people with sJIA (n=15).		baseline and 1-year data returned before 31/12/16.
Previous treatments	NSAIDs, systemic corticosteroids and csDMARDs	NSAIDs, systemic corticosteroids and csDMARDs	Methotrexate, corticosteroids, biologic treatments
Intervention	Anakinra 1 mg/kg/day	Anakinra 2 mg/kg daily	Anakinra
Comparator	Placebo	Placebo	Tocilizumab
Outcomes	Disease activity Adverse effects	Disease activity Adverse effects	Disease activity Treatment survival
JRA, juvenile rheumatoid arthritis			

AOSD:

	Nordström (2012)
Design	Two-part trial: Open-label RCT (24 weeks) Open-label extension (28 weeks)
Population	AOSD refractory to corticosteroids and DMARDs
Intervention	Anakinra 100 mg/day
Comparator	DMARDs: methotrexate, azathioprine, leflunomide, cyclosporine A, sulfasalazine
Outcomes	Disease activity Adverse effects Health-related quality of life

2.5 Key trial results

sJIA

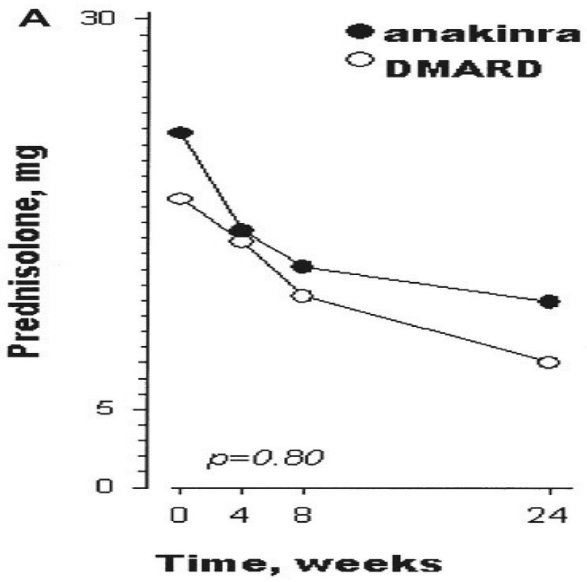
	Ilowite, 2009 (n=15 with sJIA, n=11 in double-blind phase)	**Quartier, 2011 (N=24)**	**Kearsley-Fleet, 2019 (N=76)**
Comparison	Placebo	Placebo	Tocilizumab (n=54)

Disease activity: Response /remission	Open label phase: 73% were responders on the ACRPedi scale Double-blind phase, flares at week 28: Anakinra, 2/9 Placebo, 1/2	Responders (modified ACRPedi30) at 1 month: Anakinra, 8/12 (67%) Placebo, 1/12 (8%) P = 0.003	Responders (ACRPedi90) at 1 year: Anakinra, 31% Tocilizumab, 46% OR 1.9 [95% CI 0.4, 7.8]; p=0.4

AOSD

Nordström, 2012 (N=22)	Proportion of patients in remission (%)	
Timepoint (Weeks)	Anakinra (n=12)	csDMARD (n=10)
4	50	30
8	58	50
24	50	20

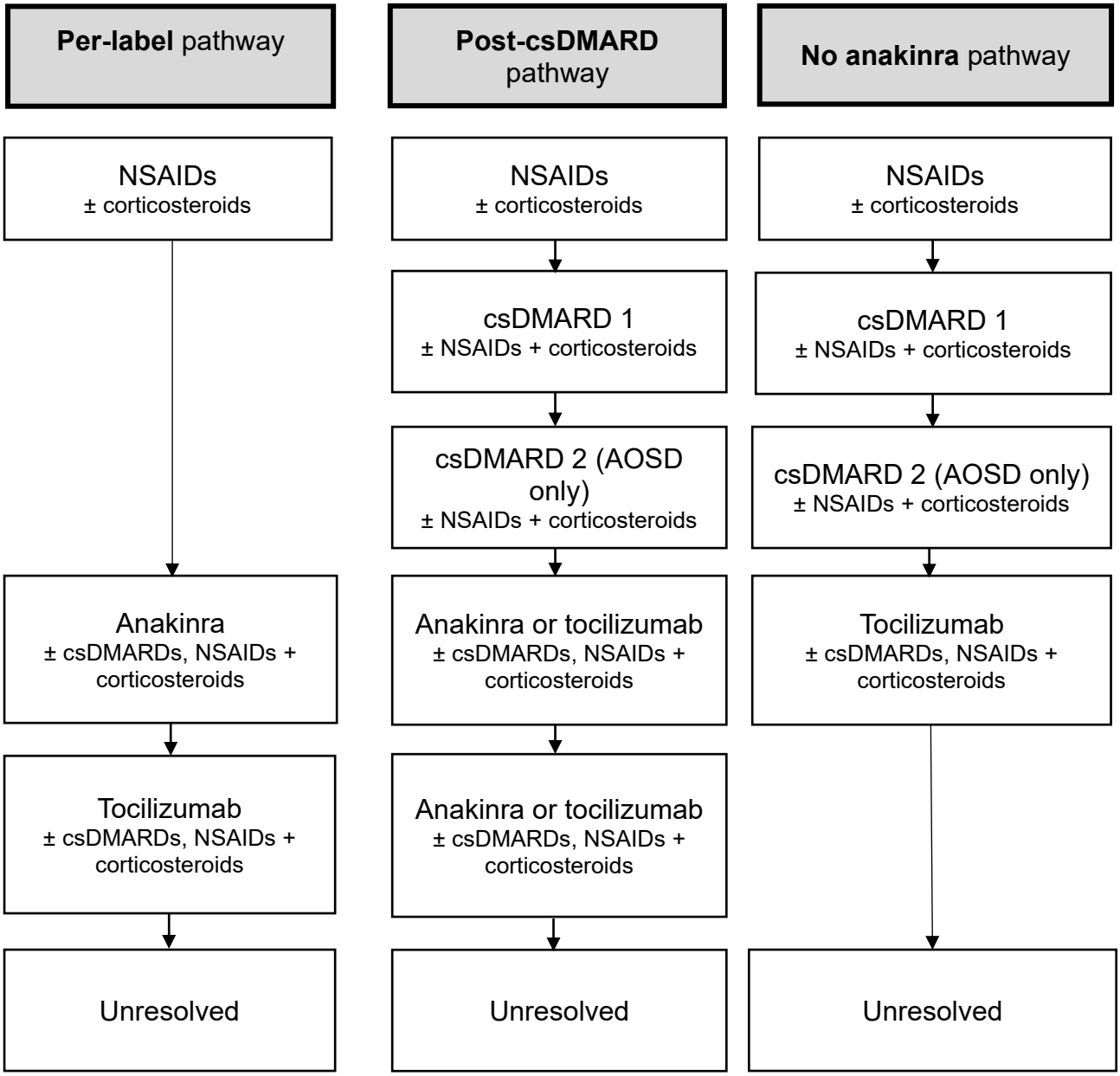
Prednisolone reduction: By week 24, prednisolone equivalent doses could be significantly reduced by a mean 10.8 mg in the anakinra group and 10.5 mg for the csDMARDs group. 3 patients on anakinra and 0 on csDMARDs discontinued oral corticosteroids but the difference was not statistically significant (p=0.22).



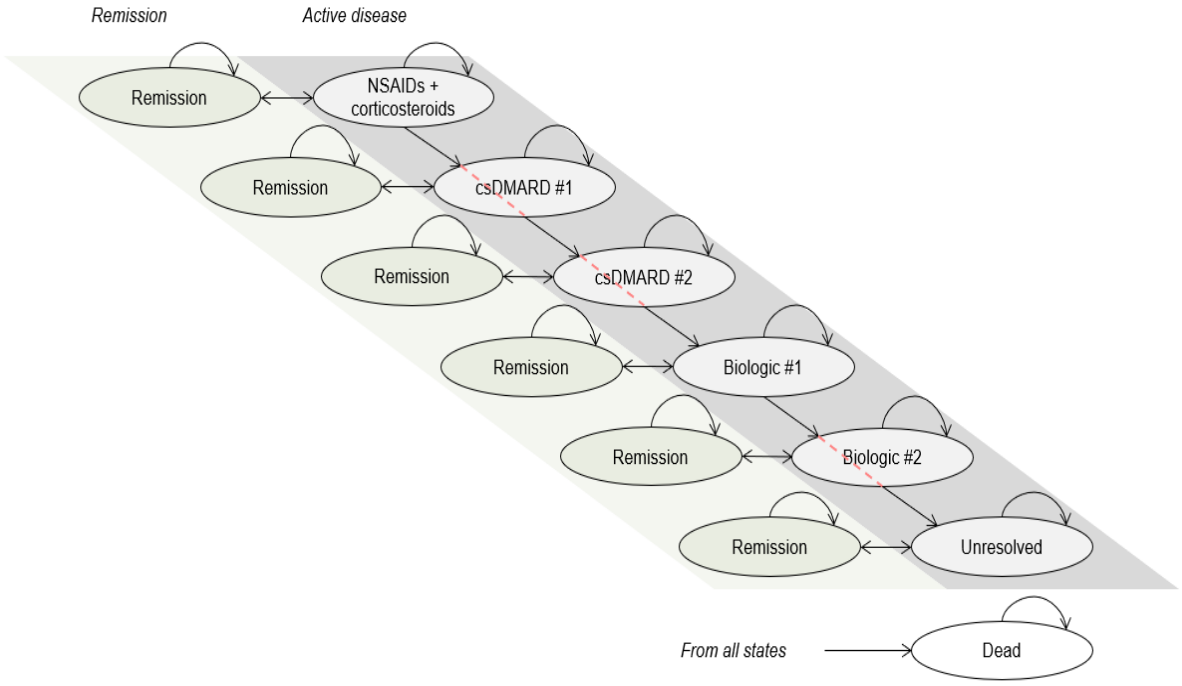
2.6 Model structure

- Considers 3 different ‘states of the world’
- Compares alternative treatment pathways, rather than comparing anakinra directly with other treatments available at each stage of the pathway

- Includes people with AOSD with monocyclic disease, AOSD with chronic disease, sJIA with monocyclic disease and sJIA with chronic disease



Model structure



- Markov state-transition model
- 30-year time horizon
- Utility values derived from non-linear model to map Childhood Health Assessment Questionnaire (CHAQ) scores to EQ-5D values, as used in TA238, and further adjusted for age
- In the company's base-case analysis, anakinra and tocilizumab are assumed to have equal efficacy (i.e. equal probability of remission).
- Following loss of remission, patients receive the last treatment they were previously given.
- Mortality is assumed equal to the general population (Office for National Statistics values), except for:
  - People with macrophage activation syndrome (MAS), at any time in pathway: 12.9% excess mortality risk for each episode, based on Kumakura et al.
  - People with bone marrow transplant (BMT), in the 'unresolved' health state: 12.5% excess mortality risk for each episode based on Silva et al. (2018).

2.7 Key model assumptions

Remission and treatment discontinuation probabilities (weekly)

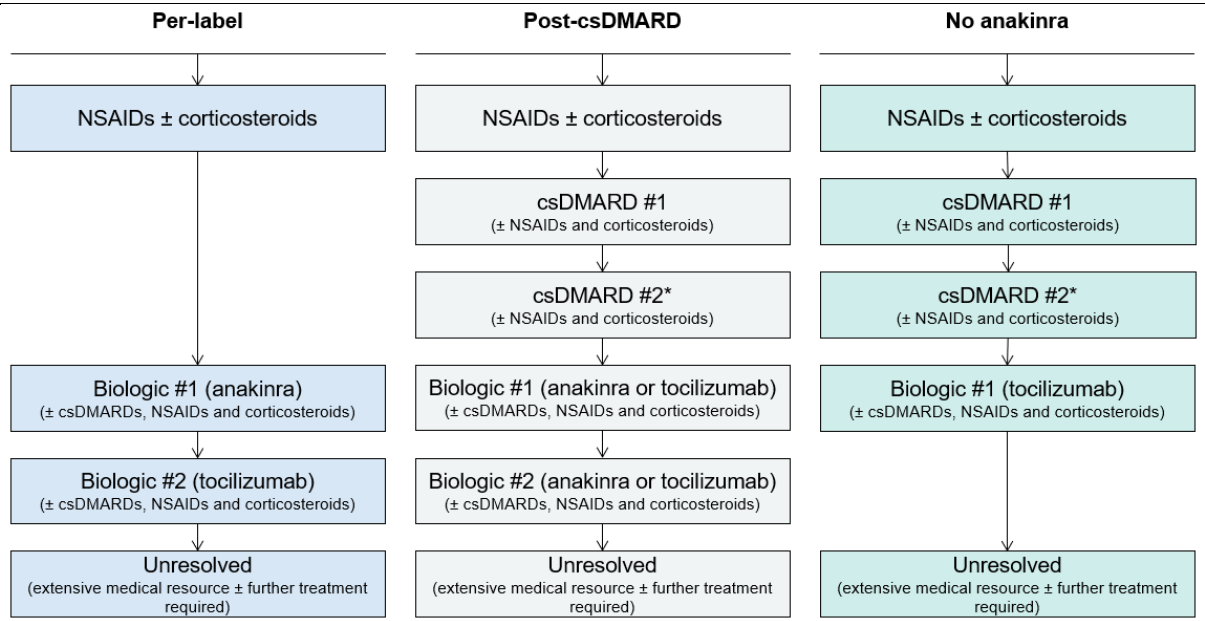
Health state	Remission	Treatment discontinuation
NSAIDs and corticosteroids – monocyclic disease	12.56%*	27.31%*
NSAIDs and corticosteroids – chronic disease	0% (expert opinion)	39.90%*
csDMARDs – monocyclic disease	0.93% (Nordström)	16.23%*
csDMARDs – chronic disease	0% (expert opinion)	17.07%*
Anakinra and tocilizumab – post-NSAIDs + corticosteroids	4.41% (Horneff)	1.14% (TA238)
Anakinra and tocilizumab – post-DMARDs	2.85% (Nordström)	1.14% (TA238)
Unresolved - canakinumab	Set to maximum of achieving remission with anakinra or tocilizumab post-DMARDs (assumed conservative)	Occupied until remission or death
Unresolved – bone marrow transplant, survivors	100% (assumed conservative)	Occupied until remission or death

*Probabilities were calculated to calibrate the model based on expected outcomes e.g. probabilities were varied until the model predicted that 5% of patients remain on treatment after 6 weeks (NSAIDs and corticosteroids) or 16 weeks (csDMARDs). Number of weeks reflects NHS England commissioning policies; 5% estimate is an arbitrary estimate made by company.

3. Key issues for consideration

Issue 1 – Treatment pathway

Questions for engagement	1. Does the 'post-csDMARD' pathway in figure 1 reflect clinical practice for treating systemic juvenile idiopathic arthritis (sJIA) and adult onset Still's disease (AOSD) in the NHS in England? In AOSD, would a biologic drug only be used after 2 conventional DMARDs? 2. Would the 'per-label' pathway in figure 1 be implemented in NHS clinical practice? That is, would anakinra and tocilizumab be used after NSAIDs and corticosteroids (rather than after csDMARDs)? 3. What treatments are likely to be used for people in the 'unresolved' health state in clinical practice? For example, would people be likely to receive NSAIDs or csDMARDs again? **Figure 1: Treatment pathways compared in the company's model (Figure 8, company's submission)**



NSAID, non-steroidal anti-inflammatory drug; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug

Background/description of issue

The company presented a cost–utility model comparing 3 treatment pathways: 'per-label', 'post-csDMARD' and 'no anakinra' (see figure 1). The company explained that Still's disease can either be monocyclic, where people only have 1 disease flare followed by lifelong remission, or chronic, where people have repeated disease flares or persistent disease. In the company's model, 74.5% of patients are assumed to have chronic disease. In the 'post-csDMARD' pathway, people with systemic juvenile idiopathic arthritis (sJIA) received only 1 csDMARD before a biologic drug, and then received tocilizumab before anakinra, in line with NHS England's commissioning policy for juvenile idiopathic arthritis (JIA) and NICE's appraisal of tocilizumab for the treatment of sJIA. People with adult-onset Still's disease (AOSD) received 2 csDMARDs before a biologic drug, and could receive either tocilizumab or anakinra as the first biologic drug, in line with NHS England's commissioning policy for AOSD. In the 'unresolved' health state, the only treatment included in the company's base-case model was bone marrow transplant.

	The company proposed that anakinra could be used as the first DMARD following NSAIDs and corticosteroids, instead of after other DMARDs (the 'per-label' pathway in figure 1). The company's base-case results showed that the 'per-label' pathway was dominant (cheaper and more effective) compared with the 'post-csDMARD' pathway, and the 'post-csDMARD' pathway was dominant compared with the 'no anakinra' pathway. **The ERG** highlighted that the clinical evidence that the company had presented only considered anakinra use after DMARDs. **The technical team** noted that in the 'per-label' pathway, both anakinra and tocilizumab were used after NSAIDs and corticosteroids, rather than after csDMARDs. This does not reflect the recommended position of tocilizumab in NHS England's commissioning policy for AOSD. The company stated that because anakinra is a biological DMARD, using tocilizumab after anakinra in the 'per-label' pathway would be consistent with the current commissioning criteria. However, the technical team noted that: • the NHS commissioning policy for AOSD states that tocilizumab will only be commissioned when disease has not responded to or is intolerant of standard immunosuppressive therapy, including at least 2 of methotrexate, cyclosporine, azathioprine, leflunomide and mycophenolate, and • NICE's appraisal of tocilizumab for the treatment of sJIA states that tocilizumab is not recommended for people who have not been treated with methotrexate.
Why this issue is important	The modelled treatment pathways should reflect current practice in the NHS and the proposed pathway if anakinra were to be recommended, so that the cost-effectiveness results are suitable for decision making.
Technical team preliminary judgement and rationale	It is unlikely that the 'per-label' pathway would be realised in NHS clinical practice because tocilizumab is only recommended for use after immunosuppressants including methotrexate.

Issue 2 – Comparators

Questions for engagement	4. Is canakinumab used in the NHS for treating sJIA and AOSD after DMARDs?
Background/description of issue	Canakinumab has a marketing authorisation for treating active Still's disease including sJIA and AOSD after NSAIDs and systemic corticosteroids. The final NICE scope for anakinra included canakinumab as a comparator. In its model, **the company** included an option for people in the 'unresolved' health state to receive canakinumab. However, in its base-case analysis, the company assumed that no one would receive canakinumab because it is not recommended in current NHS clinical commissioning policies for sJIA or AOSD. **The ERG** considered that canakinumab should have been included as a comparator because it was included in the final scope. However, clinical advice received by the ERG was that canakinumab is not routinely used in the NHS to treat Still's disease, but that it could be considered once all other treatment options have been exhausted. **The technical team** notes that canakinumab is not recommended in the NHS England commissioning policies for treating sJIA or AOSD, and that the NICE appraisal of canakinumab for treating sJIA (TA302) was terminated.
Why this issue is important	If canakinumab is used in NHS clinical practice, it would be important to include it in the analyses so that anakinra could be compared with the established current practice.
Technical team preliminary judgement and rationale	The technical team considers that canakinumab is not a relevant comparator for anakinra after DMARDs because it is not used in NHS clinical practice for treating sJIA and AOSD. However, it may be appropriate to include canakinumab in the model for some patients in the 'unresolved' health state.

Issue 3 – Relative efficacy of anakinra and tocilizumab

<table>
<tr><td>Questions for engagement</td><td>5. Do you consider the efficacy of anakinra and tocilizumab to be similar in terms of:
a) achieving and retaining remission
b) adverse events
c) treatment discontinuation rates?
6. What are the clinical reasons why either tocilizumab or anakinra would be chosen as treatment over the other?</td></tr>
<tr><td>Background/description of issue</td><td>In its model, the company assumed that anakinra and tocilizumab were equally effective in achieving remission. This assumption was based on clinical advice because there are no head-to-head randomised controlled trials comparing anakinra with tocilizumab in sJIA or AOSD.
The ERG noted that the clinical evidence used to populate the company's model was limited because the randomised trials had small numbers of patients, short follow-up and did not compare anakinra with the relevant comparators. The ERG considered that the company's cost-effectiveness results were not a suitable basis for decision making because of the weaknesses in the available clinical evidence, in addition to structural issues with the economic model (see issues 6 and 7). Therefore, the ERG did a cost minimisation analysis that also assumed equal efficacy between anakinra and tocilizumab. The assumption of equal efficacy was based on clinical advice to the ERG that the effectiveness of anakinra and tocilizumab in achieving and maintaining remission, the adverse event rates and treatment discontinuation rates are likely to be similar. The results of the ERG's cost minimisation analysis showed that the cost per week of treatment with anakinra was lower than that with tocilizumab (not including the confidential discount for tocilizumab).
<table>
<tr><th>Population</th><th>Anakinra weekly cost</th><th>Tocilizumab weekly cost</th></tr>
<tr><td>People with sJIA (weight=25kg: assuming 80% of patients receive IV tocilizumab)</td><td>£183.61</td><td>£290.28</td></tr>
<tr><td>People with sJIA (weight=50kg): assuming 80% of patients receive IV tocilizumab</td><td>£183.61</td><td>£313.11</td></tr>
<tr><td>People with AOSD</td><td>£183.61</td><td>£229.15</td></tr>
</table>
</td></tr>
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	The technical team noted that there was limited evidence that anakinra and tocilizumab were equally effective. It also noted that the NHS England Commissioning Policy stated that anakinra and tocilizumab may be used differently in clinical practice, such that tocilizumab may be used where joint inflammation predominates and anakinra where systemic symptoms predominate. Therefore the technical team was concerned about considering the 2 treatments as equal.
Why this issue is important	A cost minimisation analysis can only be conducted if the treatments are considered to have equal or similar efficacy. The company's cost–utility model also includes this assumption.
Technical team preliminary judgement and rationale	More evidence is needed to show that anakinra and tocilizumab are equally effective, both for the company's model and the ERG's cost minimisation analysis.

Issue 4 – Efficacy of biologics at different points in the treatment pathway

Questions for engagement	7. Would you expect more people to have disease remission overall if anakinra and tocilizumab were used earlier in the treatment pathway and csDMARDs were not used at all?
Background/description of issue	In **the company's** model, it is assumed that more patients would experience disease remission with anakinra and tocilizumab if they were used earlier in the treatment pathway. The remission rate was 4.4% per week if they were used directly after NSAIDs and corticosteroids, and 2.9% a week if used later in the pathway, after csDMARDs. The company's cost-effectiveness results suggested that the 'per-label' pathway, where anakinra and tocilizumab are used earlier in the pathway, would be cheaper and more effective than the 'post-csDMARD' pathway, where anakinra and tocilizumab were used after csDMARDs. The company stated that this was plausible for the following reasons: 1. The clinical evidence does not support the efficacy of methotrexate in Still's disease. 2. The 'window of opportunity' hypothesis, supported by a retrospective study of 57 patients treated with anakinra in Italy, suggests that early sJIA is driven by different mechanisms than chronic sJIA, and that it could be possible to prevent disease from becoming chronic. Therefore, the company proposed that anakinra would be more effective if given earlier in the disease pathway. **The ERG** highlighted that, at every point in the model, the proportion of patients in the unresolved health state was lower in the 'per-label' pathway (where csDMARDs are removed) than in the 'post-csDMARD' pathway (where csDMARDs are included before biologics). Therefore, removing csDMARDs from the pathway (the 'per-label' pathway) led to an increase in the proportion of patients having prolonged remission. The ERG highlighted that: 1. The company presented evidence from the Nordström study, in which 30% of patients in the csDMARD arm had disease in remission at 12 months. This suggests that csDMARDs such as methotrexate are effective for some people. 2. The weekly remission rate for biologics directly after NSAIDs and corticosteroids was derived from the 12-week rate in the Horneff study, while the weekly remission rate for biologics after csDMARDs was derived from the 24-week rate in the Nordström study. However, the Nordström study reported a higher remission rate at 8 weeks, and it was not clear why the 24-week data was selected. The ERG also considered that it was not valid to compare weekly remission rates from different studies measured as different time points.

	The technical team noted that although the company had presented some evidence about the efficacy of methotrexate in Still's disease, a systematic review had not been carried out so the studies identified may not be representative of the overall evidence base.
Why this issue is important	It is important to understand the reasons why the 'per-label' pathway is cheaper and more effective than the 'post-csDMARD' pathway in the company's results, to ensure the results are plausible.
Technical team preliminary judgement and rationale	It is plausible that the overall remission rate at the end of the treatment pathway would be the same whether the biologic drugs are used earlier or later in the pathway. Therefore, it is plausible that the remission rate for biologics may be higher if they were used earlier in the treatment pathway. However, there is insufficient evidence to suggest that the overall remission rate would be higher when there are fewer treatments available in the pathway.

Issue 5 – Tocilizumab administration

Questions for engagement	8. Of people with sJIA receiving tocilizumab, what percentage would receive it: a) subcutaneously b) intravenously? 9. Would people with AOSD receiving tocilizumab all receive it subcutaneously? 10. If someone started receiving intravenous tocilizumab as a child, would they typically continue receiving it intravenously as an adult?
Background/description of issue	A marketing authorisation for a subcutaneous formulation of tocilizumab was granted in September 2019. In **the company's** model, it assumed that of people currently receiving tocilizumab, approximately 50% receive it subcutaneously and 50% receive it intravenously, based on clinical advice to the company. No administration costs were included for people receiving tocilizumab subcutaneously as it was assumed to be self-administered. In **the ERG's** cost minimisation analysis, it assumed that of people with sJIA currently receiving tocilizumab, approximately 20% receive it subcutaneously and 80% receive it intravenously, based on clinical advice to the ERG. The ERG also assumed that everyone with AOSD receiving tocilizumab would receive it subcutaneously.
Why this issue is important	The results from the ERG's cost minimisation analysis are likely to be different if in practice a different proportion of people receive tocilizumab subcutaneously to the proportion included in the current analysis. This is because the weekly cost of subcutaneous tocilizumab could be lower than the weekly cost of intravenous tocilizumab, as no administrations costs are included for subcutaneous tocilizumab.
Technical team preliminary judgement and rationale	It is important to reflect the administration costs of tocilizumab accurately in the cost-effectiveness analysis, according to current NHS clinical practice.

Issue 6 – Treatment discontinuation

Questions for engagement	11. In clinical practice, would someone remain on treatment if it did not lead to a remission?
Background/description of issue	In **the company's** model, changing from one treatment to another in the pathway is set at a fixed probability per weekly cycle for people whose disease is not in remission. This assumption was also made in NICE's technology appraisal of tocilizumab for sJIA (TA238) and the values assumed are the same. The company considered that it is plausible for someone to remain on treatment if their disease does not reach remission because they may get other benefits from the treatment, such as symptom control. Because there are limited data to inform treatment discontinuation rates, the company presented several scenario analyses where the rate was increased or decreased by 20% after 6 or 12 months, either for all treatments or just for biologics. In all scenario analyses presented, the 'per-label' pathway was cheaper and more effective than the 'post-csDMARD' pathway, and the 'post-csDMARD' pathway was cheaper and more effective than the 'no anakinra' pathway. **The ERG** highlighted that the fixed probability for changing from one treatment to another means it is possible for a proportion of patients to remain on the same treatment for the whole of the model time horizon, without their disease reaching remission. For example, after 1 year in the model, over 55% of people receiving their first biologic treatment whose disease had not reached remission were still receiving this treatment, and 33% of people after 2 years.
Why this issue is important	It is important that the assumptions in the economic model best reflect what would happen in clinical practice.
Technical team preliminary judgement and rationale	No evidence has been presented to support any of the scenario analyses, including the company's base case, over the others.

Issue 7 – Remission rates with csDMARDs

Questions for engagement	12. What proportion of people would be likely to reach disease remission with csDMARDs? a. with monocyclic disease b. with chronic disease
Background/description of issue	**The company** assumed that the probability of reaching disease remission with csDMARDs for people with chronic disease was 0%, based on clinical advice received. The company presented a scenario analysis where the probability of reaching disease remission with csDMARDs was the same for people with chronic disease as monocyclic disease. This was a weekly remission probability of 12.56%. In the company's base case and in the scenario analysis, the 'per-label' treatment pathway was cheaper and more effective than the 'post-csDMARD' pathway, and the 'post-csDMARD' pathway was cheaper and more effective than the 'no anakinra' pathway. **The ERG** considered that it was implausible that 74.5% of people in the model would not reach disease remission with csDMARDs. The ERG explained that the remission rates for people with monocyclic disease had been taken from the Nordström study. It highlighted that 30% of patients in the csDMARDs arm of the Nordström study were in remission at 12 months, which does not support using a remission rate of 0% for csDMARDs in the model. However, the ERG stated that the Nordström study recruited patients who were refractory to csDMARDs. It therefore considered that the remission rates for csDMARDs used in the company's model were unreliable.
Why this issue is important	It is important that the assumptions in the economic model best reflect what would happen in clinical practice.
Technical team preliminary judgement and rationale	The most plausible remission rate from treatment with csDMARDs is unknown for people with chronic disease, but is likely to be higher than 0.

Issues for information

Tables 1 to 3 are provided to stakeholders for information only and not included in the technical report comments table provided.

Table 1: Technical team preferred assumptions and impact on the cost-effectiveness estimate

The cost-effective estimates include the company's assumption of the commercial arrangement for tocilizumab. Estimates with the actual commercial arrangement for tocilizumab are confidential and cannot be reported here.

Alteration	Technical team rationale	ICER	Change from base case
Company base case	**–**	**'Per-label' pathway is dominant compared with 'post-csDMARD' pathway (cheaper (-£23,026) and more effective (+0.313 QALYs)).** **'Post-csDMARD' pathway is dominant compared with 'no anakinra' pathway (-£33,764, +0.353 QALYs)**	**-**
1. The per-label pathway may not represent NHS clinical practice	Issue 1	No scenario analyses	-
2. Canakinumab should not be included as a comparator	Issue 2	No change from company's base case	-
3. Insufficient evidence to show that anakinra and tocilizumab are equally effective	Issue 3	No scenario analyses	-
4. Insufficient evidence to show that the overall remission rate would be higher when csDMARDs are	Issue 4	No scenario analyses	-

Alteration	Technical team rationale	ICER	Change from base case
removed from the pathway and biologics are used earlier			
5. Tocilizumab administration costs should reflect current NHS clinical practice	Issue 5	No scenario analyses	-
6. No evidence to support any of the scenarios above another	Issue 6	In all scenario analyses presented, the 'per-label' pathway is dominant compared with the 'post-csDMARD' pathway, and the 'post-csDMARD' pathway is dominant compared with the 'no anakinra' pathway.	-
7. Most plausible remission rate from treatment with csDMARDs is unknown for people with chronic disease, but likely to be higher than 0	Issue 7	In the scenario analysis presented, the 'per-label' pathway is dominant compared with the 'post-csDMARD' pathway, and the 'post-csDMARD' pathway is dominant compared with the 'no anakinra' pathway.	-
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate	**–**	N/A – no scenarios for technical team's conclusions.	-

Table 2: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Small patient numbers	The clinical trials only included small numbers of patients who were followed up for a short time period. • Ilowite trial (sJIA) had a randomised phase of 1 month including 11 patients (12-month open-label extension) • Quartier trial (sJIA) had a randomised phase of 16 weeks including 24 patients (12-month open-label extension) • Nordström trial (AOSD) had a randomised (open label) phase of 24 weeks including 22 patients (28-week open-label extension) The effectiveness estimates are therefore highly uncertain.	Unknown
Comparators in the trials and relevance to NHS clinical practice in England	The NICE scope and marketing authorisation is for anakinra in 3 positions in the treatment pathway: first line, second line after NSAIDs + corticosteroids, and third line after conventional DMARDs. In all 3 trials presented in the submission, patients had all received previous treatment with NSAIDs, corticosteroids and DMARDs. No clinical evidence is presented for first or second line. In third line, the relevant comparator is tocilizumab as this is used in clinical practice. In the trials, the comparator is placebo (although people received concomitant treatments) in children, and DMARDs in adults. Therefore, the effectiveness estimates relative to NHS clinical practice in England are highly uncertain.	Unknown

Table 3: Other issues for information

Issue	Comments
Innovation	The company considers anakinra to be innovative because it specifically inhibits IL-1, which reduces clinical signs and symptoms of sJIA and AOSD. It highlights that use of biologic drugs enables withdrawal of glucocorticoids and that early treatment with an IL-1 inhibitor may prevent the occurrence of chronic arthritis. The technical team considers that all relevant benefits associated with the drug are adequately captured in the model.
Equality considerations	No equalities issues were identified by the company, consultees and nominated clinical experts and patient experts.

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Technical engagement response form

Anakinra for treating Still's disease ID1463

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **Friday 30 October 2020**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.
Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

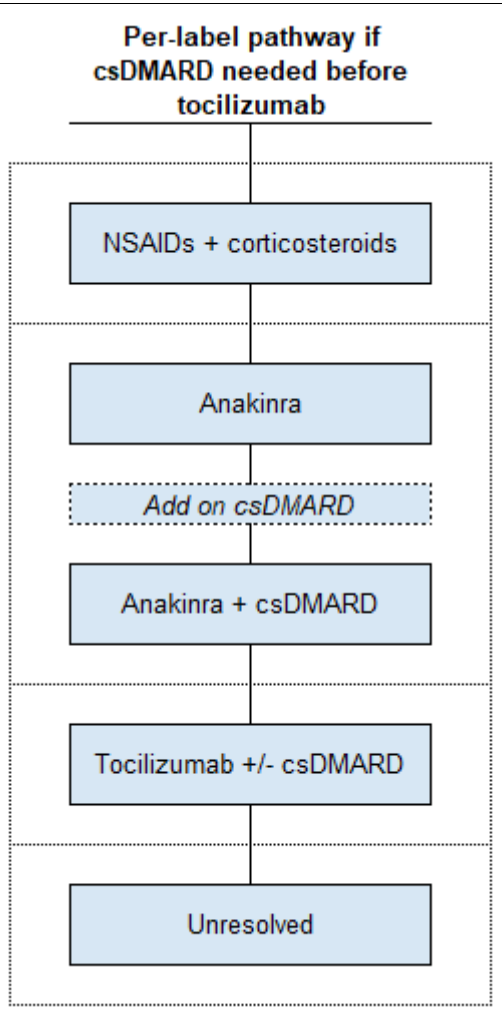
About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Swedish Orphan Biovitrum Ltd (Sobi Ltd)**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Treatment pathway	
1. Does the 'post-csDMARD' pathway in figure 1 reflect clinical practice for treating systemic juvenile idiopathic arthritis (sJIA) and adult onset Still's disease (AOSD) in the NHS in England? In AOSD, would a biologic drug only be used after 2 conventional DMARDs?	**Pathway in Figure 1 aligned with NICE and NHS England guidance** The post-csDMARD process depicted in Figure 1 aligns with current clinical practice as mandated by the NHSE policies. Systemic JIA patients are required to receive one conventional-synthetic DMARD (csDMARD) prior to access to a biologic DMARD (bDMARD), whereas AOSD patients are required to try two csDMARDs before they can access a bDMARD. Furthermore, this is supported by market research which Sobi commissioned in 2019 and shows that methotrexate is used before biologics in NHS England practice. **Management differs between sJIA and AOSD due to historic guidance, and management by paediatric versus adult specialists** Still's disease (including sJIA and AOSD) is a single disease entity with different ages of onset (as agreed within the recent SHARE guidelines).[1] The difference in the management of sJIA and AOSD has arisen from historic guidance, and because patients are managed predominantly by paediatric (sJIA) and adult (AOSD) specialists. **Exception to the pathway in current practice is linked with presence of MAS** The only exception to the pathway for current practice presented in Figure 1 applies to patients who show signs of Macrophage Activation Syndrome (MAS). In this case, the NHS England policy recommends that "where MAS is severe or steroid resistant, treatment with anakinra may be life-saving and should not be delayed."[2] This policy is for sJIA only and does not apply to Stills disease patients who present in adulthood.

2. Would the ‘per-label’ pathway in figure 1 be implemented in NHS clinical practice? That is, would anakinra and tocilizumab be used after NSAIDs and corticosteroids (rather than after csDMARDs)?	The ‘per-label’ pathway provided within Figure 1 reflects our proposed use of anakinra within its license for Stills disease and the “post-csDMARD” pathway represents current practice as required by existing clinical commissioning policies and NICE TA238 guidance.[2–4] **Clinical advice suggests ‘per-label’ pathway can be implemented – if csDMARD is required prior to tocilizumab (in keeping with TA238 guidance), this can be added to anakinra** We asked clinical advisers how the ‘per-label’ pathway may be achieved in practice, with particular reference to the csDMARD requirement of TA238. We were advised that they would add a csDMARD to anakinra if needed. If adequate response is not achieved, the csDMARD failure criterion of TA238 would have been met, allowing tocilizumab’s use. The use of either anakinra or tocilizumab with an add-on csDMARD (such as methotrexate) is within the licensed indication for both bDMARDs. This is shown in the diagram below:


Per-label pathway if csDMARD needed before tocilizumab
NSAIDs + corticosteroids
Anakinra
Add on csDMARD
Anakinra + csDMARD
Tocilizumab +/- csDMARD
Unresolved

	Therefore, we believe that the 'per-label' pathway would be possible to implement in NHS clinical practice, in keeping with TA238 guidance. This would also be in keeping with the relevant aspects of the NHS England clinical commissioning policies which may be affected by the recommendation made by NICE as a result of this appraisal. **While anakinra can be used within its license in glucocorticoid-naïve patients, clinical advice suggests this would not be practical to achieve in NHS practice, hence the 'per-label' pathway proposed includes the use of anakinra after corticosteroids** The licensed indication for anakinra is 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 NSAIDs or glucocorticoids.[5] This means that for patients with moderate-to-high disease activity, treatment with anakinra can be initiated prior to use of NSAIDs or corticosteroids. The efficacy of anakinra in glucocorticoid-naïve patients is noted within the recent SHARE consensus guidelines (which are discussed later in our response) as well as in the Vastert *et al* (2014) and Ter Haar *et al.* (2019) studies.[1,6,7] While within the label, clinical advice provided to us suggested that it would be difficult to initiate treatment with anakinra prior to steroids in current NHS practice as steroids are expected to be used as part of diagnosis.
3. What treatments are likely to be used for people in the 'unresolved' health state in clinical practice? For example, would people be likely to receive NSAIDs or csDMARDs again?	**Effective treatment options after exhaustion of 'standard' therapies are extremely limited, but a range of different approaches may be considered** For patients with disease refractory to two bDMARDs, it is very likely that NSAIDs and/or corticosteroids would be added or would not have been stopped. Following a failed trial of a second bDMARD, further treatment options in the "unresolved state" are extremely limited. Options which may be considered in practice are considered on a case-by-case basis, though the extent of their use is difficult to quantify and is not necessarily evidence based. These options include retreatment with a bDMARDs previously used, combinations of

	biologics and other therapies, off-label use of JAK inhibitors, compassionate use or enrolment in clinical trials. Failing these, as a last resort, a patient might undergo a bone marrow transplant. **Bone marrow transplants are an option, but due to the high mortality risk are avoided where possible** Advice provided to us was that while remission is the target, if remission has not been attained after several therapy trials, rather than undergo a bone marrow transplant some patients may continue bDMARD therapy if they are perceived to derive some benefits in terms of symptom control (acknowledging that it is unlikely that continued treatment would lead to remission). Every attempt is made to avoid bone marrow transplant which has a high mortality risk (12.5% according to a UK series[8], and 9% according to Dutch study[9]).
Issue 2: **Comparators**	
4. Is canakinumab used in the NHS for treating sJIA and AOSD after DMARDs?	**Canakinumab not routinely available for sJIA or AOSD patients in NHS practice** It is our understanding that canakinumab is not routinely commissioned for the treatment of sJIA or AOSD, and that access is limited to individual funding requests. Therefore, while a very small number of patients may receive canakinumab in current practice, it is not an established part of the treatment pathway and is not available on a national basis.
Issue 3: **Relative efficacy of anakinra and tocilizumab**	
5. Do you consider the efficacy of anakinra and tocilizumab to be similar in terms of: a) achieving and retaining remission b) adverse events c) treatment discontinuation rates?	**Anakinra does not seek to replace tocilizumab, but rather to add to the arsenal available for treatment** Anakinra and tocilizumab are different drugs (recombinant receptor antagonist vs monoclonal antibody) blocking different cytokines (IL-1 vs IL-6). Both cytokines are important in inflammation, but in health and disease these two cytokines play different roles and are not interchangeable. They are therefore broadly similar in both being good targets for inhibition in the treatment of Stills

	disease but different to one another in the specifics of remission and adverse events.[10,11] Both treatments are therefore important options available for patients with Still's disease.
	
	Similarities
	
	In our submission, we shared the findings of a systematic literature review (SLR) and meta-analysis of clinical studies in sJIA by Tarp *et al.*, (2016).[10] The findings of this SLR suggest that there is no statistically significant difference in efficacy between bDMARDs, though the patient numbers are small and there was notable heterogeneity between clinical study designs and patient populations.
	
	The findings from another SLR by Kuemmerle-Deschner *et al.*, (2019) found that current interventions for sJIA (including anakinra and tocilizumab) were found to be effective and generally well tolerated; though a lack of head-to-head studies limits a rigorous comparison between treatments.[11]
	
	No bDMARD therapy has been shown to be superior over another in Still's disease within the context of a meta-analysis, and so they have historically been deemed broadly equivalent in terms of their efficacy.
	
	Differences
	
	The main differences between anakinra and tocilizumab in Stills disease are:
	
	• Efficacy
	  o Efficacy by time since disease onset: The window of opportunity in early Stills disease is sensitive to IL-1 inhibition as shown in clinical studies
	  o Efficacy in the presence of MAS: Anakinra is recommended by NHS England specifically noting that *"where MAS is severe or steroid resistant, treatment with anakinra may be life-saving"*
	• Safety

	o Anakinra and tocilizumab target different cytokines which results in different safety profiles o IL-6 inhibition, and not IL-1 inhibition, abrogates the acute phase response and masks MAS and sepsis development o Anakinra is associated with injection site reactions in the early weeks of treatment ***Efficacy: "anakinra is effective in early disease course including in glucocorticoid-naïve patients" – SHARE Consensus recommendation*** Studies supporting the use of anakinra early in the disease process include Pardeo 2015, Nigrovic 2011, Vastert 2014, Ter Haar 2019, [redacted] and the Sobi-sponsored anaSTILLs RCT* (see description in Question 7 below).[6,7,12–16] These data supported the SHARE consensus group, recommending that "*anakinra is effective in early disease course including in glucocorticoid-naïve patients*". In contrast, tocilizumab is recommended later in the disease course: "*Tocilizumab, an IL-6 blocking agent, is an effective treatment option in glucocorticoid resistant or glucocorticoid dependant sJIA*". IL-1 is understood to play a particularly important role in early Stills disease, particularly in relation to the systemic features. Later in the disease process, where articular features may be more pronounced, methotrexate or an IL-6 inhibitor such as tocilizumab are considered more effective than an IL-1 inhibitor such as anakinra. Arthritis may only develop later in the disease, as noted in the recent SHARE consensus: *"Arthritis can be an important feature but may not be present at the early stage of the disease."* This distinction between anakinra and tocilizumab for use respectively

* The CSR for the anaSTILLs study is provided alongside this response to NICE. For a summary overview of the anaSTILLS study, please refer to Schanberg *et al.*, (2020); available at: https://ard.bmj.com/content/79/Suppl_1/1819.2

	in systemic and articular manifestations is borne out by the recommended in the NHS England AOSD policy.[4] The 'window of opportunity' hypothesis has been studied in clinical trials of IL-1 inhibition (and not IL-6 inhibition) in early Stills disease (Pardeo 2015, Nigrovic 2011, Vastert 2014, Ter Haar 2019, [redacted] and the Sobi-sponsored anaSTILLs RCT).[6,7,12–16] Similar studies have been conducted with canakinumab (a monoclonal antibody directed against IL-1β), but as described previously canakinumab is not readily available in NHS practice. In practice, Still's disease patients may present with a combination of systemic and articular features, and these may change over time, so both treatment options (anakinra and tocilizumab) may be considered suitable for patients. There is relatively limited evidence concerning the split of systemic versus articular patients, though a study by Vitale *et al.* reported that approximately three-quarters of AOSD patients studied had a systemic disease pattern (versus one-quarter with a chronic articular pattern).[17] While there are specific reasons one treatment may be considered in preference to another, for simplicity, both are generally considered to have equivalent efficacy for the treatment of Still's disease as a whole. However, in relation to the early use of bDMARDs specifically, IL-1 inhibition with anakinra has consistently shown efficacy over several trials in a variety of centre. ***Efficacy: Use of anakinra should not be delayed in the presence of severe or steroid-resistant MAS*** As discussed in Issue 1, NHS England recommends *"where MAS is severe or steroid resistant, treatment with anakinra may be life-saving and should not be delayed"* NHS England does not recommend the use of tocilizumab under these circumstances. It should be noted that this policy applies only in the paediatric setting, and so Still's disease patients who present with MAS over the age of 18 do not have access to anakinra (based on the AOSD policy). Clinical consensus view is that the use of anakinra in the presence of MAS is important in Still's disease as a whole

	(i.e. not just for sJIA patients), and so, in an ideal world, clinicians would have the ability to use anakinra in the presence of MAS regardless of the age of Still's disease onset. ***Safety: anakinra and tocilizumab target different cytokines which results in different safety profiles*** Both products are considered to have comparable safety profiles, though a lack of head-to-head comparisons precludes a robust comparison. We previously highlighted an analysis of registry data by Klein *et al.*, (2019) comparing outcomes for patients treated with anakinra and tocilizumab (as well as canakinumab and etanercept – treatments that are both used in Germany).[18] This study showed no statistically significant difference in adverse events of special interest (defined by the authors) between anakinra and tocilizumab, though some numerical differences were noted (namely, anakinra was associated with an increase in the risk of medically important infections, whereas tocilizumab was associated with an increase in the risk of cytopenia, anaphylaxis, hepatic events, and MAS). Further, tocilizumab is known to abrogate the acute phase response. If relying on surrogate markers from the acute phase response, detection of MAS or sepsis easy to miss. The European SmPC describes this special precaution: *"Vigilance for the timely detection of serious infection is recommended for patients receiving immunosuppressive agents such as RoActemra as signs and symptoms of acute inflammation may be lessened, due to suppression of the acute phase reactants. The effects of RoActemra on C-reactive protein (CRP), neutrophils and signs and symptoms of infection should be considered when evaluating a patient for a potential infection. Patients, and parents/guardians of sJIA or pJIA patients, should be instructed to contact their healthcare professional immediately when any symptoms suggesting infection appear, in order to assure rapid evaluation and appropriate treatment."*[19] Similarly an FDA warning: *"Closely monitor patients for the development of signs and symptoms of infection during and after treatment with ACTEMRA, as signs and symptoms of acute inflammation may be lessened due to suppression of the acute phase reactants."*[20]

	Challenges with considering a cost-minimisation analysis (assuming entirely equal safety and efficacy) For the reasons highlighted above, it is challenging to consider a cost-minimisation analysis within the context of comparing anakinra and tocilizumab, as in a real-world scenario both treatment options are available and could be considered for the same patient, depending on the predominant disease features (i.e. systemic and/or articular). It is therefore not appropriate to consider the displacement of tocilizumab with anakinra (or *vice versa*) as both options are extremely important treatment options for patients with Still's disease. Instead, the cost-effectiveness analysis presented considers the use of both anakinra and tocilizumab regardless of whether anakinra is used prior to csDMARDs (the 'per label' pathway, where we propose the use of anakinra) or after csDMARDs (the 'post-csDMARD' pathway, which we understand to reflect current NHS practice). **No expected difference in treatment discontinuation rates** We are unaware of any data comparing treatment discontinuation rates with anakinra versus tocilizumab. However, the discontinuation rate applied within the cost-effectiveness analysis is based on the previous NICE TA238 model. The clinical advice we received did not suggest any substantial difference in the long-term treatment discontinuation rates between bDMARDs.

6. What are the clinical reasons why either tocilizumab or anakinra would be chosen as treatment over the other?	Clinical reasons include: • Clinical manifestation – anakinra in systemic features or MAS/HLH, tocilizumab or methotrexate in articular disease • Time since disease onset – window of opportunity and IL-1 inhibition in early disease • Patient choice (injection/infusion frequency) • Compliance – infusion if non-compliance suspected, daily injection if established routine useful Please see our response to question 5 for further detail.
Issue 4: Efficacy of biologics at different points in the treatment pathway	
7. Would you expect more people to have disease remission overall if anakinra and tocilizumab were used earlier in the treatment pathway and csDMARDs were not used at all?	**Improved remission for anakinra used earlier in the treatment pathway aligned with window of opportunity hypothesis, but this only applies to IL-1 inhibition** The expectation of overall improved remission rates if anakinra is made available earlier in the treatment pathway (and csDMARDs were removed entirely) is aligned with the 'window of opportunity' hypothesis. The 'window of opportunity' hypothesis is based on the role of IL-1, and so the expectation of improved outcomes does not directly apply to tocilizumab (an IL-6 inhibitor). **anaSTILLS study findings are now available, which provide some extra information, but this study is limited due to early termination (issues with recruitment)** We note that data from the anaSTILLS study may be helpful within the context of this question, as these data comprise a group of patients treated with anakinra prior to the use of csDMARDs.[15] anaSTILLS is a randomised, placebo-controlled trial of anakinra in Still's disease which was conducted to further evaluate efficacy and safety of anakinra in patients with Still´s disease across all age groups. However, owing to issues with recruitment, the study was terminated early, and a

	total of n=11 patients were analysed for efficacy (enrolment target was n=81 patients). In spite of the study considering only a comparison of n=6 anakinra and n=5 placebo patients, the study met its primary endpoint: all patients on anakinra but none on placebo achieved ACR30 response with absence of fever at Week 2 (p-value=0.0022). In addition, 5 of the 6 anakinra patients had sustained ACR90 response by the end of follow-up (with the remaining patient having sustained ACR70 response), versus none of the placebo patients. The CSR from the anaSTILLS study, and an abstract which was recently published about the anaSTILLS study are provided alongside our response. **Five studies provide support for the window of opportunity hypothesis** In addition to the anaSTILLS study described above, four other recent studies provide useful information concerning outcomes for treatment with anakinra prior to csDMARDs. ***Nigrovic et al 2011***[13] Nigrovic et al reviewed the medical records of patients with sJIA who received anakinra as part of their initial treatment regimen. Results from 46 patients in 11 centres in four countries (US, the Netherlands, Italy and Canada) were analysed. The patients included received either anakinra alone, anakinra with DMARDs (no steroids), anakinra with steroids (no DMARDs) or anakinra with steroids and DMARDs. Patients were recently diagnosed - median time from disease onset to initiation of anakinra was 82.4 days (2.7 months). 27/59 (59%) showed a complete response, while another 39% showed a partial response. This was associated with a rapid resolution of systemic symptoms – fever and rash resolved completely in 86% of 25 evaluable patients, typically within 1-2 days. By 30 days, fever and rash had resolved in 97% of 36 evaluable patients. ***Pardeo* et al *2015***[12] This group of Italian researchers retrospectively analysed 25 patients with sJIA who had received anakinra for 6 months. They compared the characteristics of responders with non-responders.

	The only characteristic with a significant difference was time from disease onset to anakinra administration in months (median 1.9 months in responders vs 24.5 months in non-responders). [redacted] ***Vastert* et al *2014 and Ter Haar* et al *2019***[6,7] These two studies report clinical outcomes for a consecutive cohort of sJIA patients presenting to a single centre in the Netherlands. Vastert *et al* 2014 reports results from 20 patients in the first 4 years of initiation of a treat to target strategy in which anakinra was used before glucocorticoids. These 20 patients were included in the subsequent paper by Ter Haar *et al* (2019). Ter Haar *et al* (2019) describe the results of 42 consecutive patients treated with NSAIDS and then anakinra. Lack of response at 1 month and 3 months led to either an increase of dose or switch to another therapy. The primary endpoint, clinically inactive disease at 1 year, was met by 76% of patients treated with this treat to target strategy. Further, a tapering strategy allowed just over half (52%) to be in drug-free remission. Our cost-effectiveness analysis does not take into account the full cost savings associated with drug tapering and drug-free remission shown within the Ter Haar *et al.* (2019) study, and may therefore be considered to present a conservative estimate of the likely long-term costs associated with anakinra were it reimbursed in the pre-csDMARD setting. [redacted]

	[redacted] **SHARE guidelines**[1] The SHARE consensus group presented their consensus statements and recommendations concerning the management of sJIA during the recent PReS 2020 congress. The final manuscript is expected to be published in November 2020. The consensus statements include that anakinra is an effective treatment option early in the disease course of sJIA, including in glucocorticoid naïve patients. **Summary** In summary, we expect earlier use of anakinra to allow more people to achieve remission versus its current use after csDMARDs. This is for two reasons: • Mandated early use of methotrexate, a drug unlicenced and unproven in Stills disease delays the initiation of truly disease modifying therapy (also discussed in Issue 7).[1,21–24] • The window of opportunity, which applies specifically to the role of IL-1 inhibition early in Stills disease, is missed if biologic initiation is delayed by a methotrexate trial. The benefits or not of using tocilizumab in the window of opportunity early in Stills disease have not been established.
Issue 5: Tocilizumab administration	
8. Of people with sJIA receiving tocilizumab, what percentage would receive it: a) subcutaneously b) intravenously?	**No data available to quantify the precise proportion of patients receiving IV versus SC** Data concerning the proportion of NHS patients in England that receive subcutaneous (SC) versus intravenous (IV) tocilizumab in Still's disease (sJIA and AOSD) are unavailable to us.

Advice provided to us was documented in our submission, which suggested an approximate 50:50 split of SC:IV use of tocilizumab.

The practicalities of administration to children likely influence choice of tocilizumab route of administration

Stills disease manifests in both children (sJIA) and adults (AOSD and sJIA patients once reaching adulthood). IV over SC administration in paediatrics may at times preferred considering the practicalities of carer-administration at home. Similarly, it is our understanding that administration of tocilizumab for a person with sJIA reaching adulthood would be approached in the same manner as for an adult diagnosed with AOSD. (This is also in relation to question 10)

Both routes of administration are expected to be used in practice, but clinical expert advice needed for more precise estimates

While we are unsure of the proportion of patients that receive IV versus SC tocilizumab, we expect a non-zero proportion of patients to be treated with either option, owing to the fact that each route of administration may have its benefits under certain circumstances (e.g. IV for speed of delivery or where compliance to self-administration is a concern, versus SC for home administration).

The cost-effectiveness analysis assumption on the tocilizumab SC/IV split is not a key driver of results

Within the context of the economic model, we have run scenarios considered 100% use of IV tocilizumab and 100% use of SC tocilizumab, which are presented below. These results are based on a longer time horizon than the originally-submitted base-case analysis (up to 90 years, based on feedback from the ERG), and assuming a [redacted] PAS discount on the list price of tocilizumab.

Base-case analysis (with 90-year time horizon)

Arm	Total		
	Costs (£)	QALYs	LYs
No anakinra	351,641	14.113	52.514
Post-csDMARD	316,902	14.547	53.329

	Per-label | 290,919 | 14.971 | 54.259 **Assuming 100% IV tocilizumab** **Arm** | **Total** | | | **Costs (£)** | **QALYs** | **LYs** No anakinra | 359,604 | 14.113 | 52.514 Post-csDMARD | 323,501 | 14.547 | 53.329 Per-label | 295,068 | 14.971 | 54.259 **Assuming 100% SC tocilizumab** **Arm** | **Total** | | | **Costs (£)** | **QALYs** | **LYs** No anakinra | 343,679 | 14.113 | 52.514 Post-csDMARD | 310,303 | 14.547 | 53.329 Per-label | 286,770 | 14.971 | 54.259 The results of the sensitivity analysis show that the conclusion is unchanged were tocilizumab administered completely via IV infusion or SC injection – that is, the 'per-label' pathway continues to dominate the 'post-csDMARD' and 'no anakinra' pathways. However, the total costs are greater for when IV tocilizumab is considered, based on the requirement for administration to take place within an outpatient setting.
9. Would people with AOSD receiving tocilizumab all receive it subcutaneously?	Please see our response to question 8 with regards to SC versus IV use of tocilizumab in general.
10. If someone started receiving intravenous tocilizumab as a child, would they typically continue receiving it intravenously as an adult?	Please see our response to question 8 with regards to SC versus IV use of tocilizumab in general.
Issue 6: Treatment discontinuation	

11. In clinical practice, would someone remain on treatment if it did not lead to a remission?	There are several reasons why some patients in clinical practice would continue to receive treatment with a bDMARD if it did not lead to remission. However, patients are not expected to receive long-term treatment with corticosteroids or csDMARDs (such as methotrexate), owing to glucocorticoid toxicity and a lack of efficacy relating to the systemic features of Still's disease, respectively. **Some patients may have exhausted all other 'standard' treatment options** Patients may receive bDMARD therapy without the expectation of remission if they have otherwise exhausted all other treatment options. This would be considered appropriate if patients are deriving some benefit (in terms of symptom control) from their bDMARD therapy, even if remission is unlikely to be achieved. This course may be chosen in preference to the high mortality rate of a bone marrow transplant once all other options are exhausted. The proportion of patients requiring long-term bDMARD therapy to address symptoms of chronic course Still's disease is however expected to be lower were anakinra made available earlier in the treatment pathway (Ter Haar *et al*, 2019).[7] **Some patients may continue treatment as symptom control benefits outweigh risks of discontinuing and trying a different treatment** Some patients may also continue treatment with bDMARD therapy without remission if they have flared previously and may therefore be anxious about discontinuing treatment. This is especially important within the context of patients that have a history of (or considered to be at a high risk of developing) macrophage activation syndrome (MAS), which could be fatal.
Issue 7: Remission rates with csDMARDs	
12. What proportion of people would be likely to reach disease remission with csDMARDs?	**SHARE recommendations: "Methotrexate can be of some benefit in the treatment of arthritis in sJIA, but has no proven benefit in systemic features"**

a. with monocyclic disease b. with chronic disease	The SHARE recommendations emerged by consensus following a systematic literature review and expert consensus meetings conducted between June 2013 and 2020.[1] We were unable to gain a copy of the pre-publication manuscript, but it is expected to be published in November 2020. The group's consensus recommendation within the SHARE recommendations is clear that methotrexate does not have a proven benefit in the systemic features of Still's disease. We refer to our response to question 5 of the Additional clarification questions February 2020 in which we expanded on the results of several studies of methotrexate in Stills disease in substantiation of the clinical need for earlier biologics. (Halle and Prieur, 1991; Speckmaier *et al*., 1989; Woo *et al.* 2000; Nordström *et* al., 2012).[21–24] **UK expert view of the efficacy of methotrexate in treating the systemic features of Still's disease is consistent with the SHARE recommendations** The SHARE consensus recommendation referred to above was concluded by 26 clinicians with expertise treating Stills disease, 2 of whom were UK clinicians. During the informal technical engagement call with NICE and the ERG, we understood that it may be helpful to obtain further UK clinicians' views to supplement the SHARE consensus recommendation on methotrexate in Stills disease. For 10 days after the technical engagement call, the Sobi medical team surveyed 20 clinicians in at least 12 trusts to gain their views.† This confirmed that methotrexate is not believed to be of use in the systemic features of Stills disease and that while methotrexate is used in order to meet funding criteria for biologics, clinicians believe this delays the initiation of effective therapy. Those in whom methotrexate is said to have led to remission were thought to have had the monocyclic variant of the disease which would have resolved without methotrexate. **Precedence for csDMARD bypass in other rheumatological conditions** There is also precedence for the limited role of csDMARDs (or methotrexate specifically) in other sub-types of rheumatic diseases where they are not considered effective. For example,

[redacted]

	methotrexate is bypassed in enthesitis-related JIA in favour of adalimumab and etanercept (NICE TA373).[25] **Methotrexate plays a part in treating articular features and needs to be available as an add-on therapy, but should not delay initiation of a true *disease modifying therapy*** As methotrexate is understood to have no impact on the systemic features of Still's disease, it is not considered possible to achieve remission in patients with a chronic disease course through the use of csDMARDs alone.[26] The use of csDMARDs in Still's disease in NHS practice is based funding requirements, the rheumatology tradition of methotrexate as an anchor drug, and methotrexate's benefits in articular symptom control. The modern practice treatment goal is aimed at achieving clinically-inactive disease (i.e. remission). **Steroids and methotrexate are not licensed for use in Still's disease, but only steroids are recognised to be effective in terms of the systemic features of the disease** Anakinra and tocilizumab are licensed for the treatment of sJIA, and only anakinra is licensed for the treatment of AOSD. NSAIDs, corticosteroids, and csDMARDs (such as methotrexate) are not licensed for the treatment of Still's disease. We acknowledge that NICE considers the current treatment pathway, including off-label therapies. However, unlike corticosteroids, csDMARDs have no proven efficacy in the treatment of the systemic features of Still's disease. Corticosteroids are effective in the treatment of Still's disease (even though their use is off-label), yet their long-term use is limited due to glucocorticoid toxicity.[1] **Subcutaneous methotrexate (via an injection pen), predominantly used in paediatrics, is more expensive than oral methotrexate.** Oral methotrexate is known to be an inexpensive treatment (£0.86 for 24x 2.5mg tablets, which is more than enough for a weeks' supply [see CS for original costing approach]), but for ease of administration subcutaneous methotrexate (£16.06 per week for 1x 20 mg injection pen [Nordimet®, Nordic Pharma Ltd] [27]) is used predominantly in paediatric settings. For the context of the economic model, all methotrexate use was conservatively assumed to be oral, but the true

	costs of methotrexate in current practice would be reduced markedly were anakinra recommended aligned with the 'per-label' pathway. **Methotrexate is poorly tolerated by patients.** In a consumer priorities survey conducted by NIHR CRN: Children/Versus Arthritis Paediatric Rheumatology CSG survey of 223 people living with musculoskeletal conditions asked what their top research priorities would be across the entire experience of living with their condition, 37% (83 respondents) chose methotrexate usage and tolerability as a top concern.[28] **Acute presentation of macrophage activation syndrome (MAS) in adults** MAS is a severe, acute, life-threatening systemic manifestation of Stills disease. The underlying disease process is hyperinflammation. A patient with Stills disease under the age of 18 presenting with MAS has access to anakinra under the current commissioning policy for JIA: *"where MAS is severe or steroid resistant, treatment with anakinra may be life-saving and should not be delayed"*.[2] A patient with Stills disease over the age of 18 presenting with MAS has no such access (based on national guidelines) and is required to trial two csDMARDs. Patients presenting with hyperinflammation (MAS) are acutely unwell, the hyperinflammation must be controlled quickly. Steroids and anakinra are both effective options. High dose steroids are started along with methotrexate. Methotrexate is not effective in hyperinflammation but it is given to eventually allow access to anakinra. Adult Stills disease patients in MAS often presents with liver abnormalities (ALT>100), complicating methotrexate prescription. The effect of methotrexate is seen after 3 weeks. Clinical response to anakinra administration in the acute presentation of hyperinflammation is seen within a day. Methotrexate therefore delays access to effective therapy not only in terms of resolving the systemic features of Stills disease, but also addressing MAS: a potentially-fatal manifestation of Still's disease. The steroid dose required to control the

	hyperinflammation in the absence of anakinra, also results in accumulation of steroid-related toxicities. **Summary** Methotrexate in Stills diseases is unlicenced, ineffective for systemic features and poorly tolerated.[1,21–24,26] In addition, the use of subcutaneous methotrexate in current practice for paediatric patients is associated with far greater cost versus tablets, the implications of which were conservatively not reflected within the cost-effectiveness analysis submitted. While methotrexate has value as an adjunct to biologics in the case of articular features, a mandated trial of methotrexate monotherapy delays initiation of a Stills disease modifying therapy.

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Technical engagement response form

Anakinra for treating Still's disease ID1463

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **Friday 30 October 2020**.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
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- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
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- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Eslam Al-Abadi**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nil to disclose**

Questions for engagement

Issue 1: Treatment pathway	
1. Does the 'post-csDMARD' pathway in figure 1 reflect clinical practice for treating systemic juvenile idiopathic arthritis (sJIA) and adult onset Still's disease (AOSD) in the NHS in England? In AOSD, would a biologic drug only be used after 2 conventional DMARDs?	The 'post-csDMARD' pathway reflects the current funding arrangement by NHSE but would not, in my view, represent how clinicians would design it today.
2. Would the 'per-label' pathway in figure 1 be implemented in NHS clinical practice? That is, would anakinra and tocilizumab be used after NSAIDs and corticosteroids (rather than after csDMARDs)?	Yes, both anakinra and tocilizumab would be used after NSAIDs+/- corticosteroids. There would be no standard order to which would be used first. Clinicians would make individual decisions about which to use first based on the clinical picture of the individual patient.
3. What treatments are likely to be used for people in the 'unresolved' health state in clinical practice? For example, would people be likely to receive NSAIDs or csDMARDs again?	IVIG, Janus Kinase inhibitors, csDMARD as well as NSAIDs and corticosteroids would all be considered in the unresolved category as mono-therapy or in combination with a biologic..
Issue 2: Comparators	
4. Is canakinumab used in the NHS for treating sJIA and AOSD after DMARDs?	It is not funded by NHSE, however, it is used either through an IFR or as continuation of treatment for those who have had participated in a Canakinumab trial.
Issue 3: Relative efficacy of anakinra and tocilizumab	
5. Do you consider the efficacy of anakinra and tocilizumab to be similar in terms of: a) achieving and retaining remission	a) Yes. This is my anecdotal opinion since the 2 drugs have never been compared. b) Yes, although they are different side effects.

b) adverse events c) treatment discontinuation rates?	c) Yes, although for different reasons. This is my anecdotal opinion since the 2 drugs have never been compared. b&c - There is an initial injection site reaction in some patients on Anakinra that resolves with time. On the other hand, Tocilizumab obliterates the occurrence of fever and blunts the CRP response to bacterial infections. Therefore, this can be a serious risk in primary care and emergency departments when such knowledge is not common place and may lead to underestimating how ill a patient really is.
6. What are the clinical reasons why either tocilizumab or anakinra would be chosen as treatment over the other?	There is no published evidence to support the use of one over the other. In my experience and through discussions with colleagues I consider there to be trends: 1. Predominant systemic features, with minimal or no arthritis, and a hyperinflammtory clinical picture: Anakinra is likely to be an initial choice 2. Predominant polyarthritis with milder systemic features: Tocilizumab is likely to be an initial choice. 3. Mix of mild-moderate systemic features and milder arthritis: either could be initial choice. In any of the above, if there is no or suboptimal response, the clinician is likely to, in no particular order, either: 1. Swap from one to the other; or 2. Add in a csDMARD 3. Re-introduce corticosteroids
Issue 4: Efficacy of biologics at different points in the treatment pathway	
7. Would you expect more people to have disease remission overall if anakinra and tocilizumab were used earlier in the treatment pathway and csDMARDs were not used at all?	Yes. There is evidence that there is a window of opportunity when the disease is predominantly of an autoinflammtory nature (affect the innate immune system that is hard wired into us from birth), this is cytokine (inflammation driving molecule) driven and therefore responds well to anakinra and tocilizumab but not to csDMARDs. Later on the cytokines lead to increased number of inflammatory cells involved in autoimmunity (affects the adaptive immune system which our body

	learns what to respond to through previous exposure). The latter is a more complex cycle and overlapping pathways of inflammation that are more difficult to treat. There is no way to predict with any certainty which phase the patient is in since the clinical feature and investigations are similar. However, it is safe to say that the patient who no longer has systemic features and only suffers with a resistant polyarthritis is most likely in the later phase.
Issue 5: Tocilizumab adminstration	
8. Of people with sJIA receiving tocilizumab, what percentage would receive it: a) subcutaneously b) intravenously?	Such data does not exist. Partly because the subcutaneous injections became available later and only recently in children. There was a drive towards offering patients the choice which then was accelerated and became a necessity due to COVID and the need to reduce hospital attendances for these patients. Therefore, I suspect that currently the vast majority are given subcutaneously. However, many colleagues are reporting loss of disease control on switching to the subcutaneous injection and the need for either more frequent dosing or switching back to the intravenous infusions.
9. Would people with AOSD receiving tocilizumab all receive it subcutaneously?	Unless there is a patient specific reason why not to or a contraindication, I would presume that to be the case.
10. If someone started receiving intravenous tocilizumab as a child, would they typically continue receiving it intravenously as an adult?	No, almost all would be changed to subcutaneous injections unless there was a specific reason or contraindication.
Issue 6: Treatment discontinuation	
11. In clinical practice, would someone remain on	Yes. The evidence is towards using a treat to target approach. This is an outcome agreed

treatment if it did not lead to a remission?	between the clinician and the patient in advance. The standard target is steroid free disease remission, however, its well-known that is not achievable in all patients and therefore, minimal disease activity would be an appropriate target for some patients. Moderate to high disease activity would prompt a change in approach by either swapping treatments or using combination treatment with corticosteroids or csDMARDs.
Issue 7: Remission rates with csDMARDs	
12. What proportion of people would be likely to reach disease remission with csDMARDs? a. with monocyclic disease b. with chronic disease	No high quality data exists to answer this. My opinion would be: a) Majority, circa 65%. However, they form a smaller fraction of patients, circa 20% b) Minimal if high dose and prolonged steroid use is avoided, circa <5%. If high dose steroids are used and continued, almost all will go into remission but at a significant burden of side effects that is often worse than the disease. This has been demonstrated by data from the UK Biologics in Children with Rheumatic Diseases registry. When assessing the prescribing patterns in sJIA it was noticed that 39 out of 41 patients who were never prescribed a biologic were taking steroids. Furthermore, the registry shows that the policy of sequential use of biologics after failing csDMARD results in over 80% combination treatment of a biologic+ csDMARD (i.e MTX) and sadly a near 60% concomitant use of steroids. I would conclude from that that the current policy is not good enough compared to the Vastert et al data that is supported by similar national guidelines in North America and Germany where the physician has the parallel option of using NSAIDs, steroids, csDMARD or a biologic as first line with the option to change/add treatments based on the evolving

	phenotype.

NICE National Institute for Health and Care Excellence

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About you

Your name	**Dr Lisa Dunkley**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nil**

Questions for engagement

Issue 1: Treatment pathway	
1. Does the 'post-csDMARD' pathway in figure 1 reflect clinical practice for treating systemic juvenile idiopathic arthritis (sJIA) and adult onset Still's disease (AOSD) in the NHS in England? In AOSD, would a biologic drug only be used after 2 conventional DMARDs?	**Yes. iN AOSD the current NHSe guidance is that 2 DMARDS are used prior to either Anakinra/ Tocilizumab. If a patient presents with MAS, there are likely to be local variations to this if special permission has been sought to use Anakinra early for life-threatening MAS.**
2. Would the 'per-label' pathway in figure 1 be implemented in NHS clinical practice? That is, would anakinra and tocilizumab be used after NSAIDs and corticosteroids (rather than after csDMARDs)?	**I think it unlikely that NSAIDS/ steroids straight to biologic would be implemented for all patients. The important thing is that Anakinra for (impending) MAS is available for anyone who needs it. So for some patients the "per label" pathway will be right, but for others (the majority?) the post DMARDs pathway will be fine.**
3. What treatments are likely to be used for people in the 'unresolved' health state in clinical practice? For example, would people be likely to receive NSAIDs or csDMARDs again?	**If unresolved – trial of other treatments in the pathway eg revisitng csDMARD/ using steroids/ alternative biologic would be used in clinical practice.**
Issue 2: Comparators	
4. Is canakinumab used in the NHS for treating sJIA and AOSD after DMARDs?	**Not standardly & I have never used.**
Issue 3: Relative efficacy of anakinra and tocilizumab	
5. Do you consider the efficacy of anakinra and tocilizumab to be similar in terms of: a) achieving and retaining remission	**Yes – but Anakinra has a place in management of MAS that TOCI doesn't have.**

b) adverse events c) treatment discontinuation rates?	
6. What are the clinical reasons why either tocilizumab or anakinra would be chosen as treatment over the other?	**TOCI – joint predominant disease** Anakinra – MAS/ systemic predominant disease
Issue 4: Efficacy of biologics at different points in the treatment pathway	
7. Would you expect more people to have disease remission overall if anakinra and tocilizumab were used earlier in the treatment pathway and csDMARDs were not used at all?	For people whose disease does not switch off quickly with csDMARDs then yes, as with all inflammatory conditions, the quicker you can reduce the inflammatory burden, the better the longer term outcomes and the more likely a sustained remission will be.
Issue 5: Tocilizumab adminstration	
8. Of people with sJIA receiving tocilizumab, what percentage would receive it: a) subcutaneously b) intravenously?	Traditionally most sJIA patients had iv TOCI. Locally we have now switched/ offered all sJIA patients sc TOCI as standard so for our service >75% are now on sc TOCI. This probably does not reflect that national picture but I am unable to give figures from elsewhere
9. Would people with AOSD receiving tocilizumab all receive it subcutaneously?	The majority – yes – but there are always patients who need iv preparations for a variety of reasons (concordance/ efficacy/ pt dislike of giving own injections etc)
10. If someone started receiving intravenous tocilizumab as a child, would they typically continue receiving it intravenously as an adult?	Not in our service, at transition to adult services we review all meds and offer switches where clinically appropriate if a patient would like to switch. However, anyone already on iv medicine can remain on that if that is either their personal choice, or if clinically this is the right decision.
Issue 6: Treatment discontinuation	

11. In clinical practice, would someone remain on treatment if it did not lead to a remission?	If no evidence of any benefit = no. If partial benefit, then maybe yes with adjunctive treatments added. If a viable alternative treatment exists in the case of partial remission, then this would usually be the next step.
Issue 7: Remission rates with csDMARDs	
12. What proportion of people would be likely to reach disease remission with csDMARDs? a. with monocyclic disease b. with chronic disease	a. 50% b 25-30%

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**British Society for Rheumatology**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None from Tobacco** **Speaker fees and Consultancy fees from Sobi and Novartis**

Questions for engagement

Issue 1: Treatment pathway	
1. Does the 'post-csDMARD' pathway in figure 1 reflect clinical practice for treating systemic juvenile idiopathic arthritis (sJIA) and adult onset Still's disease (AOSD) in the NHS in England? In AOSD, would a biologic drug only be used after 2 conventional DMARDs?	Yes, the Figure is broadly representative. However,. a biologic drug may be used earlier if a case is unwell with severe AOSD and MAS or severe AOSD alone. In the former the rate of onset of action of csDMARDS is too slow and they efficacy may be modest anyway in severe cases. As an example, a new case on ICU refractory to iv steroids should be offered biological therapy and ankinra if superimposed MAS. Such a case belongs in the Pre-label group on the left of Figure 1
2. Would the 'per-label' pathway in figure 1 be implemented in NHS clinical practice? That is, would anakinra and tocilizumab be used after NSAIDs and corticosteroids (rather than after csDMARDs)?	In a very severe acute presentation where high dose steroids fail, it would be desirable to move to biological therapy rapidly due to more rapid onset of action compared to DMARDS. This pre-label pathway is an important safety net for sick cases.
3. What treatments are likely to be used for people in the 'unresolved' health state in clinical practice? For example, would people be likely to receive NSAIDs or csDMARDs again?	Some of unresolved heath status could be secondary Osteoarthritis if AOSD presents with arthritis. So a careful assessment of what is linked to AOSD and what is not linked is needed. For genuine unresolved joint disease, we increasingly move to JAK inhibition although there is currently limited evidence.
Issue 2: Comparators	
4. Is canakinumab used in the NHS for treating sJIA and AOSD after DMARDs?	For AOSD we use Anakinra. It suffers from the drawback of the perception that like tocilizumab, it may not work in cases with SJIA who are destined to progress to MAS.
Issue 3: Relative efficacy of anakinra and tocilizumab	
5. Do you consider the efficacy of anakinra and tocilizumab to be similar in terms of:	Remission-There is a general feeling that Tocilizumab works better in cases with prominent SJIA arthritis and that Anakinra works better in the more "systemic" non arthritis group. We cannot say

a) achieving and retaining remission b) adverse events c) treatment discontinuation rates?	if this is the case in adults where the disease rarer. If the AOSD case has associated MAS, then on balance and based on extrapolation from SJIA, we would use anakinra over tocilizumab or canakinumab.
6. What are the clinical reasons why either tocilizumab or anakinra would be chosen as treatment over the other?	AOSD+ MAS- Anakinra preferred Tocilizumab if needle phobia Tocilizumab if prominent arthritis In reality we may cycle from one to the other for resistant cases
Issue 4: Efficacy of biologics at different points in the treatment pathway	
7. Would you expect more people to have disease remission overall if anakinra and tocilizumab were used earlier in the treatment pathway and csDMARDs were not used at all?	This question seems to stem from the Rheumatology academic perception fuelled by industry support that you can switch of RA if you treat early with biologics. Certainly better short term outcomes, maybe. AOSD may be monophasic self limiting to chronic and we don't know which ones are in each group at the outset. So this makes it hard to consider even studying "AOSD natural history interception"
Issue 5: Tocilizumab administration	
8. Of people with sJIA receiving tocilizumab, what percentage would receive it: a) subcutaneously b) intravenously?	We don't treat SJIA but in adults with RA we have moved to subcut For AOSD, we would generally start iv for quick loading and response.
9. Would people with AOSD receiving tocilizumab all receive it subcutaneously?	Depending on patient choice we could switch to subcut. As the general Rheumatology use of subct Toci increases, this method of admin will likely become more common.

10. If someone started receiving intravenous tocilizumab as a child, would they typically continue receiving it intravenously as an adult?	Again, patient choice would be an issue
Issue 6: Treatment discontinuation	
11. In clinical practice, would someone remain on treatment if it did not lead to a remission?	A. If a case had life threatening AOSD with MAS and MAS resolved but some ongoing disease we would continue biologic with lowest dose steroid and consider other DMARDs B. For a genuine non-response, we would switch between toci and ankinra C. In 2020 for refractory disease we would likely then move towards IFR pathway (answer could well be a no) and consider JAK inhibition
Issue 7: Remission rates with csDMARDs	
12. What proportion of people would be likely to reach disease remission with csDMARDs? a. with monocyclic disease b. with chronic disease	A. The question is difficult. Monophasic disease may go away independent of therapy, it is just that therapy hastens disease resolution. No evidence that therapy "switches off disease". Practically speaking, a severe AOSD presentation that responds to anakinra or toci and are in complete remission, then we stop steroid completely. We then taper the biologic and reduce dosing frequency. This is standard practice for many Rheumatologists in many disease areas such as RA. For AOSD, aware of the fact that disease may be monophasic we works towards stopping therapy. If flare we restart long term. If flare after several years we would again aim to taper. So for monophasic disease, if that is what it is, all csDMARD or biologic DMARD would be

	stopped. However, we run a dedicated auto inflammatory service and I think the tapering issue should be highlight to minimise costs and potential toxicity. B. Chronic disease- Ongoing symptoms such as rash, serositis, fever, arthritis and other symptoms and abnormal blood tests in face of therapy or disease punctuated by mini flares. So when a case goes into remission on csDMARDS the first thing to ask if this is a monophasic intrinsically self-limiting disease. So it is hard to give figures. Where csDMARDs induce remission in chronic AOSD it is likely to be the milder end of the spectrum of chronic disease. So it is hard to say and there is no data that I am aware of.

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Royal College of Physicians (RCP)**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nil**

Questions for engagement

Issue 1: Treatment pathway	
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2. Would the 'per-label' pathway in figure 1 be implemented in NHS clinical practice? That is, would anakinra and tocilizumab be used after NSAIDs and corticosteroids (rather than after csDMARDs)?	It unlikely that NSAIDS/ steroids straight to biologic would be implemented for all patients. The important thing is that Anakinra for (impending) MAS is available for anyone who needs it. So for some patients the "per label" pathway will be right, but for others (the majority?) the post DMARDs pathway will be fine.
3. What treatments are likely to be used for people in the 'unresolved' health state in clinical practice? For example, would people be likely to receive NSAIDs or csDMARDs again?	If unresolved – trial of other treatments in the pathway eg revisitng csDMARD/ using steroids/ alternative biologic would be used in clinical practice.
Issue 2: Comparators	
4. Is canakinumab used in the NHS for treating sJIA and AOSD after DMARDs?	Not standardly
Issue 3: Relative efficacy of anakinra and tocilizumab	
5. Do you consider the efficacy of anakinra and tocilizumab to be similar in terms of: a) achieving and retaining remission	Yes – but Anakinra has a place in management of MAS that TOCI doesn't have.

b) adverse events c) treatment discontinuation rates?	
6. What are the clinical reasons why either tocilizumab or anakinra would be chosen as treatment over the other?	**TOCI – joint predominant disease** Anakinra – MAS/ systemic predominant disease
Issue 4: Efficacy of biologics at different points in the treatment pathway	
7. Would you expect more people to have disease remission overall if anakinra and tocilizumab were used earlier in the treatment pathway and csDMARDs were not used at all?	For people whose disease does not switch off quickly with csDMARDs then yes, as with all inflammatory conditions, the quicker you can reduce the inflammatory burden, the better the longer term outcomes and the more likely a sustained remission will be.
Issue 5: Tocilizumab adminstration	
8. Of people with sJIA receiving tocilizumab, what percentage would receive it: a) subcutaneously b) intravenously?	Traditionally most sJIA patients had iv TOCI. Locally we have now switched/ offered all sJIA patients sc TOCI as standard so for our service >75% are now on sc TOCI. This probably does not reflect that national picture but I am unable to give figures from elsewhere
9. Would people with AOSD receiving tocilizumab all receive it subcutaneously?	The majority – yes – but there are always patients who need iv preparations for a variety of reasons (concordance/ efficacy/ pt dislike of giving own injections etc)
10. If someone started receiving intravenous tocilizumab as a child, would they typically continue receiving it intravenously as an adult?	Not in our service, at transition to adult services we review all meds and offer switches where clinically appropriate if a patient would like to switch. However, anyone already on iv medicine can remain on that if that is either their personal choice, or if clinically this is the right decision.
Issue 6: Treatment discontinuation	

11. In clinical practice, would someone remain on treatment if it did not lead to a remission?	If no evidence of any benefit = no. If partial benefit, then maybe yes with adjunctive treatments added. If a viable alternative treatment exists in the case of partial remission, then this would usually be the next step.
Issue 7: Remission rates with csDMARDs	
12. What proportion of people would be likely to reach disease remission with csDMARDs? a. with monocyclic disease b. with chronic disease	a. 50% b 25-30%

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Novartis Pharmaceuticals UK Ltd.**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

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Issue 1: Treatment pathway	
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2. Would the 'per-label' pathway in figure 1 be implemented in NHS clinical practice? That is, would anakinra and tocilizumab be used after NSAIDs and corticosteroids (rather than after csDMARDs)?	**No comment**
3. What treatments are likely to be used for people in the 'unresolved' health state in clinical practice? For example, would people be likely to receive NSAIDs or csDMARDs again?	**No comment**
Issue 2: Comparators	
4. Is canakinumab used in the NHS for treating sJIA and AOSD after DMARDs?	**Canakinumab is not funded by the NHS for treating either SJIA or AOSD.** [redacted]

Issue 3: Relative efficacy of anakinra and tocilizumab	
5. Do you consider the efficacy of anakinra and tocilizumab to be similar in terms of: a) achieving and retaining remission b) adverse events c) treatment discontinuation rates?	**No comment**
6. What are the clinical reasons why either tocilizumab or anakinra would be chosen as treatment over the other?	**No comment**
Issue 4: Efficacy of biologics at different points in the treatment pathway	
7. Would you expect more people to have disease remission overall if anakinra and tocilizumab were used earlier in the treatment pathway and csDMARDs were not used at all?	**No comment**
Issue 5: Tocilizumab adminstration	
8. Of people with sJIA receiving tocilizumab, what percentage would receive it: a) subcutaneously b) intravenously?	**No comment**
9. Would people with AOSD receiving tocilizumab all receive it subcutaneously?	**No comment**
10. If someone started receiving intravenous tocilizumab as a child, would they typically continue receiving it intravenously as an adult?	**No comment**
Issue 6: Treatment discontinuation	

11. In clinical practice, would someone remain on treatment if it did not lead to a remission?	**No comment**
Issue 7: Remission rates with csDMARDs	
12. What proportion of people would be likely to reach disease remission with csDMARDs? a. with monocyclic disease b. with chronic disease	**No comment**

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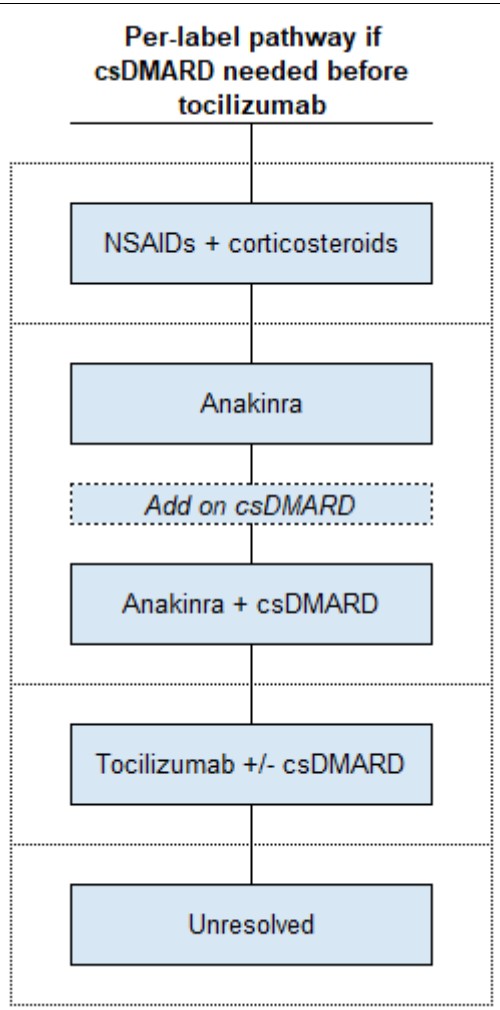
About you

Your name	**Shelley Watcham**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Swedish Orphan Biovitrum Ltd (Sobi Ltd)**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Critique provided by	**Liverpool Reviews and Implementation Group**

Questions for engagement

Issue 1: Treatment pathway	
1. Does the 'post-csDMARD' pathway in figure 1 reflect clinical practice for treating systemic juvenile idiopathic arthritis (sJIA) and adult onset Still's disease (AOSD) in the NHS in England? In AOSD, would a biologic drug only be used after 2 conventional DMARDs?	Pathway in Figure 1 aligned with NICE and NHS England guidance The post-csDMARD process depicted in Figure 1 aligns with current clinical practice as mandated by the NHSE policies. Systemic JIA patients are required to receive one conventional-synthetic DMARD (csDMARD) prior to access to a biologic DMARD (bDMARD), whereas AOSD patients are required to try two csDMARDs before they can access a bDMARD. Furthermore, this is supported by market research which Sobi commissioned in 2019 and shows that methotrexate is used before biologics in NHS England practice. **Management differs between sJIA and AOSD due to historic guidance, and management by paediatric versus adult specialists** Still's disease (including sJIA and AOSD) is a single disease entity with different ages of onset (as agreed within the recent SHARE guidelines).[1] The difference in the management of sJIA and AOSD has arisen from historic guidance, and because patients are managed predominantly by paediatric (sJIA) and adult (AOSD) specialists. **Exception to the pathway in current practice is linked with presence of MAS** The only exception to the pathway for current practice presented in Figure 1 applies to patients who show signs of Macrophage Activation Syndrome (MAS). In this case, the NHS England policy recommends that "where MAS is severe or steroid resistant, treatment with anakinra may be life-saving and should not be delayed."[2] This policy is for sJIA only and does not apply to Stills disease patients who present in adulthood.
ERG Comment	No further comment

2. Would the 'per-label' pathway in figure 1 be implemented in NHS clinical practice? That is, would anakinra and tocilizumab be used after NSAIDs and corticosteroids (rather than after csDMARDs)?	The 'per-label' pathway provided within Figure 1 reflects our proposed use of anakinra within its license for Stills disease and the "post-csDMARD" pathway represents current practice as required by existing clinical commissioning policies and NICE TA238 guidance.[2–4] **Clinical advice suggests 'per-label' pathway can be implemented – if csDMARD is required prior to tocilizumab (in keeping with TA238 guidance), this can be added to anakinra** We asked clinical advisers how the 'per-label' pathway may be achieved in practice, with particular reference to the csDMARD requirement of TA238. We were advised that they would add a csDMARD to anakinra if needed. If adequate response is not achieved, the csDMARD failure criterion of TA238 would have been met, allowing tocilizumab's use. The use of either anakinra or tocilizumab with an add-on csDMARD (such as methotrexate) is within the licensed indication for both bDMARDs. This is shown in the diagram below:


Per-label pathway if csDMARD needed before tocilizumab
NSAIDs + corticosteroids
Anakinra
Add on csDMARD
Anakinra + csDMARD
Tocilizumab +/- csDMARD
Unresolved

	Therefore, we believe that the 'per-label' pathway would be possible to implement in NHS clinical practice, in keeping with TA238 guidance. This would also be in keeping with the relevant aspects of the NHS England clinical commissioning policies which may be affected by the recommendation made by NICE as a result of this appraisal. **While anakinra can be used within its license in glucocorticoid-naïve patients, clinical advice suggests this would not be practical to achieve in NHS practice, hence the 'per-label' pathway proposed includes the use of anakinra after corticosteroids** The licensed indication for anakinra is 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 NSAIDs or glucocorticoids.[5] This means that for patients with moderate-to-high disease activity, treatment with anakinra can be initiated prior to use of NSAIDs or corticosteroids. The efficacy of anakinra in glucocorticoid-naïve patients is noted within the recent SHARE consensus guidelines (which are discussed later in our response) as well as in the Vastert *et al* (2014) and Ter Haar *et al.* (2019) studies.[1,6,7] While within the label, clinical advice provided to us suggested that it would be difficult to initiate treatment with anakinra prior to steroids in current NHS practice as steroids are expected to be used as part of diagnosis.
ERG Comment	No further comment
3. What treatments are likely to be used for people in the 'unresolved' health state in clinical practice? For example, would people be likely to receive NSAIDs or csDMARDs again?	Effective treatment options after exhaustion of 'standard' therapies are extremely limited, but a range of different approaches may be considered For patients with disease refractory to two bDMARDs, it is very likely that NSAIDs and/or corticosteroids would be added or would not have been stopped. Following a failed trial of a second bDMARD, further treatment options in the "unresolved state" are extremely limited. Options which may be considered in practice are considered on a case-by-case basis, though the extent of their use is difficult to quantify and is not necessarily evidence based. These options include retreatment with a bDMARDs

	previously used, combinations of biologics and other therapies, off-label use of JAK inhibitors, compassionate use or enrolment in clinical trials. Failing these, as a last resort, a patient might undergo a bone marrow transplant. **Bone marrow transplants are an option, but due to the high mortality risk are avoided where possible** Advice provided to us was that while remission is the target, if remission has not been attained after several therapy trials, rather than undergo a bone marrow transplant some patients may continue bDMARD therapy if they are perceived to derive some benefits in terms of symptom control (acknowledging that it is unlikely that continued treatment would lead to remission). Every attempt is made to avoid bone marrow transplant which has a high mortality risk (12.5% according to a UK series[8], and 9% according to Dutch study[9]).
ERG Comment	No further comment
Issue 2: **Comparators**	
4. Is canakinumab used in the NHS for treating sJIA and AOSD after DMARDs?	Canakinumab not routinely available for sJIA or AOSD patients in NHS practice It is our understanding that canakinumab is not routinely commissioned for the treatment of sJIA or AOSD, and that access is limited to individual funding requests. Therefore, while a very small number of patients may receive canakinumab in current practice, it is not an established part of the treatment pathway and is not available on a national basis.
ERG comment	No further comment
Issue 3: **Relative efficacy of anakinra and tocilizumab**	
5. Do you consider the efficacy of anakinra and tocilizumab to be similar in terms of:	Anakinra does not seek to replace tocilizumab, but rather to add to the arsenal available for treatment Anakinra and tocilizumab are different drugs (recombinant receptor antagonist vs monoclonal antibody) blocking different cytokines (IL-1 vs IL-6). Both cytokines are important in inflammation, but in health and disease these two cytokines play different roles and are not interchangeable. They are therefore broadly similar in both being good

a) achieving and retaining remission
 	
b) adverse events
 	
c) treatment discontinuation rates?
	targets for inhibition in the treatment of Stills disease but different to one another in the specifics of remission and adverse events.[10,11] Both treatments are therefore important options available for patients with Still's disease.
	
	Similarities
	
	In our submission, we shared the findings of a systematic literature review (SLR) and meta-analysis of clinical studies in sJIA by Tarp *et al.*, (2016).[10] The findings of this SLR suggest that there is no statistically significant difference in efficacy between bDMARDs, though the patient numbers are small and there was notable heterogeneity between clinical study designs and patient populations.
	
	The findings from another SLR by Kuemmerle-Deschner *et al.*, (2019) found that current interventions for sJIA (including anakinra and tocilizumab) were found to be effective and generally well tolerated; though a lack of head-to-head studies limits a rigorous comparison between treatments.[11]
	
	No bDMARD therapy has been shown to be superior over another in Still's disease within the context of a meta-analysis, and so they have historically been deemed broadly equivalent in terms of their efficacy.
	
	Differences
	
	The main differences between anakinra and tocilizumab in Stills disease are:
	
	• Efficacy
	  o Efficacy by time since disease onset: The window of opportunity in early Stills disease is sensitive to IL-1 inhibition as shown in clinical studies
	  o Efficacy in the presence of MAS: Anakinra is recommended by NHS England specifically noting that *"where MAS is severe or steroid resistant, treatment with anakinra may be life-saving"*
	• Safety
	  o Anakinra and tocilizumab target different cytokines which results in different safety profiles
	  o IL-6 inhibition, and not IL-1 inhibition, abrogates the acute phase response and masks MAS and sepsis development

	o Anakinra is associated with injection site reactions in the early weeks of treatment ***Efficacy: "anakinra is effective in early disease course including in glucocorticoid-naïve patients" – SHARE Consensus recommendation*** Studies supporting the use of anakinra early in the disease process include Pardeo 2015, Nigrovic 2011, Vastert 2014, Ter Haar 2019, [redacted] and the Sobi-sponsored anaSTILLs RCT* (see description in Question 7 below).[6,7,12–16] These data supported the SHARE consensus group, recommending that "*anakinra is effective in early disease course including in glucocorticoid-naïve patients*". In contrast, tocilizumab is recommended later in the disease course: "*Tocilizumab, an IL-6 blocking agent, is an effective treatment option in glucocorticoid resistant or glucocorticoid dependant sJIA*". IL-1 is understood to play a particularly important role in early Stills disease, particularly in relation to the systemic features. Later in the disease process, where articular features may be more pronounced, methotrexate or an IL-6 inhibitor such as tocilizumab are considered more effective than an IL-1 inhibitor such as anakinra. Arthritis may only develop later in the disease, as noted in the recent SHARE consensus: *"Arthritis can be an important feature but may not be present at the early stage of the disease."* This distinction between anakinra and tocilizumab for use respectively in systemic and articular manifestations is borne out by the recommended in the NHS England AOSD policy.[4] The 'window of opportunity' hypothesis has been studied in clinical trials of IL-1 inhibition (and not IL-6 inhibition) in early Stills disease (Pardeo 2015, Nigrovic 2011, Vastert 2014, Ter Haar 2019, [redacted] and the Sobi-sponsored anaSTILLs RCT).[6,7,12–16] Similar studies have been conducted with canakinumab (a monoclonal antibody directed against IL-1β), but as described previously canakinumab is not readily available in NHS practice. In practice, Still's disease patients may present with a combination of systemic and articular features, and these may change over time, so both treatment options (anakinra and tocilizumab) may be considered suitable for patients. There is relatively limited evidence concerning the split of systemic versus articular patients, though a study by Vitale

* The CSR for the anaSTILLs study is provided alongside this response to NICE. For a summary overview of the anaSTILLS study, please refer to Schanberg *et al.*, (2020); available at: https://ard.bmj.com/content/79/Suppl_1/1819.2

	et al. reported that approximately three-quarters of AOSD patients studied had a systemic disease pattern (versus one-quarter with a chronic articular pattern).[17] While there are specific reasons one treatment may be considered in preference to another, for simplicity, both are generally considered to have equivalent efficacy for the treatment of Still's disease as a whole. However, in relation to the early use of bDMARDs specifically, IL-1 inhibition with anakinra has consistently shown efficacy over several trials in a variety of centre. ***Efficacy: Use of anakinra should not be delayed in the presence of severe or steroid-resistant MAS*** As discussed in Issue 1, NHS England recommends *"where MAS is severe or steroid resistant, treatment with anakinra may be life-saving and should not be delayed"* NHS England does not recommend the use of tocilizumab under these circumstances. It should be noted that this policy applies only in the paediatric setting, and so Still's disease patients who present with MAS over the age of 18 do not have access to anakinra (based on the AOSD policy). Clinical consensus view is that the use of anakinra in the presence of MAS is important in Still's disease as a whole (i.e. not just for sJIA patients), and so, in an ideal world, clinicians would have the ability to use anakinra in the presence of MAS regardless of the age of Still's disease onset. ***Safety: anakinra and tocilizumab target different cytokines which results in different safety profiles*** Both products are considered to have comparable safety profiles, though a lack of head-to-head comparisons precludes a robust comparison. We previously highlighted an analysis of registry data by Klein *et al.*, (2019) comparing outcomes for patients treated with anakinra and tocilizumab (as well as canakinumab and etanercept – treatments that are both used in Germany).[18] This study showed no statistically significant difference in adverse events of special interest (defined by the authors) between anakinra and tocilizumab, though some numerical differences were noted (namely, anakinra was associated with an increase in the risk of medically important infections, whereas tocilizumab was associated with an increase in the risk of cytopenia, anaphylaxis, hepatic events, and MAS). Further, tocilizumab is known to abrogate the acute phase response. If relying on surrogate markers from the acute phase response, detection of MAS or sepsis easy to miss. The European SmPC describes this special precaution: *"Vigilance for the timely detection of serious infection is recommended for patients receiving immunosuppressive*

	agents such as RoActemra as signs and symptoms of acute inflammation may be lessened, due to suppression of the acute phase reactants. The effects of RoActemra on C-reactive protein (CRP), neutrophils and signs and symptoms of infection should be considered when evaluating a patient for a potential infection. Patients, and parents/guardians of sJIA or pJIA patients, should be instructed to contact their healthcare professional immediately when any symptoms suggesting infection appear, in order to assure rapid evaluation and appropriate treatment."[19] Similarly an FDA warning: *"Closely monitor patients for the development of signs and symptoms of infection during and after treatment with ACTEMRA, as signs and symptoms of acute inflammation may be lessened due to suppression of the acute phase reactants."*[20] **Challenges with considering a cost-minimisation analysis (assuming entirely equal safety and efficacy)** For the reasons highlighted above, it is challenging to consider a cost-minimisation analysis within the context of comparing anakinra and tocilizumab, as in a real-world scenario both treatment options are available and could be considered for the same patient, depending on the predominant disease features (i.e. systemic and/or articular). It is therefore not appropriate to consider the displacement of tocilizumab with anakinra (or *vice versa*) as both options are extremely important treatment options for patients with Still's disease. Instead, the cost-effectiveness analysis presented considers the use of both anakinra and tocilizumab regardless of whether anakinra is used prior to csDMARDs (the 'per label' pathway, where we propose the use of anakinra) or after csDMARDs (the 'post-csDMARD' pathway, which we understand to reflect current NHS practice). **No expected difference in treatment discontinuation rates** We are unaware of any data comparing treatment discontinuation rates with anakinra versus tocilizumab. However, the discontinuation rate applied within the cost-effectiveness analysis is based on the previous NICE TA238 model. The clinical advice we received did not suggest any substantial difference in the long-term treatment discontinuation rates between bDMARDs.

ERG Comment	Similarities between anakinra and tocilizumab Evidence from a network meta-analysis and systematic review: as noted in our ERG report (Section 4.2.3 and Section 5.5.1) there are a number of issues with the Tarp et al 2016 NMA that render the results and conclusions unreliable. The five included trials (one trial each of anakinra, tocilizumab and canakinumab, two trials of rilonacept) were small and employed different study designs, different trial eligibility criteria and used an inappropriate outcome measure (modified JIA ACR 30). All these limitations were noted by the study authors, the company and the ERG the Kuemmerle-Deschner et al 2019 systematic review publication is a conference abstract. The review included eight RCTs (one trial each of anakinra, tocilizumab, canakinumab, etanercept, methotrexate; a withdrawal trial of tocilizumab; two trials of rilonacept) and 54 real world studies. The main outcome reported for the results of the RCTs is the JIA ACR 30. The authors of the study concluded that the current interventions, especially anakinra, canakinumab, etanercept and tocilizumab were effective and generally well-tolerated for SJIA. However, the lack of head to head studies limits a rigorous comparison. The evidence from the Tarp et al 2016 NMA and the Kuemmerle-Deschner et al 2019 systematic review highlights the lack of evidence available for the clinical effectiveness of anakinra compared with tocilizumab. ***Anakinra is effective in early disease course including in glucocorticoid-naïve patients" – SHARE Consensus recommendation and the 'window of opportunity hypothesis'*** The ERG has no comment on the SHARE Consensus recommendation, but notes the new evidence provided by the company ([redacted]) and the anaSTILLs RCT). [redacted] The anaSTILLS RCT, included 12 patients (the planned enrolment target was 81 patients). Six patients were randomised to treatment with anakinra for 12 weeks and six were randomised to placebo for 12 weeks. All patients treated with anakinra achieved

	an ACR30 response at Week 2 (primary outcome). None of the patients in the placebo arm achieved an ACR30 response at Week 2. The ERG considers that the 'window of opportunity' hypothesis remains clinical speculation at best for treatment with anakinra. **Challenges with considering a cost-minimisation analysis (assuming entirely equal safety and efficacy):** The company states that it is challenging to consider a cost-minimisation analysis within the context of comparing anakinra and tocilizumab, as in a real-world scenario both treatment options are available and could be considered for the same patient, depending on the predominant disease features (i.e. systemic and/or articular). The ERG notes that in the final scope issued by NICE, subgroup analysis based on systemic or articular disease features is not specified. The company has not presented any evidence on the differential effectiveness of anakinra on articular and/or systemic disease features.
6. What are the clinical reasons why either tocilizumab or anakinra would be chosen as treatment over the other?	Clinical reasons include: • Clinical manifestation – anakinra in systemic features or MAS/HLH, tocilizumab or methotrexate in articular disease • Time since disease onset – window of opportunity and IL-1 inhibition in early disease • Patient choice (injection/infusion frequency) • Compliance – infusion if non-compliance suspected, daily injection if established routine useful Please see our response to question 5 for further detail.
ERG comment	The company has not presented any evidence on the differential effectiveness of anakinra on articular and/or systemic disease features.

Issue 4: Efficacy of biologics at different points in the treatment pathway	
7. Would you expect more people to have disease remission overall if anakinra and tocilizumab were used earlier in the treatment pathway and csDMARDs were not used at all?	Improved remission for anakinra used earlier in the treatment pathway aligned with window of opportunity hypothesis, but this only applies to IL-1 inhibition The expectation of overall improved remission rates if anakinra is made available earlier in the treatment pathway (and csDMARDs were removed entirely) is aligned with the 'window of opportunity' hypothesis. The 'window of opportunity' hypothesis is based on the role of IL-1, and so the expectation of improved outcomes does not directly apply to tocilizumab (an IL-6 inhibitor). **anaSTILLS study findings are now available, which provide some extra information, but this study is limited due to early termination (issues with recruitment)** We note that data from the anaSTILLS study may be helpful within the context of this question, as these data comprise a group of patients treated with anakinra prior to the use of csDMARDs.[15] anaSTILLS is a randomised, placebo-controlled trial of anakinra in Still's disease which was conducted to further evaluate efficacy and safety of anakinra in patients with Still´s disease across all age groups. However, owing to issues with recruitment, the study was terminated early, and a total of n=11 patients were analysed for efficacy (enrolment target was n=81 patients). In spite of the study considering only a comparison of n=6 anakinra and n=5 placebo patients, the study met its primary endpoint: all patients on anakinra but none on placebo achieved ACR30 response with absence of fever at Week 2 (p-value=0.0022). In addition, 5 of the 6 anakinra patients had sustained ACR90 response by the end of follow-up (with the remaining patient having sustained ACR70 response), versus none of the placebo patients. The CSR from the anaSTILLS study, and an abstract which was recently published about the anaSTILLS study are provided alongside our response. **Five studies provide support for the window of opportunity hypothesis** In addition to the anaSTILLS study described above, four other recent studies provide useful information concerning outcomes for treatment with anakinra prior to csDMARDs. ***Nigrovic et al 2011***[13]

	Nigrovic et al reviewed the medical records of patients with sJIA who received anakinra as part of their initial treatment regimen. Results from 46 patients in 11 centres in four countries (US, the Netherlands, Italy and Canada) were analysed. The patients included received either anakinra alone, anakinra with DMARDs (no steroids), anakinra with steroids (no DMARDs) or anakinra with steroids and DMARDs. Patients were recently diagnosed - median time from disease onset to initiation of anakinra was 82.4 days (2.7 months). 27/59 (59%) showed a complete response, while another 39% showed a partial response. This was associated with a rapid resolution of systemic symptoms – fever and rash resolved completely in 86% of 25 evaluable patients, typically within 1-2 days. By 30 days, fever and rash had resolved in 97% of 36 evaluable patients. ***Pardeo* et al *2015***[12] This group of Italian researchers retrospectively analysed 25 patients with sJIA who had received anakinra for 6 months. They compared the characteristics of responders with non-responders. The only characteristic with a significant difference was time from disease onset to anakinra administration in months (median 1.9 months in responders vs 24.5 months in non-responders [redacted] ***Vastert* et al *2014 and Ter Haar* et al *2019***[6,7] These two studies report clinical outcomes for a consecutive cohort of sJIA patients presenting to a single centre in the Netherlands. Vastert *et al* 2014 reports results from 20 patients in the first 4 years of initiation of a treat to target strategy in which anakinra was used before glucocorticoids. These 20 patients were included in the subsequent paper by Ter Haar *et al* (2019). Ter Haar *et al* (2019) describe the results of 42 consecutive patients treated with NSAIDS and then anakinra. Lack of response at 1 month and 3 months led to either an increase of dose or switch to another therapy. The primary endpoint, clinically inactive disease at 1 year, was met by 76% of patients treated with this treat to target strategy. Further, a tapering strategy allowed just over half (52%) to be in drug-free remission. Our cost-effectiveness analysis does not take into account the full cost savings associated with drug tapering and drug-free remission shown within the Ter Haar *et al.* (2019) study, and may therefore be considered to present a

conservative estimate of the likely long-term costs associated with anakinra were it reimbursed in the pre-csDMARD setting.

[redacted]

SHARE guidelines[1]

The SHARE consensus group presented their consensus statements and recommendations concerning the management of sJIA during the recent PReS 2020 congress. The final manuscript is expected to be published in November 2020. The consensus statements include that anakinra is an effective treatment option early in the disease course of sJIA, including in glucocorticoid naïve patients.

Summary

In summary, we expect earlier use of anakinra to allow more people to achieve remission versus its current use after csDMARDs. This is for two reasons:

- Mandated early use of methotrexate, a drug unlicenced and unproven in Stills disease delays the initiation of truly disease modifying therapy (also discussed in Issue 7).[1,21–24]
- The window of opportunity, which applies specifically to the role of IL-1 inhibition early in Stills disease, is missed if biologic initiation is delayed by a methotrexate trial. The benefits or not of using tocilizumab in the window of opportunity early in Stills disease have not been established.

ERG comment	Overall, the ERG concludes that the 'window of opportunity' hypothesis remains clinical speculation at best for treatment with anakinra.
Issue 5: Tocilizumab administration	
8. Of people with sJIA receiving tocilizumab, what percentage would receive it: a) subcutaneously b) intravenously?	No data available to quantify the precise proportion of patients receiving IV versus SC Data concerning the proportion of NHS patients in England that receive subcutaneous (SC) versus intravenous (IV) tocilizumab in Still's disease (sJIA and AOSD) are unavailable to us. Advice provided to us was documented in our submission, which suggested an approximate 50:50 split of SC:IV use of tocilizumab. **The practicalities of administration to children likely influence choice of tocilizumab route of administration** Stills disease manifests in both children (sJIA) and adults (AOSD and sJIA patients once reaching adulthood). IV over SC administration in paediatrics may at times preferred considering the practicalities of carer-administration at home. Similarly, it is our understanding that administration of tocilizumab for a person with sJIA reaching adulthood would be approached in the same manner as for an adult diagnosed with AOSD. (This is also in relation to question 10) **Both routes of administration are expected to be used in practice, but clinical expert advice needed for more precise estimates** While we are unsure of the proportion of patients that receive IV versus SC tocilizumab, we expect a non-zero proportion of patients to be treated with either option, owing to the fact that each route of administration may have its benefits under certain circumstances (e.g. IV for speed of delivery or where compliance to self-administration is a concern, versus SC for home administration). **The cost-effectiveness analysis assumption on the tocilizumab SC/IV split is not a key driver of results** Within the context of the economic model, we have run scenarios considered 100% use of IV tocilizumab and 100% use of SC tocilizumab, which are presented below. These results are based on a longer time horizon than the originally-submitted base-case analysis (up to 90 years, based on feedback from the ERG), and assuming a [redacted] PAS discount on the list price of tocilizumab.

<table>
<tr><td></td><td>
<u>Base-case analysis (with 90-year time horizon)</u>
<table>
<tr><th rowspan="2">Arm</th><th colspan="3">Total</th></tr>
<tr><th>Costs (£)</th><th>QALYs</th><th>LYs</th></tr>
<tr><td>No anakinra</td><td>351,641</td><td>14.113</td><td>52.514</td></tr>
<tr><td>Post-csDMARD</td><td>316,902</td><td>14.547</td><td>53.329</td></tr>
<tr><td>Per-label</td><td>290,919</td><td>14.971</td><td>54.259</td></tr>
</table>
<u>Assuming 100% IV tocilizumab</u>
<table>
<tr><th rowspan="2">Arm</th><th colspan="3">Total</th></tr>
<tr><th>Costs (£)</th><th>QALYs</th><th>LYs</th></tr>
<tr><td>No anakinra</td><td>359,604</td><td>14.113</td><td>52.514</td></tr>
<tr><td>Post-csDMARD</td><td>323,501</td><td>14.547</td><td>53.329</td></tr>
<tr><td>Per-label</td><td>295,068</td><td>14.971</td><td>54.259</td></tr>
</table>
<u>Assuming 100% SC tocilizumab</u>
<table>
<tr><th rowspan="2">Arm</th><th colspan="3">Total</th></tr>
<tr><th>Costs (£)</th><th>QALYs</th><th>LYs</th></tr>
<tr><td>No anakinra</td><td>343,679</td><td>14.113</td><td>52.514</td></tr>
<tr><td>Post-csDMARD</td><td>310,303</td><td>14.547</td><td>53.329</td></tr>
<tr><td>Per-label</td><td>286,770</td><td>14.971</td><td>54.259</td></tr>
</table>
The results of the sensitivity analysis show that the conclusion is unchanged were tocilizumab administered completely via IV infusion or SC injection – that is, the ‘per-label’ pathway continues to dominate the ‘post-csDMARD’ and ‘no anakinra’ pathways. However, the total costs are greater for when IV tocilizumab is considered, based on the requirement for administration to take place within an outpatient setting.
</td></tr>
<tr><td>ERG comment</td><td>The structural issues in the company model mean that no robust ICERs per QALY gained can be generated for any treatment comparison.</td></tr>
<tr><td>9. Would people with AOSD receiving tocilizumab all receive it subcutaneously?</td><td>Please see our response to question 8 with regards to SC versus IV use of tocilizumab in general.</td></tr>
</table>

ERG comment	No further comment
10. If someone started receiving intravenous tocilizumab as a child, would they typically continue receiving it intravenously as an adult?	Please see our response to question 8 with regards to SC versus IV use of tocilizumab in general.
ERG comment	No further comment
Issue 6: Treatment discontinuation	
11. In clinical practice, would someone remain on treatment if it did not lead to a remission?	There are several reasons why some patients in clinical practice would continue to receive treatment with a bDMARD if it did not lead to remission. However, patients are not expected to receive long-term treatment with corticosteroids or csDMARDs (such as methotrexate), owing to glucocorticoid toxicity and a lack of efficacy relating to the systemic features of Still's disease, respectively. **Some patients may have exhausted all other 'standard' treatment options** Patients may receive bDMARD therapy without the expectation of remission if they have otherwise exhausted all other treatment options. This would be considered appropriate if patients are deriving some benefit (in terms of symptom control) from their bDMARD therapy, even if remission is unlikely to be achieved. This course may be chosen in preference to the high mortality rate of a bone marrow transplant once all other options are exhausted. The proportion of patients requiring long-term bDMARD therapy to address symptoms of chronic course Still's disease is however expected to be lower were anakinra made available earlier in the treatment pathway (Ter Haar *et al*, 2019).[7] **Some patients may continue treatment as symptom control benefits outweigh risks of discontinuing and trying a different treatment**

	Some patients may also continue treatment with bDMARD therapy without remission if they have flared previously and may therefore be anxious about discontinuing treatment. This is especially important within the context of patients that have a history of (or considered to be at a high risk of developing) macrophage activation syndrome (MAS), which could be fatal.
ERG comment	No further comment
Issue 7: Remission rates with csDMARDs	
12. What proportion of people would be likely to reach disease remission with csDMARDs? a. with monocyclic disease b. with chronic disease	**SHARE recommendations: "Methotrexate can be of some benefit in the treatment of arthritis in sJIA, but has no proven benefit in systemic features"** The SHARE recommendations emerged by consensus following a systematic literature review and expert consensus meetings conducted between June 2013 and 2020.[1] We were unable to gain a copy of the pre-publication manuscript, but it is expected to be published in November 2020. The group's consensus recommendation within the SHARE recommendations is clear that methotrexate does not have a proven benefit in the systemic features of Still's disease. We refer to our response to question 5 of the Additional clarification questions February 2020 in which we expanded on the results of several studies of methotrexate in Stills disease in substantiation of the clinical need for earlier biologics. (Halle and Prieur, 1991; Speckmaier *et al*., 1989; Woo *et al.* 2000; Nordström *et* al., 2012).[21–24] **UK expert view of the efficacy of methotrexate in treating the systemic features of Still's disease is consistent with the SHARE recommendations** The SHARE consensus recommendation referred to above was concluded by 26 clinicians with expertise treating Stills disease, 2 of whom were UK clinicians. During the informal technical engagement call with NICE and the ERG, we understood that it may be helpful to obtain further UK clinicians' views to supplement the SHARE consensus recommendation on methotrexate in Stills disease. For 10 days after the technical engagement call, the Sobi medical

	team surveyed 20 clinicians in at least 12 trusts to gain their views.† This confirmed that methotrexate is not believed to be of use in the systemic features of Stills disease and that while methotrexate is used in order to meet funding criteria for biologics, clinicians believe this delays the initiation of effective therapy. Those in whom methotrexate is said to have led to remission were thought to have had the monocyclic variant of the disease which would have resolved without methotrexate. **Precedence for csDMARD bypass in other rheumatological conditions** There is also precedence for the limited role of csDMARDs (or methotrexate specifically) in other sub-types of rheumatic diseases where they are not considered effective. For example, methotrexate is bypassed in enthesitis-related JIA in favour of adalimumab and etanercept (NICE TA373).[25] **Methotrexate plays a part in treating articular features and needs to be available as an add-on therapy, but should not delay initiation of a true *disease modifying therapy*** As methotrexate is understood to have no impact on the systemic features of Still's disease, it is not considered possible to achieve remission in patients with a chronic disease course through the use of csDMARDs alone.[26] The use of csDMARDs in Still's disease in NHS practice is based funding requirements, the rheumatology tradition of methotrexate as an anchor drug, and methotrexate's benefits in articular symptom control. The modern practice treatment goal is aimed at achieving clinically-inactive disease (i.e. remission). Steroids and methotrexate are not licensed for use in Still's disease, but only steroids are recognised to be effective in terms of the systemic features of the disease Anakinra and tocilizumab are licensed for the treatment of sJIA, and only anakinra is licensed for the treatment of AOSD. NSAIDs, corticosteroids, and csDMARDs (such as methotrexate) are not licensed for the treatment of Still's disease. We acknowledge that NICE considers the current treatment pathway, including off-label therapies. However, unlike corticosteroids, csDMARDs have no proven efficacy in the treatment of the systemic features of Still's disease.

[redacted]

	Corticosteroids are effective in the treatment of Still's disease (even though their use is off-label), yet their long-term use is limited due to glucocorticoid toxicity.[1] **Subcutaneous methotrexate (via an injection pen), predominantly used in paediatrics, is more expensive than oral methotrexate.** Oral methotrexate is known to be an inexpensive treatment (£0.86 for 24x 2.5mg tablets, which is more than enough for a weeks' supply [see CS for original costing approach]), but for ease of administration subcutaneous methotrexate (£16.06 per week for 1x 20 mg injection pen [Nordimet®, Nordic Pharma Ltd] [27]) is used predominantly in paediatric settings. For the context of the economic model, all methotrexate use was conservatively assumed to be oral, but the true costs of methotrexate in current practice would be reduced markedly were anakinra recommended aligned with the 'per-label' pathway. **Methotrexate is poorly tolerated by patients.** In a consumer priorities survey conducted by NIHR CRN: Children/Versus Arthritis Paediatric Rheumatology CSG survey of 223 people living with musculoskeletal conditions asked what their top research priorities would be across the entire experience of living with their condition, 37% (83 respondents) chose methotrexate usage and tolerability as a top concern.[28] **Acute presentation of macrophage activation syndrome (MAS) in adults** MAS is a severe, acute, life-threatening systemic manifestation of Stills disease. The underlying disease process is hyperinflammation. A patient with Stills disease under the age of 18 presenting with MAS has access to anakinra under the current commissioning policy for JIA: *"where MAS is severe or steroid resistant, treatment with anakinra may be life-saving and should not be delayed"*.[2] A patient with Stills disease over the age of 18 presenting with MAS has no such access (based on national guidelines) and is required to trial two csDMARDs. Patients presenting with hyperinflammation (MAS) are acutely unwell, the hyperinflammation must be controlled quickly. Steroids and anakinra are both effective options. High dose steroids are started along with methotrexate. Methotrexate is not effective in hyperinflammation but it is given to

	eventually allow access to anakinra. Adult Stills disease patients in MAS often presents with liver abnormalities (ALT>100), complicating methotrexate prescription. The effect of methotrexate is seen after 3 weeks. Clinical response to anakinra administration in the acute presentation of hyperinflammation is seen within a day. Methotrexate therefore delays access to effective therapy not only in terms of resolving the systemic features of Stills disease, but also addressing MAS: a potentially-fatal manifestation of Still's disease. The steroid dose required to control the hyperinflammation in the absence of anakinra, also results in accumulation of steroid-related toxicities. **Summary** Methotrexate in Stills diseases is unlicenced, ineffective for systemic features and poorly tolerated.[1,21–24,26] In addition, the use of subcutaneous methotrexate in current practice for paediatric patients is associated with far greater cost versus tablets, the implications of which were conservatively not reflected within the cost-effectiveness analysis submitted. While methotrexate has value as an adjunct to biologics in the case of articular features, a mandated trial of methotrexate monotherapy delays initiation of a Stills disease modifying therapy.
ERG comment	No further comment

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