

**NIHR Innovation Observatory
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Anakinra for Still's disease

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LAY SUMMARY

Still's disease is a rare auto inflammatory disease which can affect adults (adult onset Still's disease) or children (systemic idiopathic juvenile arthritis). The symptoms of Still's disease can develop quickly or over time and include a daily fever which usually peaks in the late afternoon/early evening, joint pain and swelling and a pink rash. The cause of Still's disease is unknown although it is thought that abnormalities in a particular part of the immune system causes episodes of inflammation to occur in the body. Still's disease is usually treated first with non-steroidal anti-inflammatory drugs (NSAIDs) or steroids, however in some people, these drugs will fail to control and treat the disease. In these cases, different drugs are needed to treat the disease.

Anakinra is a drug which blocks a particular inflammatory protein which causes inflammation and is thought to play a role in the activity of Still's disease. Anakinra is administered by injection under the skin (subcutaneously) and can be used in new onset patients or those with continued disease activity. As of February 2018, anakinra has been licenced for the treatment of adults, adolescents, children and infants aged 8 months and older patients with Still's disease who have not responded to treatment with NSAIDs or steroids, and therefore require further treatment to control their disease.

This briefing reflects the evidence available at the time of writing. A version of the briefing was sent to the company for a factual accuracy check. The company was available to provide comment. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

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TARGET GROUP

Stills disease - including Systemic Juvenile Idiopathic Arthritis and Adult-Onset Still's Disease (active systemic features of moderate to high disease activity or in patients with continued disease activity after treatment with NSAIDs or glucocorticoids, children over 8 months old and adults with a body weight of 10kg or above)

TECHNOLOGY

DESCRIPTION

Anakinra (Kineret) is an immunosuppressant that neutralises the biologic activity of interleukin-1 α (IL-1 α) and interleukin-1 β (IL-1 β) by competitively inhibiting their binding to interleukin-1 type I receptor (IL-1RI). Interleukin-1 (IL-1) is a pivotal pro-inflammatory cytokine mediating many cellular responses including those important in synovial inflammation. Anakinra inhibits responses elicited by IL-1 in vitro, including the induction of nitric oxide and prostaglandin E2 and/or collagenase production by synovial cells, fibroblasts, and chondrocytes.¹

The dose of anakinra used in the phase III trial (NCT03265132) was 2mg/kg/day (with a maximum of 100mg/day) or 4mg/kg/day (with a maximum of 200mg/day) by subcutaneous injection for 12 weeks.²

Anakinra is licenced for use in the EU as follows:³

- 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 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

The most common side effects of anakinra use (occurring in more than 1 in 10 patients) include: headache, injection site reactions and increased blood cholesterol.¹

Anakinra is currently in phase II trials for the treatment of acute gouty arthritis.⁴

INNOVATION and/or ADVANTAGES

Licensed therapeutic options are required for the treatment of active still's disease (both Adult Onset Stills Disease (AOSD) and systemic juvenile idiopathic arthritis (SJIA)) who do not respond to Non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. It is important that more treatment options are made available for refractory still's disease, as this disease has high levels of remission failure after treatment with NSAIDs (80% remission failure) and corticosteroids (40% remission failure). In addition, standard treatments have the potential to cause adverse events (AEs) in Still's disease patients, with 20% NSAIDs users experiencing AEs and 45% experiencing steroid dependency.⁵

Anakinra is one of two biological therapies (along with Canakinumab) licenced specifically for the treatment of Still's disease (both AOSD and SJIA) in patients who have disease refractory to NSAIDs or glucocorticoid treatment. Anakinra is the only biological therapy available for the treatment of Still's disease in children aged 8 months to 2 years old.^{3,6}

DEVELOPER

Swedish Orphan Biovitrum Ltd

REGULATORY INFORMATION/ MARKETING PLANS

Anakinra was designated US orphan drug status by the FDA in September 2015.⁷

The company received a positive CHMP (Committee for Medicinal Products for Human use) on 22 February 2018.³

PATIENT GROUP

BACKGROUND

Adult Onset Still's Disease (AOSD) is a rare systemic inflammatory disorder which is the adult form of systemic juvenile idiopathic arthritis (SJIA), otherwise known as 'juvenile Still's disease'.⁸ It is still contested whether AOSD and SJIA belong to the same continuum of disease, but evidence suggests they are the same disease.⁵ AOSD primarily affects young adults aged 16-35 years old while SJIA affects children below 16 years old, with onset usually between 3-5 years old.^{9,10,11}

People with Still's disease will develop a combination of symptoms normally associated with systemic inflammatory disease, including a spiking fever greater than 39°C which usually peak in the late afternoon/early evening, joint pain and inflammation (commonly in the knees, wrists and ankles), muscle pain and a pink/salmon coloured rash (usually during the fever episodes and affecting the chest, thighs, arms, legs and face). 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). Signs and symptoms of AOSD are highly variable between individuals with episode of disease occurring at variable frequencies and durations.⁸ Based on which symptoms predominate, the disease activity and evolution, two 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). Within the systemic phenotype, the disease may be self-limiting (30% cases), intermittent (30% cases) or chronic (40%) in course.¹²

The causes of Still's disease are unknown although it is believed to be an auto inflammatory syndrome in which abnormalities in the innate immune system cause recurrent inflammatory episodes (these are different to autoimmune diseases in which the adaptive immune system mistakenly attacks healthy tissue). It may be caused by an abnormal or exaggerated response to an infection or toxin. Cytokines, such as IL-1 which mediate cell responses to inflammation, may also play a role in Still's disease.⁸

It is difficult to diagnose Still's disease 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.⁸ 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).⁹ Potential differential diagnosis for SJIA include infections, connective tissue disease (e.g. lupus), acute leukaemia and other auto-inflammatory diseases.¹⁰

In children (SJIA), the disease resolves before adulthood in approximately 50% of patients and in the remaining the arthritis will persist, with or without fever. Severe subsequent disease episodes are seen in 20% of SJIA cases which can result in delayed growth, bone and cartilage erosion with functional handicap and risk of osteopenia.¹⁰ SJIA can also lead to amyloidosis and macrophage activation syndrome which can be fatal if not recognised early and treated aggressively.¹¹ Prognosis of AOSD is generally good once any life threatening manifestations (e.g. hemophagocytic lymphohistiocytosis) have been controlled, although some patients with chronic disease and major joint involvement may have a significantly altered quality of life.⁹

CLINICAL NEED and BURDEN OF DISEASE

AOSD is a rare disease with an estimated incidence of 1-2 per 1,000,000 and an estimated incidence of 55-110 cases per year in England. Prevalence of AOSD is estimated at 400-800 patients in England.¹² SJIA is also a rare disease which makes up approximately 10% JIA diagnoses. The estimated UK incidence of JIA is 0.1 per 1000 children per year (the equivalent to 1000 children diagnosed per year) which equates to a SJIA incidence rate of 0.1 per 10,000 children per year (equivalent to 100 children diagnosed per year). The estimated UK prevalence of JIA is 1 per 1000 children (the equivalent to 10,000 children affected by JIA at any time) which equates to a SJIA prevalence of 1 per 10,000 children (equivalent to 1000 children affected by SJIA at any time).¹¹

There are several life-threatening complications of AOSD which can cause distress, disability and mortality. Reactive Hemophagocytic Lymphohistiocytosis (RHL) (uncontrollable activation of the reticuloendothelial system leading to phagocytosis of haemopoietic cells by activated tissue macrophages) has an incidence of 12-17% in AOSD and has a 10-22% mortality rate. Myocarditis is an early life-threatening complication of AOSD but has a good prognosis when recognised and treated early, with a reported fatality rate of 4%. Other more rare complications of AOSD include disseminated intravascular coagulopathy (fewer than 10 reported cases), thrombotic thrombocytopenia purpura (about 10 reported cases) and diffuse alveolar haemorrhage.⁵

In the UK in 2016-2017, there were 629 hospital admissions and 721 finished consultant episodes for Adult- Onset Still's Disease (ICD 10: M06.1) and 1,286 hospital admissions and 1,307 finished consultant episodes for Juvenile arthritis with systemic onset (ICD 10: M08.2).¹³

In the UK in 2016, there was 1 registered death due to AOSD (ICD10: M06.1) and 2 registered deaths due to SJIA (ICD10: M08.2).¹⁴

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Juvenile idiopathic arthritis – abatacept (ID27). Expected publication date TBC.
- NICE technology appraisal guidance in development. Juvenile idiopathic arthritis – adalimumab (ID385). Expected publication date TBC.
- NICE technology appraisal guidance. Abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis (TA373). December 2015.
- NICE technology appraisal guidance. Tocilizumab for the treatment of systemic juvenile idiopathic arthritis (TA238). December 2011.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract Paediatric Medicine: Rheumatology. E03/S/b.
- NHS England. 2013/14 NHS Standard Contract for Severe Immunodeficiency and Related Disorders Service (Children). B04/S(HSS)/b.
- NHS England. Clinical Commissioning Policy Proposition: Anakinra/Tocilizumab for the treatment of Adult onset Still's Disease refractory to second line therapy (adults). NHS England 1609. First published TBC.
- NHS England. Interim Clinical Commissioning Policy Statement: Biologic Therapies for the treatment of Juvenile idiopathic Arthritis (JIA). NHS England E03/PS/a. January 2015.

OTHER GUIDANCE

- National Rheumatoid Arthritis Society. A focus on Juvenile Idiopathic Arthritis. February 2014.¹⁵
- American College of Rheumatology. 2013 Update of the 2011 American College of Rheumatology Recommendations for the treatment of Juvenile Idiopathic Arthritis. October 2013.¹⁶
- British Society for Paediatric and Adolescent Rheumatology (BSPAR). Standards of care for children and young people with Juvenile Idiopathic Arthritis. January 2012.¹⁷

CURRENT TREATMENT OPTIONS

Many treatments have been tried in the treatment of Still's disease, however no single treatment has proved to be consistently effective in all cases. Therefore a variety of different drugs, alone and in combination, can be used to treat patients.⁸ The aim of treatment is to resolve the disease flare, induce clinical remission, normalise biochemical markers and improve quality of life.¹² The treatment pathways for SJIA and AOSD are similar but not identical, as specified below.

First line treatment for ASOD and SJIA are NSAIDs, usually given to control symptoms before diagnosis; analgesics and corticosteroids are usually given after diagnosis is confirmed at a dose of 0.8-1 mg/day.^{11, 12}

Second line treatment, for those who fail to achieve remission after the above treatment or who are dependant of steroids for symptomatic control, may be given the disease-modifying anti-rheumatic drug (DMARD) methotrexate as well (at a dose of 7.5-20mg/week).^{11, 12}

Third line treatment, for those who do not achieve remission after NSAIDs, corticosteroids and methotrexate includes the use of biological therapies. Anakinra (a IL-1 inhibitor) has been considered as a follow on therapy for AOSD, although at the time of writing, according the NHS England document outlining these treatment options, the use anakinra was unlicensed for this indication.¹² However a Marketing Authorisation Approval has now been granted for treatment of Still’s disease by the European Medicines Agency (EMA).³

Tocilizumab has also been suggested for the treatment of arthritis predominant AOSD which is refractory to methotrexate and for systemic predominant AOSD which is refractory to methotrexate and anakinra. Tocilizumab (as a monotherapy or in combination with methotrexate) is licenced for the treatment of active SJIA in patients over 2 years who have responded inadequately to NSAIDs and systemic corticosteroids but not currently in AOSD.^{11, 12} Canakinumab was licenced for the treatment of active still’s disease including AOSD and SJIA in patients 2 years and older who have responded inadequately to NSAIDs and systemic corticosteroids.⁶ Etanercept, abatacept and adalimumab are not specifically licenced for use in active SJIA, but are licenced for use in other types of JIA who have not adequately responded to DMARDs.¹¹

EFFICACY and SAFETY

Trial	anaSTILLS, , NCT03265132, Sobi.ANAKIN-301; any age with a body weight ≥10kg; Anakinra vs. placebo; phase III
Sponsor	Swedish Orphan Biovitrum (SOBI)
Status	Ongoing - recruiting
Source of Information	Trial registry ²
Location	USA
Design	Randomised, double blind, placebo-controlled
Participants	n=81 (planned); any age (child, adult and senior); diagnosis of still’s disease; body weight >10kg; females; active disease.
Schedule	Randomised to one of 2 study arms: <ol style="list-style-type: none"> 1. Anakinra 2mg/kg/day (max 100mg/day) or 4mg/kg/day (max 200mg/day) by subcutaneous injection for 12 weeks 2. Placebo corresponding to volume of anakinra 2mg/kg/day or 4mg/kg/day by subcutaneous injection for 12 weeks
Follow-up	Active treatment for 12 weeks with 4 week follow up
Primary Outcomes	Proportion of ACR30 responders with absence of fever attributable to the disease during the 7 days preceding week 2. [Time Frame: Week 2] ACR30 response is defined as an improvement of ≥ 30% from baseline in at least 3 of any 6 variables listed. Also no more than 1 of the 6 variables may worsen by >30% from baseline. Variables include: physician global assessment of disease activity - assessed on a Visual Analogue Scale (VAS) from no disease activity (0 mm) to very severe disease activity (100 mm), patient/parent global assessment of overall well-being - assessed on a VAS from very well (0 mm) to very poor (100 mm), number of joints with active arthritis, number of joints with limitation of movement, assessment of physical function - Patient Reported Outcome

	instruments : Childhood Health Assessment Questionnaire (CHAQ) /Stanford Health Assessment Questionnaire (SHAQ) and C-Reactive Protein (CRP) (mg/L).
Secondary Outcomes	<ul style="list-style-type: none"> • Proportion of ACR30 responders with absence of fever during 24 hours preceding Week 1 [Time Frame: Week 1]: ACR30 response is defined as an improvement of $\geq 30\%$ from baseline in at least 3 of any 6 variables listed in the description of the primary outcome measure. Also no more than 1 of the 6 variables may worsen by $>30\%$ from baseline • Proportion of ACR50 responders with absence of fever during 24 hours preceding Week 1 [Time Frame: Week 1]: ACR50 response is defined as an improvement of $\geq 50\%$ from baseline in at least 3 of any 6 variables listed in the description of the primary outcome measure. Also no more than 1 of the 6 variables may worsen by $>30\%$ from baseline • Proportion of ACR70 responders with absence of fever during 24 hours preceding Week 1 [Time Frame: Week 1]: ACR70 response is defined as an improvement of $\geq 70\%$ from baseline in at least 3 of any 6 variables listed in the description of the primary outcome measure. Also no more than 1 of the 6 variables may worsen by $>30\%$ from baseline • Proportion of ACR90 responders with absence of fever during 24 hours preceding Week 1 [Time Frame: Week 1]: ACR90 response is defined as an improvement of $\geq 90\%$ from baseline in at least 3 of any 6 variables listed in the description of the primary outcome measure. Also no more than 1 of the 6 variables may worsen by $>30\%$ from baseline • Proportion of ACR50 responders with absence of fever during 7 days preceding Week 2 [Time Frame: Week 2] • Proportion of ACR70 responders with absence of fever during 7 days preceding Week 2 [Time Frame: Week 2] • Proportion of ACR90 responders with absence of fever during 7 days preceding Week 2 [Time Frame: Week 2] • Proportion of responders in Physician global assessment of disease activity. [Time Frame: Day 1, Week 1 and Week 2]: response is defined as an improvement of $\geq 30\%$, 50%, 70% and 90% from baseline • Proportion of responders in Patient/parent global assessment of overall well-being. [Time Frame: Day 1, Week 1 and Week 2]: response is defined as an improvement of $\geq 30\%$, 50%, 70% and 90% from baseline • Proportion of responders in number of joints with active arthritis. [Time Frame: Day 1, Week 1 and Week 2]: response is defined as an improvement of $\geq 30\%$, 50%, 70% and 90% from baseline. • Proportion of responders in number of joints with limitation of movement. [Time Frame: Day 1, Week 1 and Week 2]: response is defined as an improvement of $\geq 30\%$, 50%, 70% and 90% from baseline • Proportion of responders in assessment of physical function (CHAQ/SHAQ). [Time Frame: Day 1, Week 1 and Week 2]: response is defined as an improvement of $\geq 30\%$, 50%, 70% and 90% from baseline. • Proportion of responders in CRP (mg/L). [Time Frame: Day 1, Week 1 and Week 2]: response is defined as an improvement of $\geq 30\%$, 50%, 70% and 90% from baseline • Proportion of patients with absence of fever during the 7 days preceding Week 2. • Proportion of patients with absence of fever during the 24 hours preceding week 1

- Change from baseline in Physician global assessment of disease activity at Week 1
- Change from baseline in patient/parent global assessment of overall well-being at Week 1
- Change from baseline in CRP. [Time Frame: Day 1 to Week 1]
- Proportion of patients with sustained ACR30, ACR50, ACR70 and ACR90 response. [Time Frame: Week 2, Week 4, Week 8 and Week 12]
- Proportion of patients with sustained ACR30, ACR50, ACR70 and ACR90 response in relation to glucocorticoid tapering. [Time Frame: Week 2, Week 4, Week 8 and Week 12]
- Proportion of patients with ACR30, ACR50, ACR70 and ACR90 response. [Time Frame: Week 4, Week 8 and Week 12]
- Proportion of patients with absence of rash. [Time Frame: Week 1, Week 2, Week 4, Week 8 and Week 12]
- Change from baseline in CRP. [Time Frame: Day 1, Week 1, Week 2, Week 4, Week 8 and Week 12]
- Change from baseline in Hemoglobin (Hb). [Time Frame: Day 1, Week 1, Week 2, Week 4, Week 8 and Week 12]
- Change from baseline in platelet count. [Time Frame: Day 1, Week 1, Week 2, Week 4, Week 8 and Week 12]
- Change from baseline in ferritin. [Time Frame: Day 1, Week 1, Week 2, Week 4, Week 8 and Week 12]
- Change from baseline in patient/parent global assessment of disease related pain. [Time Frame: Day 1, Week 1, Week 2, Week 4, Week 8 and Week 12]
- Time to early termination (withdrawal due to any reason). [Time Frame: From Day 1 to Week 12]
- Time to early termination due to lack of efficacy or progressive disease. [Time Frame: From Day 1 to Week 12]
- Proportion of patients who have initiated tapering of glucocorticoids. [Time Frame: From Week 2 to Week 12]
- Proportion of patients that have decreased the glucocorticoid dose with at least 50% from baseline. [Time Frame: From Week 2 to Week 12]
- Percentage decrease of the glucocorticoid dose from baseline [Time Frame: From Day 1 to Week 12]
- Proportion of patients with at least one adverse event. [Time Frame: From Day 1 to Week 16]
- Proportion of patients with at least one serious adverse event including death [Time Frame: from Informed consent to Week 16]
- Proportion of patients with Macrophage Activation Syndrome (MAS) [Time Frame: from Day 1 to Week 16]
- Proportion of patients with antidrug antibodies (ADA) against anakinra [Time Frame: Week 1, Week 2, Week 4, Week 8 and Week 12]
- Proportion of patients with neutralizing antibodies [Time Frame: Week 1, Week 2, Week 4, Week 8 and Week 12]
- Anakinra serum pre-dose concentrations [Time Frame: Week 1, Week 2, Week 4, Week 8 and Week 12]
- Anakinra serum pharmacokinetic parameters, C_{max}, t_{max}, AUC_{last}, AUC_{0-24h}, V_{d/F}, t_{1/2}, CL/F [Time Frame: Week 12]
- Number of days off school or work due to Still's disease [Time Frame: Week 1, Week 2, Week 4, Week 8 and Week 12]

	<ul style="list-style-type: none"> • Proportion of patients with inactive disease [Time Frame: Week 12] • Change from baseline in JADAS27 [Time Frame: Week 2 and Week 12] • Change from baseline in IL-6. [Time Frame: Day 1, Week 1, Week 2, Week 12] • Change from baseline in IL-18. [Time Frame: Day 1, Week 1, Week 2, Week 12] • Change from baseline in serum calprotectin [Time Frame: Day 1, Week 1, Week 2 and Week 12] • Change from baseline in neopterin [Time Frame: Day 1, Week 1, Week 2 and Week 12]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as December 2019

ESTIMATED COST and IMPACT

COST

Anakinra is already marketed in the UK for the treatment of rheumatoid arthritis (in combination with methotrexate) which has not responded to methotrexate alone; the NHS indicative price for 28 pre-filled disposable 100mg/0.67ml solution injections is £734.¹⁸

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

- | | |
|---|--|
| <input type="checkbox"/> Reduced mortality/increased length of survival | <input checked="" type="checkbox"/> Reduced symptoms or disability |
| <input checked="" type="checkbox"/> Other: <i>specify, wider societal benefits (e.g. earlier return to normal activities, including employment)</i> | <input type="checkbox"/> No impact identified |

IMPACT ON HEALTH and SOCIAL CARE SERVICES

- | | |
|---|---|
| <input type="checkbox"/> Increased use of existing services | <input type="checkbox"/> Decreased use of existing services |
| <input type="checkbox"/> Re-organisation of existing services | <input type="checkbox"/> Need for new services |
| <input type="checkbox"/> Other | <input checked="" type="checkbox"/> None identified |

IMPACT ON COSTS and OTHER RESOURCE USE

- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs: *additional staff training required, additional costs for subcutaneous administration in clinic*
- Other reduction in costs
- Other
- None identified

OTHER ISSUES

- Clinical uncertainty or other research question identified
- None identified

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