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Newcastle University

# Health Technology Briefing
# March 2023

## Sarilumab for treating Polyarticular-course Juvenile idiopathic arthritis in children and adolescents

| Company/Developer | Sanofi |
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☐ New Active Substance ☒ Significant Licence Extension (SLE)

| NIHRIO ID: 12549 | NICE TSID: 10237 | UKPS ID: 652321 |
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## Licensing and Market Availability Plans

Currently in Phase II trials

## Summary

Sarilumab is currently in clinical development for the treatment of children and adolescents aged 2-17 with polyarticular Juvenile Idiopathic Arthritis (JIA) or oligoarticular extended JIA subtype. Arthritis is inflammation of the joints, and juvenile idiopathic arthritis means the arthritis of unknown origin present in children and adolescents. Symptoms of polyarticular JIA include joint pain, swelling and stiffness, which can last from a few months to many years. There are currently limited treatment options for this patient group.

Sarilumab is administered as a subcutaneous injection. It is an inhibitor of a protein called interleukin-6 (IL-6), which is a pro-inflammatory protein. IL-6 is found in high levels in inflamed arthritic joins and plays a key role in the immune activity and inflammation associated with JIA. If licensed, sarilumab will offer an additional treatment option to patients with polyarticular JIA.

## Proposed Indication

Treatment of patients aged 2 – 17 years old with a diagnosis of rheumatoid factor-negative or rheumatoid factor-positive polyarticular-course Juvenile Idiopathic Arthritis (JIA) subtype or oligoarticular extended

JIA subtype who are considered candidates for biologic disease-modifying anti-rheumatic drugs (DMARDs).[1]

## Technology

### Description

Sarilumab (Kevzara, SAR153191, REGN88) is a human monoclonal antibody (IgG1 subtype) that specifically binds to both soluble and membrane-bound interleukin-6 (IL-6) receptors (IL-6Rα) and inhibits IL-6-mediated signalling which involves ubiquitous signal-transducing glycoprotein 130 (gp130) and the Signal Transducer and Activator of Transcription-3 (STAT-3).[2,3] IL-6 is found in inflamed arthritic joints[4] and is involved in diverse physiological processes such as migration and activation of T-cells, B-cells, monocytes, and osteoclasts leading to systemic inflammation, synovial inflammation, and bone erosion in patients with RA.[3] It also plays a key role in the immune activity and inflammation associated with JIA.[4] The activity of sarilumab in reducing inflammation is associated with laboratory changes such as a decrease in absolute neutrophil count (ANC) and elevation in lipids.[3]

In the ongoing phase II clinical trial (SKYPP, NCT02776735), participants received one of the three ascending dose regimens of sarilumab by subcutaneous (SC) injection based on body weight during a 12-week core treatment phase. This was followed by a 144-week extension treatment phase for participants enrolled in dose-finding and second portions, and 84 weeks for participants enrolled in third portion.[1]

### Key Innovation

Given the absence of a cure, the goal of JIA therapy remains the achievement of inactive disease and clinical remission to avoid joint damage and limit the negative impact of JIA on patient growth and development.[5] DMARDs, biologic or synthetic are recommended for clinical use with varying strengths of supportive evidence[6] to control active arthritis, and form part of the early treatment for patients with polyarticular and systemic JIA.[6,7] However, an observational study looking at treatment outcomes in JIA patients after treatment with DMARDs found that children and adolescents in the United States with JIA treated with greater than one biological DMARD still had chronically uncontrolled JIA (symptoms) despite taking at least two DMARDs.[8] There is therefore a need to develop alternative treatment options, that target different mechanisms of action compared to currently recommended DMARDs,[9] to address this unmet need.

Inflammation associated with JIA is largely mediated by cytokines including IL-6.[10] Sarilumab targets IL-6 and IL-6Rα (IL-6 receptor). Fluctuations in IL-6 and its related molecules can modulate the pathogenesis and the clinical presentation positively or negatively.[10] The recent clinical impact of IL-6 blockade on JIA has begun a therapeutic paradigm shift towards IL-6 inhibitors.[10] Once an IL-6 inhibitor binds to the IL-6 receptor, the signalling process which often leads to the activation of T and B-cells and various pro-inflammatory cytokines targeted by other recommended drugs, will be prevented from happening.[11,12] IL-6 inhibitors can therefore prevent signal transduction activity that leads to inflammation earlier in the pathway. Currently, tocilizumab is the only recommended IL-6 inhibitor for JIA[9]. If licensed, sarilumab will offer an additional treatment option for polyarticular-course JIA in children and adolescents.

### Regulatory & Development Status

Sarilumab currently has Marketing Authorisation in the EU and UK for the treatment of moderately to severely active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs (DMARDs).[2,3]

Sarilumab is currently in phase III/II clinical development for a number of indications including[13]:

- Systemic Juvenile Idiopathic Arthritis
- Rheumatoid Arthritis
- Polymyalgia Rheumatica

## Patient Group

### Disease Area and Clinical Need

JIA is an autoimmune disease that occur in children under 16 years, when the body's immune system attacks its own cells causing inflammation in the synovium (the tissue lining around a joint that produces fluid that cushions joints and helps them move smoothly).[14] It affects five or more small and large joints within the first six months of onset.[14,15] Polyarticular JIA can be further categorised as either rheumatoid factor (RF) negative, and RF positive if RF is detected on two occasions at least 3 months apart.[16] The word 'Idiopathic' means it is not known why children develop JIA.[14] Several genetic risk loci have been identified conferring increased susceptibility to JIA, many within the human leukocyte antigen region.[17] It~~'s~~ is also possible that a child may start off with one type of JIA but develop symptoms of another type later.[14] The symptoms of polyarticular JIA include joint pain, swelling and stiffness, which limit movement and can permanently disable patients.[18] [19] If JIA inflammation goes unchecked, it can damage the cartilage and bones themselves. It can also affect other parts of the body such as eyes, skin, lungs, heart, digestive tract, and reproductive organs.[14]

Polyarticular JIA, is the second most common type of JIA, occurring in about 20% of children with JIA in the UK.[16] These are two clinically distinct subsets of the disease with RF positive being more severe.[16,20] Less than 5% of the total JIA population have RF positive polyarticular JIA.[16] In the United Kingdom, t~~T~~he prevalence of JIA has increased over the years from approximately 10 cases per 100,000 in 2003 to 31 per 100,000 in 2018.[21] The age-standardised prevalence rate in 2018 was 43.5 per 100,000.[21] The incidence rate of JIA between 2003-2018 in England was 5.88 per 100,000 population using a validated list of cases linked to the England Hospital Episode Statistics (HES) data.[21] 63.6% of cases were female. For all cases, the first JIA code occurred, on average, between 8 and 9 years of age. [21]

England' s hospital episode statistics for the period between 2021–22, reported 16,649 total diagnoses of Juvenile Arthritis (ICD-10 code M08) from 11,416 Finished Consultant Episodes (FCEs), which resulted in 11,366 admissions, 2,368 FCE bed days and 9,719 day cases.[22] Of these, there were 2,307 FCEs and 2301 admissions for a primary diagnosis of seronegative (RF negative) Juvenile polyarthritis (ICD-10 code M08.3) resulted in 1827 day cases and 421 FCE bed days.[22] There were also 156 total hospital attendances comprising of 18 first appointments, for a primary diagnosis of seronegative Juvenile polyarthritis (ICD-10 code M08.3).[23]

### Recommended Treatment Options

Management of juvenile idiopathic arthritis requires symptomatic treatment to relieve pain, swelling, and stiffness such as non-steroidal anti-inflammatory drugs (NSAIDs),[24] together with non-biologic disease

modifying antirheumatic drugs (DMARDs) such as methotrexate to control and suppress disease activity.[25]

The National Institute for Health and Care Excellence (NICE) recommends the following for the treatment of polyarticular juvenile idiopathic arthritis:[9]

- Etanercept
- Abatacept
- Adalimumab
- Tocilizumab
- Tofacitinib[26]

## Clinical Trial Information

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| Trial | **SKYPP**; NCT02776735; EUDRA CT 2015-003999-79<br>An Open-label, Sequential, Ascending, Repeated Dose-finding Study of Sarilumab, Administered With Subcutaneous (SC) Injection, in Children and Adolescents, Aged 2 to 17 Years, With Polyarticular-course Juvenile Idiopathic Arthritis (pcJIA) Followed by an extension phase.<br>**Phase II:** Active, Not Recruiting<br>**Location(s)**: Europe (incl. UK), USA, Canada, and other countries<br>**Estimated study completion date**: December 28, 2023 |
| Trial Design | Single group assignment, Open label, non-randomised |
| Population | N = 100 (planned); patients between 2 to 17 years of age with RF positive or negative polyarticular-course JIA or oligoarticular subtype JIA with at least 5 active joints who have had an inadequate response to current treatment and considered as a candidate for a biologic DMARD. |
| Intervention(s) | One of three ascending dose regimens of Sarilumab by subcutaneous (SC) injection based on body weight during a 12-week core treatment phase followed by an extension phase (144 weeks for approximately 72 patients enrolled in dose-finding and second portions and 84 weeks for approximately 28 patients enrolled in third portions). |
| Comparator(s) | No comparator |
| Outcome(s) | Primary outcomes:<br>• Assessment of pharmacokinetic (PK) parameter: maximum serum concentration observed (Cmax). Time frame: up to week 12<br>• Assessment of PK parameter: Area under the serum concentration versus time curve calculate using the trapezoidal method during a dose interval (AUC0-t). Time frame: up to week 12<br>• Assessment of PK parameter: concentration observed before treatment administration during repeated dosing (Ctrough). Time frame: up to week 12.<br><br>See trial record for full list of other outcomes. |
| Results (efficacy) | - |

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| Results (safety) | - |

## Estimated Cost

Sarilumab is already marketed in the UK for the treatment of moderate to severe rheumatoid arthritis in patients who have had an inadequate response to or are intolerant to one or more DMARD (as monotherapy or in combination with methotrexate.[27]

The NHS indicative price for a pack of 2 pre-filled pens or syringes of Sarilumab is £912.25 for either a 150mg/1.14ml solution or a 200mg/1.14ml solution of Sarilumab.[28]

## Relevant Guidance

### NICE Guidance

- NICE technology appraisal in development. Baricitinib for treating juvenile idiopathic arthritis in children and young people aged 1 to 17. (GID-TA11066). Expected publication date to be confirmed.
- NICE technology appraisal. Tofacitinib for treating juvenile idiopathic arthritis (TA735). October 2021.
- NICE technology appraisal. Abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis (TA373). December 2015.

### NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy Statement: Biologic Therapies for the treatment of Juvenile Idiopathic Arthritis (JIA). E03/P/d. July 2015.
- NHS England. Appendix A: Suggested Treatment Flow-chart for JIA. E03/P/d Juvenile Idiopathic Arthritis (JIA) July 2015.
- NHS England. Standard Contract. Paediatric Medicine: rheumatology. E03/S/b. October 2013.

### Other Guidance

- Arthritis and Musculoskeletal Alliance & British Society for Rheumatology. Standards of Care for children and young people with Juvenile Idiopathic Arthritis. 2013.[29]
- British Society for Rheumatology. Guidance for Methotrexate use in paediatric adolescent rheumatology. Information for health professionals.[30]
- British Society for Rheumatology. Guidance for Adalimumab use in paediatric adolescent rheumatology. Information for health professionals.[31]
- British Society for Rheumatology. Guidance for Tocilizumab use in paediatric adolescent rheumatology. Information for health professionals.[32]
- Arthritis Foundation. Treatment Guidelines for JIA. 2019. Revised 2022.[33]
- 2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Oligoarthritis, Temporomandibular Joint Arthritis, and Systemic Juvenile Idiopathic Arthritis.[34]

## Additional Information

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