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HEALTH TECHNOLOGY BRIEFING NOVEMBER 2019

Secukinumab for enthesitis-related arthritis and juvenile psoriatic arthritis in children and adolescents from the age of 2 years

NIHRIO ID	13727	**NICE ID**	10091
Developer/Company	Novartis Pharmaceuticals UK Ltd	**UKPS ID**	644577

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Secukinumab as a subcutaneous injection is in clinical development for the treatment of enthesitis related arthritis (ERA) and juvenile psoriatic arthritis (JPsA). These conditions belong to a group of arthritis conditions of unknown cause known as juvenile idiopathic arthritis which affect children. JPsA patients have arthritis and psoriasis, an inflammatory skin disease and ERA patients have arthritis and enthesitis, inflammation of the ligaments and tendons. These conditions are the result of the immune system mistakenly attacking the body's own cells at the joints and the skin or tendons, causing swelling, pain and reduced mobility.

Secukinumab is a monoclonal antibody, a type of protein, designed to recognise and attach to a messenger molecule in the immune system called interleukin 17A (IL-17). Interleukin 17A is part of the inflammation processes in ERA and JPsA, and by attaching to and blocking the action of IL-17A, secukinumab reduces the symptoms of these conditions. If licensed, secukinumab will offer a treatment option in children and adolescents with JPsA and ERA, including those whose disease has not responded to previous treatments.

PROPOSED INDICATION

First line biological treatment for active enthesitis-related arthritis (ERA) and juvenile psoriatic arthritis (JPsA) in children and adolescents from the age of 2 years with active disease despite current or previous non-steroidal anti-inflammatory drug (NSAID) and/or disease-modifying antirheumatic drug (DMARD) therapy.[a]

TECHNOLOGY

DESCRIPTION

Secukinumab (Cosenytx, AIN457) is a fully human IgG1/kappa isotype monoclonal antibody that selectively binds to and neutralises the proinflammatory cytokine interleukin-17A (IL-17A). Secukinumab works by targeting IL-17A and inhibiting its interaction with the IL-17 receptor, which is expressed on various cell types. As a result, secukinumab inhibits the release of further proinflammatory cytokines, chemokines and mediators of tissue damage and reduces IL-17A-mediated contributions to autoimmune and inflammatory diseases. IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. IL-17A plays a key role in the pathogenesis of plaque psoriasis, psoriatic arthritis and ankylosing spondylitis and is up-regulated in lesional skin in contrast to non-lesional skin of plaque psoriasis patients and in synovial tissue of psoriatic arthritis patients.[1,2,3]

Secukinumab is currently in development for the treatment of ERA and JPsA in patients aged 2 to 18 years with active disease despite current or previous NSAID and/or DMARD therapy. In a phase III trial participants were administered secukinumab subcutaneously via pre-filled syringe. Patients receive a low dose (75mg) if they weigh less than 50kg and a high dose (150mg) if they weigh greater than 50kg, although uptitration to 150mg and 300mg respectively, was allowed in the extension study.[b] Loading doses are given weekly for 5 weeks followed by monthly maintenance dosing.[4,5]

INNOVATION AND/OR ADVANTAGES

The safety and efficacy of secukinumab in JIA patients below the age of 18 years have not yet been established, therefore this technology and indication is new for this patient age.[2,3]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Secukinumab is currently available in the UK as a ready-to-use solution in a pre-filled syringe or pen injector for the following therapeutic indications in adults:[3]

- moderate to severe plaque psoriasis
- alone or in combination with methotrexate (MTX) for the treatment of psoriatic arthritis
- active ankylosing spondylitis in adults who have responded inadequately to conventional therapy.

In 2018, the European Medicines Agency (EMA) accepted a modification of an agreed paediatric investigation plan for secukinumab (P/0372/2018).[6]

The most common (which may affect more than 1 in 10 people) adverse events reported for secukinumab across a variety of indications is an increased risk of upper respiratory tract infections. Other common side effects are mild to moderate in severity including rhinorrhoea

[a] Information provided by Novartis Pharmaceuticals UK Ltd on UK PharmaScan
[b] Information provided by Novartis Pharmaceuticals UK Ltd

and diarrhoea. Because secukinumab may increase the risk of infection, it must not be given to patients with serious active infections such as tuberculosis.[3,7,8]

Secukinumab is currently in Phase III trials for:[9]

- hidradenitis suppurativa
- axial spondyloarthritis.
- moderate to severe plaque psoriasis in children.

Secukinumab is currently in phase II trials for:[10]

- giant cell arteritis
- congenital ichthyosis
- tendinopathy
- pyoderma gangrenosum
- necrobiosis lipoidica diabeticorum (NLD)
- discoid lupus erythematosus (DLE), and
- atopic dermatitis

PATIENT GROUP

DISEASE BACKGROUND

Juvenile idiopathic arthritis (JIA) describes a group of autoimmune conditions where the cause is unknown. The conditions are characterized by joint inflammation which lasts for more than 6 weeks and an age of onset of younger than 16 years. The inflammation is caused by the patient's immune system attacking the lining tissue of the joint and can result in swelling, pain and reduced movement. The specific joints affected can vary between patients and subtypes, as can the severity. While the cause of the conditions is unknown, it is thought to involve genetic susceptibility linked to variants of the human leukocyte antigen (HLA) genes combined with an environmental trigger such as an infection.[11]

ERA is a subtype of JIA in which the inflammation is not limited to the joints and can also be found where tendons meet the bone. It can be diagnosed if the JIA patient has sacroiliac tenderness or inflammatory spinal pain, if the patient is positive for HLA-B27 or has a family history of HLA-B27-associated disease. Patients with ERA may develop cardiopulmonary and cerebrovascular complications, which are also a leading cause of shorter life expectancy.[12]

JPsA, another subtype of JIA, has the typical joint inflammation of JIA accompanied by the skin condition, psoriasis. Psoriasis is the result of the immune system attacking the skin leading to a faster production of skin cells. This can cause rashes with dry red skin lesions (called plaques) covered in silver scales which commonly appear on the elbows and knees. It can also be accompanied by swelling of the fingers and toes called dactylitis, and nail pitting.[13] JPsA is more common in children who have first-degree relatives with psoriasis and may be linked to childhood obesity.[14] It is important to note that these subtypes of JIA can share many symptoms but a patient is usually only diagnosed with one.[13]

Morbidity due to disease activity and complications is common in JIA and ERA is associated with poorer physical outcomes than other JIA subtypes.[15]

Uveitis, swelling in the eye, is a common complication of JIA and can affect over 10% of children with ERA. If the uveitis is persistent it can lead to iris scarring, glaucoma, cataracts, macular oedema, and visual impairment. ERA that persists for more than 5 years predicts future disability. [12,16]

These conditions cause pain, swelling and limitation of movement that can impair social functioning and development. Affected children have lower self-esteem and are more likely to have behavioural problems than their peers because of the mobility problems and pain.[11] Children often miss out on school and activities, and parents and carers may miss work to provide care.[17] Severe cases of JIA can cause growth retardation, joint disease, eye problems and permanent disability.[11,16]

CLINICAL NEED AND BURDEN OF DISEASE

About 1,000 children are diagnosed with JIA per year, equating to around 10,000 affected children in the UK.[16] According to the International League Against Rheumatism (ILAR) ERA accounts for 3-11% of all cases of JIA and JPsA accounts for approximately 2-11% of all cases of JIA.[18]

Based on a prevalence of 0.5 per 1000 for all JIA, the ONS mid-2017 estimate for UK population aged 16 or under (13.2m) and mid-points of ranges for JPsA and ERA as proportions of all JIA; the company estimated the eligible patient population to be approximately 500 JPsA patients and approximately 460 ERA patients.[c]

Generally JPsA is more common in European populations and ERA is more common in males over the age of 6.[12] Although JIA and its subtypes are diagnosed in children, the condition may continue into adulthood so there are adults also affected.[16]

The Hospital Episode Statistics for England 2018/19 recorded a total of 260 finished consultant episodes and 258 admissions for primary diagnosis Juvenile arthritis in psoriasis (ICD-10 code M09.0). ERA as a primary diagnosis is included in the ICD-10 code M08.8 (Other juvenile arthritis) for which there were a total of 1,359 finished consultant episodes and 1,356 admissions in England.[19,20]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The aim of treatments for JIA is to control symptoms and improve quality of life. The optimal approach to the management of a child with JIA is based on a multidisciplinary team comprising a paediatric rheumatologist, ophthalmologist, orthopaedic surgeon, specialist nurse, physical therapist, occupational therapist, and psychologist. Non-pharmacological and pharmacological interventions may aid in the management of JIA patients.[21]
Non-pharmacological options include: physiotherapy, pain relief techniques, splints, insoles and mobility aids.

Pharmacological options involve pain relief and NSAIDS to reduce swelling and stiffness. Intra-articular corticosteroids are used to achieve disease remission in the joints but systemic steroids are only recommended for short periods of time in children due to side effects.[22] Methotrexate, a disease-modifying antirheumatic drug (DMARD), can be taken to slow disease progression, usually in weekly oral doses or by IV. JIA patients that do not respond to NSAIDS/DMARDS can be treated with biological therapies targeting pro-inflammatory responses including TNFa inhibitors like adalimumab and etanercept, T-cell co-stimulation inhibitor abatacept and interlueken-6 inhibitor tocilizumab.[11]

[c] Information provided by Novartis Pharmaceuticals UK Ltd on UK PharmaScan

CURRENT TREATMENT OPTIONS

For ERA and JPsA patients whose disease has responded inadequately to, or who are intolerant of, methotrexate, the current biological therapy options are:[16]

- adalimumab and etanercept are recommended for treating ERA for people 6 years and older (adalimumab) and 12 years and older (etanercept).
- etanercept is recommended as an option for treating JPsA in people aged 12 years and older.

PLACE OF TECHNOLOGY

If licensed, secukinumab would offer an additional treatment option for patients with ERA and JPsA whose disease is inadequately controlled on NSAIDs and/or DMARD therapy. It would become the first licensed biological treatment for ERA patients under 6 years and JPsA patients under 12.[16,d]

CLINICAL TRIAL INFORMATION

Trial	**NCT03031782, CAIN457F2304; EudraCT: 2016-003761-26; 2 to 17 years old; secukinumab vs placebo; phase III.**	**NCT03769168, CAIN457F2304E1, EudraCT: 2018-002521-30; 2 years and older; secukinumab 75 mg vs secukinumab 150 mg; phase III extension**
Sponsor	Novartis Pharmaceuticals	Novartis Pharmaceuticals
Status	Ongoing	Ongoing
Source of Information	Trial registry[4,23]	Trial registry[5,24], Novartis Pharmaceuticals.[e]
Location	EU (inc the UK), USA, Russia and South Africa.	2 EU Countries (not inc the UK)
Design	Three-part Randomized, Double-blind, Placebo-controlled Study	Non-randomized
Participants	N=86, aged 2 to 17 years, Enthesitis-related arthritis (ERA) or Juvenile psoriatic arthritis (JPsA), inadequate response to nonsteroidal anti-inflammatory drugs (NSAID) and Disease-modifying antirheumatic drugs (DMARD).	N=64 (planned), aged 2+ Years, must that have participated in core study CAIN457F2304 completing treatment up to Week 104 and deemed to benefit from continued secukinumab therapy.
Schedule	During period 1 patients receive weekly open label secukinumab 75 or 150 mg, based on their body weight (<50 kg or >50 kg) to maintain secukinumab blood levels equivalent to the adult 150 mg dose, at baseline, weeks 1, 2, 3, 4, and 8. At week 12, responders (minimum JIA ACR Pedi 30 response) enter treatment period 2	Experiment group 1: 75mg secukinumab dose as 75mg/0.5mL subcutaneous injection, uptitration to 150mg allowed Experiment group 2: 150mg secukinumab dose as 150mg/1.0mL subcutaneous injection depending on bodyweight, uptitration to 300mg allowed.

[d] Information provided by Novartis Pharmaceuticals UK Ltd on UK PharmaScan
[e] Information provided by Novartis Pharmaceuticals UK Ltd

	and are randomised to receive secukinumab or a matching placebo every 4 weeks. Patients enter treatment period 3 if they experience a disease flare or when the treatment period 2 closes for the entire study because the target number of flares has been reached. Upon entering treatment period 3, patients receive open-label secukinumab every 4 weeks until week 100 and are then followed up until week 112.	
Follow-up	Active treatment up to 100 weeks, 12 week follow up.	Up to 4 yrs of active treatment.
Primary Outcomes	Time to flare in Treatment Period 2 [Time Frame: From Week 12 until max Week 104]	Number of participants with JIA ACR30 response [Time Frame: 308 weeks] JIA ACR 30 is defined as 30% improvement from baseline in a minimum of three out of six variables with no more than one variable worsening more than 30% as defined in the ACR criteria. The six variables assessed in order to calculate JIA ACR 30 are: • Physician global assessment of overall disease activity • Parent's or patients' global assessment of patient's overall well-being • Functional ability (CHAQ: Childhood Health Assessment Questionnaire) • Number of joints with active arthritis • Number of joints with limited range of motion • Index of inflammation: C-reactive Protein (CRP)
Secondary Outcomes	• Change from baseline for Juvenile idiopathic arthritis (JIA) American college of rheumatology (ACR) 30/50/70/90/100 response [Time Frame: 12 weeks] • Change from baseline for JIA ACR core components [Time Frame: 12 weeks] • Change from baseline Juvenile Arthritis Disease Activity Score (JADAS) score [Time Frame: 12 weeks]	• Number of participants with JIA ACR 50/70/90/100 response [Time Frame: 308 weeks] • Number of participants with inactive disease status [Time Frame: 308 weeks] • Number of participants with Juvenile Arthritis Disease Activity Score (JADAS) [Time Frame: 308 weeks] • Number of participants with total Enthesitis count [Time Frame: 308 weeks]

	• Change from baseline in total enthesitis count [Time Frame: 12 weeks] • Change from baseline in total dactylitis count [Time Frame: 12 weeks] • Percentage of participants with JIA ACR 30/50/70/90/100 and inactive disease [Time Frame: From week 12 to up to week 104], to evaluate the effect of withdrawal of secukinumab treatment • Number of participants with reported Adverse Events [Time Frame: 104 weeks] • Percentage of participants with anti-secukinumab antibodies [Time Frame: 104 weeks], will be assessed by immunogenicity techniques from blood samples drawn during the study. • Change from baseline for inactive disease status [Time Frame: 12 weeks]	• Number of participants with total Dactylitis count [Time Frame: 308 weeks] • Pharmacokinetics (PK) of secukinumab [Time Frame: 308 weeks]
Key Results	-	-
Adverse effects (AEs)	-	-
Expected reporting date	Estimated primary completion date October 2019. Estimated study completion date December 2020.	Estimated primary completion date October 2024. Estimated study completion date November 2024.

ESTIMATED COST

The NHS indicative price of 2 pre-filled disposable pens of secukinumab 150mg/1ml solution for injection is £1218.78.[8]

RELEVANT GUIDANCE

NICE GUIDANCE

- 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 (POLICY/COMMISSIONING) GUIDANCE

- NHS England. Clinical Commissioning Policy Statement: Biologic Therapies for the treatment of Juvenile Idiopathic Arthritis (JIA). NHS England E03X04. July 2015.
- NHS England. NHS Standard Contract Paediatric Medicine: Rheumatology. E03/S/b. 2013.
- NHS Standard Contract for Severe Immunodeficiency and Related Disorders Service (Children). B04/S(HSS)/b. 2013/14.

OTHER GUIDANCE

- American College of Rheumatology. 2013 Update of the 2011 American College of Rheumatology Recommendations for the Treatment of Juvenile Idiopathic Arthritis. October 2013.[25]
- British Society for Paediatric and Adolescent Rheumatology. Standards of care for children and young people with juvenile idiopathic arthritis. 2010.[21]

ADDITIONAL INFORMATION

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