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HEALTH TECHNOLOGY BRIEFING
OCTOBER 2019

Tofacitinib for polyarticular juvenile idiopathic arthritis

NIHRIO ID	8550	**NICE ID**	10052
Developer/Company	Pfizer Limited UK	**UKPS ID**	651586

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

SUMMARY

Tofacitinib is in development for the treatment of polyarticular juvenile idiopathic arthritis (JIA). JIA is defined as arthritis of unknown aetiology that manifests itself before the age of 16 years and persists for at least 6 weeks, while excluding other known conditions. Polyarticular JIA, a subgroup of JIA is characterised by the involvement of five or more joints during the first 6 months of the disease and can be considered rheumatoid factor positive or negative. The most common symptoms include joint swelling, pain and limited range of motion. Currently available treatment of JIA aims to control symptoms, reduce the possibility of joint damage and improve quality of life.

Tofacitinib works by blocking the action of enzymes known as Janus kinases. These enzymes play an important role in the inflammatory process. By blocking the enzymes' action, tofacitinib helps reduce the inflammation and other symptoms of these diseases. Tofacitinib is an oral alternative to the available biological medicines for children with JIA, most of which are administered by injection. If licensed, tofacitinib may offer an additional treatment option for polyarticular JIA with the potential advantage of improving the quality of life of children due to its oral formulation.

This briefing reflects the evidence available at the time of writing and a limited literature search. 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. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

PROPOSED INDICATION

Treatment of polyarticular juvenile idiopathic arthritis in children and adolescents.[1a]

TECHNOLOGY

DESCRIPTION

Tofacitinib (Xeljanz) is a potent, selective inhibitor of the Janus kinase (JAK) family. In enzymatic assays, tofacitinib inhibits JAK1, JAK2, JAK3, and to a lesser extent TyK2. In contrast, tofacitinib has a high degree of selectivity against other kinases in the human genome. In human cells, tofacitinib preferentially inhibits signalling by heterodimeric cytokine receptors that associate with JAK3 and/or JAK1 with functional selectivity over cytokine receptors that signal via pairs of JAK2. Inhibition of JAK1 and JAK3 by tofacitinib attenuates signalling of interleukins (IL-2, -4, -6, -7, -9, -15, -21) and type I and type II interferons, which will result in modulation of the immune and inflammatory response.[2]

Tofacitinib is currently in clinical development for the treatment of polyarticular course juvenile idiopathic arthritis. In phase III clinical trial (NCT02592434), patients received tofacitinib tablet or solution oral, twice daily based on body weight. Details of the dosing regimen and administration schedule assessed are detailed in the clinical trial table section of this briefing document.[1]

INNOVATION AND/OR ADVANTAGES

Patients with systemic juvenile idiopathic arthritis (sJIA) often exhibit poor response to conventional disease modifying anti-rheumatic drugs (DMARDs), and chronic glucocorticoid use is associated with significant adverse effects. Although biologics used to target IL1 and IL6 are efficacious, the long-term commitment to frequent injections or infusions remains a challenge in young children. JAK inhibitors block the signalling of numerous proinflammatory cytokines and are now used clinically for the treatment of rheumatoid arthritis in adults.[3]

Tofacitinib is recommended by NICE for the treatment of moderate to severe rheumatoid arthritis in adults as clinical trial evidence shows tofacitinib plus conventional disease-modifying anti-rheumatic drugs (DMARDs) is more effective than conventional DMARDs alone for treating rheumatoid arthritis that has not responded adequately to conventional or biological DMARDs.[4]

In addition, tofacitinb being administered orally offers potential service impact advantages over conventional and biological DMARDs that are administered by subcutaneous injections.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Currently, tofacitinib is licensed in the EU/UK for the following indications[2]

Rheumatoid arthritis
Tofacitinib in combination with methotrexate (MTX) is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying antirheumatic drugs. Tofacitinib can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate.

[a] Information provided by Pfizer Limited on the UK PharmaScan

Psoriatic arthritis
Tofacitinib in combination with MTX is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy.

Ulcerative colitis
Tofacitinib is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent.

The most common serious adverse reactions were serious infections. The most common serious infections among the rheumatoid arthritis patients were pneumonia, cellulitis, herpes zoster, urinary tract infection, diverticulitis, and appendicitis. The most commonly reported adverse reactions during the first 3 months in controlled clinical trials were headache, upper respiratory tract infections, nasopharyngitis, diarrhoea, nausea and hypertension. Among the ulcerative colitis patients the most commonly reported adverse reactions were headache, nasopharyngitis, nausea, and arthralgia.[2]

Besides of assessment for the treatment of JIA, tofacitinib has completed or is in phase II and III clinical trials for the treatment of the following conditions:[6]

- Rheumatoid arthritis
- Psoriatic arthritis
- Ankylosing spondylitis
- Atopic dermatitis
- Ulcerative colitis
- Systemic sclerosis
- Scleroderma
- Cutaneous lupus
- Systemic lupus erythematosus
- Crohn's disease
- Kidney transplantation

PATIENT GROUP

DISEASE BACKGROUND

Juvenile idiopathic arthritis (JIA) is the most common form of childhood arthritis and one of the more common chronic childhood illnesses. JIA is defined as arthritis of unknown aetiology that manifests itself before the age of 16 years and persists for at least 6 weeks, while excluding other known conditions. In fact, JIA is an umbrella term that refers to a group of disorders that have in common chronic arthritis. Diagnosis requires a combination of data from history, physical examination, and laboratory testing. Juvenile idiopathic arthritis is subdivided into seven categories: systemic, polyarthritis (polyarticular) (rheumatoid factor positive, polyarthritis rheumatoid factor negative, oligoarthritis (subcategories of persistent and extended), psoriatic arthritis, enthesitis-related arthritis and undifferentiated arthritis.[7]

To be characterised as having polyarticular JIA, a child must have arthritis in five or more joints during the first 6 months of the disease. To be considered rheumatoid factor positive, the patient must have at least two positive results for rheumatoid factor at least 3 months apart during the first 6 months of disease. Clinical manifestations and outcome of both polyarticular JIA categories are highly variable, and include fatigue, anorexia, protein–caloric malnutrition, anaemia, growth retardation, delay in sexual maturation, and osteopenia.[7]

CLINICAL NEED AND BURDEN OF DISEASE

There are different JIA subtypes, the polyarthritis JIA rheumatoid factor negative is more common, accounting for approximately 10% to 28% of all cases. Polyarticular JIA rheumatoid factor positive patients (approximately 2% to 10% of all children with JIA) are almost always girls with later disease onset (at least 8 years old) who are usually HLA-DR4 positive, have symmetric small joint arthritis and are at greater risk for developing erosions, nodules, and poor functional outcome compared with rheumatoid factor negative patients. Polyarticular JIA rheumatoid factor positive resembles adult-onset rheumatoid arthritis more than any other JIA subset.[7]

In 2017-2018 were 12,949 admissions (of which 12,128 were day case) for primary diagnosis of juvenile arthritis and juvenile arthritis in diseases classified elsewhere (ICD-10 codes M08 and M09) in England, which resulted in 13,117 finished consultant episodes (FCE) and 2,270 FCE bed days.[8]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The aim of treatment for JIA is to control the symptoms of arthritis, enable the subjects to lead an active life at school or college, enable the subjects to enjoy an active family and social life, and help the subjects become an independent adult.[9]

Some drugs such as painkillers, non-steroidal anti-inflammatory drugs (NSAIDS), conventional synthetic DMARD (csDMARD), biological DMARD (bDMARD), and steroids with different mechanisms of action are available and can be used to help to control the pain, stiffness and swelling.[9]

Other adjunct alternatives to disease-modifying agents can be considered to make the patients feel better such as physiotherapy and occupational therapy, use of hot and cold pads, acupuncture, massage, hydrotherapy and relaxation, use of aids or splints as shoe inserts, pencil grips, grips for knives and forks, splints to help rest the joint and make it less uncomfortable, and splints to straighten the joint.[9,10]

CURRENT TREATMENT OPTIONS

Drugs can not cure arthritis, but they can control the symptoms and help to reduce the possibility of joint damage. Pharmacological treatments for people with JIA include:[9,11]

Painkillers
These drugs help to control the pain of arthritis. Common painkillers include paracetamol, codeine or combinations.[9] Codeine is indicated in patients older than 12 years of age for the treatment of acute moderate pain which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen (alone).[12]

NSAIDs
These drugs help to reduce pain, stiffness and swelling. Examples of the many NSAIDs include ibuprofen, piroxicam, naproxen and diclofenac.[13-16]

csDMARD
DMARDs dampen down inflammation and can reduce the joint damage caused by arthritis. Methotrexate is the most commonly used csDMARD in JIA.

bDMARD
These drugs are prescribed for patients that do not respond to DMARDs such as methotrexate. The main biological therapies used for JIA are abatacept, adalimumab, anakinra, etanercept, infliximab, rituximab and tocilizumab.[17]

Systemic corticosteroids
These drugs are used to control inflammation, pain and stiffness.

PLACE OF TECHNOLOGY

If licensed, tofacitinib will offer an additional oral treatment option for paediatric patients with polyarticular JIA.

CLINICAL TRIAL INFORMATION

Trial	NCT03000439, A3921165; age 2 to 17 years; tofacitinib vs placebo; phase III	NCT01500551, A3921145, EudraCT 2011-004915-22; age 2 to 17 years; tofacitinib based on body weight; phase III, extension
Sponsor	Pfizer	Pfizer
Status	Ongoing	Pfizer
Source of Information	Trial registry[18]	Trial registry[19,20]
Location	Canada, United States and other countries	EU (including the UK), Canada, United States and other countries
Design	Randomised, placebo-controlled, quadruple-blind	Single group assignment and open label
Participants	n=100 (planned); aged 2 to 17 years old and with active sJIA disease according to ILAR criteria for at least 6 weeks before screening; treatment with stable doses of methotrexate ≤25 mg/week or ≤20 mg/m2/week, whichever is lower, is permitted; treatment with a stable dose of oral prednisone ≤1 mg/kg/day up to a maximum of 30 mg/day, or equivalent, for at least 1 week before the first study drug dose is permitted.	n=340; aged 2 to 18 years, paediatric subjects with JIA aged from 2 to less than 18 years who have previously completed participation in a qualifying study of tofacitinib for the treatment of JIA.
Schedule	Subjects in open-label phase receive tofacitinib at a dose of 5 mg orally, twice daily tablet or solution form. In double blind phase, subjects receive tofacitinib at a dose of 5 mg orally, twice daily in tablet or solution form or placebo.	Tofacitinib will be administered orally twice daily (BID), based on body weight. 5 mg BID Dose Level Body Weight (Dose in tablet [mg BID] or solution [ml BID]) 5 - < 7 kg (2 mg or 2 ml) 7 - < 10 kg (2.5 mg or 2.5 ml) 10 - <15 kg (3 mg or 3 ml) 15 - <25 kg (3.5 mg or 3.5 ml) 25 - <40

		kg (4 mg or 4 ml) >=40 kg (5 mg or 5 ml) Oral solution (1 mg/mL concentration) will be used for subjects weighing <40 kg. Oral tablets (5 mg) will be used for subjects weighing >=40 kg; subjects who are unable to swallow tablets will have the option of taking oral solution. For participants rolling over from study A3921165: 10 mg BID Dose Level Body Weight (Dose in tablet [mg BID] or solution [ml BID]) 5 - < 7 kg (4 mg or 4 ml) 7 - < 10 kg (5 mg or 5 ml) 10 - <15 kg (6 mg or 6 ml) 15 - <25 kg (7 mg or 7 ml) 25 - <40 kg (8 mg or 8 ml) >=40 kg (10 mg or 10 ml) Oral solution (1 mg/mL concentration) will be used for subjects weighing <40 kg. Oral tablets (5 mg) will be used for subjects weighing >=40 kg; subjects who are unable to swallow tablets will have the option of taking oral solution.
Follow-up	Up to 82 weeks after randomisation	Up to 8 years
Primary Outcomes	Time to flare [Time Frame: Up to 82 weeks after randomization]	Standard laboratory safety data and adverse event (AE) reports. Body weight, height and Tanner Stages will collected to assess growth and physical development. [Time frame: up to 8 years]
Secondary Outcomes	• Occurrence of disease flare in double-blind phase [Time frame: up to 82 weeks after randomisation] • Achievement of corticosteroid tapering at the end of the open-label phase [Time frame: 12 to 40 weeks] • Achievement of a corticosteroid dose of 0.2 mg/kg/day or 10 mg/day (whichever is lower) at the end of the open label treatment period [Time frame: 12 to 40 weeks] • Adapted sJIA ACR 30/50/70/90/100 response at every visit from day 7 onward in the open label and double blind	• Physician global evaluation of disease activity at each visit. [Time frame: up to 8 years] • Number of joints with active arthritis at each visit. [Time frame: up to 8 years] • Number of joints with limitation of motion at each visit. [Time frame: up to 8 years] • Index of inflammation (C-reactive protein [CRP] and Erythrocyte Sedimentation Rate [ESR]) at each visit. [Time frame: up to 8 years] • Parent's Assessment of Physical Function (Childhood Health

	phase. [Time frame: up to 82 weeks after randomisation] • Fever (Temp >38 Degrees Celsius) attributed to sJIA at day 3, day 7 and day 14 of the open label phase. [Time frame: day 3, day 7, day 14] • CRP ≤ 10 mg/L at every visit of the open label phase. [Time frame: 12 to 40 weeks] • "Absence of fever", defined as absence of fever due to sJIA in the week preceding the assessment at every visit from day 7 onward in the open label and double blind phase. [Time frame: up to 82 weeks after randomisation] • Time to first Adapted JIA ACR 30 response in part 1 of the open label phase. [Time frame: 12 to 40 weeks] • Change from baseline in Juvenile Arthritis Disease Activity Score (JADAS 27) at every visit from day 7 onward in the open label and double blind phase. [Time frame: up to 82 weeks after randomisation] • Change from baseline in each JIA ACR core variable at every visit from day 7 onward in the open label and double blind phase. [Time frame: up to 82 weeks after randomisation] • Change from baseline in Child Health Questionnaire (CHQ) responses at the end of part 1 and part 2 of the open label phase, at randomization and every 3 months thereafter. [Time frame: up to 82 weeks after randomisation] • Change from baseline in Child Health Assessment Questionnaire (CHAQ) at every visit from day 7 onward in the open label and double blind phase. [Time frame: up to 82 weeks after randomisation] • Occurrence of inactive disease status and minimal disease activity clinical remission at every visit from day 7 onward	Assessment Questionnaire [CHAQ] Disability Index) at each visit. [Time frame: up to 8 years] • Parent's Assessment of Child's Arthritis Pain (Childhood Health Assessment Questionnaire [CHAQ] Discomfort Index, Visual Analog Scale [VAS]) at each visit. [Time frame: up to 8 years] • Parent's Global Assessment of Overall Wellbeing (Childhood Health Assessment Questionnaire [CHAQ] subsection, Visual Analog Scale [VAS]) at each visit. [Time frame: up to 8 years] • JIA American College of Rheumatology (ACR) response and occurrence of JIA ACR disease flare at each visit. [Time frame: up to 8 years] • JIA ACR Clinical Inactive Disease status and Clinical Remission on Medication at each visit. [Time frame: up to 8 years] • Change from baseline in Juvenile Arthritis Disease Activity Score (JADAS) 27- CRP and JADAS 27-ESR, and occurrence of JADAS minimum disease activity and inactive disease at each visit. [Time frame: up to 8 years] • In subjects with Enthesitis Related Arthritis (ERA): Change from baseline in the Tender Entheseal Assessment, Modified Schober's Test, Overall Back Pain and Nocturnal Back Pain responses at various visits. [Time frame: up to 8 years] • In subjects with psoriatic arthritis (PsA): Change from baseline in body surface area (BSA) affected by psoriasis and Physician's Global Assessment (PGA) of psoriasis) at various

	(JADAS 27) in the open label and double blind phase. [Time Frame: Up to 82 weeks after randomisation] • Occurrence of inactive disease status and clinical remission at every visit from day 7 onward (JIA ACR) in the open label and double blind phase. [Time frame: up to 82 weeks after randomisation]	visits. [Time frame: up to 8 years] • In subjects with sJIA: "Absence of Fever", defined as absence of fever due to sJIA in the week preceding the assessment at each visit. [Time frame: up to 8 years] • Eligibility of tapering defined per protocol for corticosteroids [Time frame: up to 8 years] • Eligibility of tapering defined per protocol for methotrexate [Time frame: up to 8 years] • Eligibility of tapering defined per protocol for leflunomide [Time frame: Up to 8 years] • Eligibility of tapering defined per protocol for tofacitinib [Time frame: Up to 8 years]
Key Results	-	-
Adverse effects (AEs)	-	-
Expected reporting date	Estimated primary completion date in August 2023.	Estimated primary completion date in March 2021.

Trial	NCT02592434, A3921104, EudraCT 2015-001438-46; age 2 to 17 years; tofacitinib vs placebo; phase III
Sponsor	Pfizer
Status	Completed
Source of Information	Trial registry[1,21]
Location	EU (including the UK), Canada, United States and other countries
Design	Randomised, placebo-controlled, quadruple-blind
Participants	n=223; aged 2 to 17 years old. Subjects with polyarticular course JIA (e.g., extended oligoarthritis, polyarthritis RF+, polyarthritis RF-, systemic JIA with active arthritis but without active systemic features) must have a minimum of 5 active joints (an active joint is defined as a joint with swelling or, in the absence of swelling, limited range of motion accompanied by either pain on motion or tenderness) at screening and baseline to be eligible for study entry. Subjects with psoriatic or enthesitis related arthritis must have a minimum of 3 active joints (an active joint is defined as a joint with swelling or, in the absence of swelling, limited range of motion accompanied by either pain on motion or tenderness) at screening and baseline to be eligible for study entry.
Schedule	During the open label run in phase, all subjects will receive active tofacitinib oral tablets or oral solution twice daily orally, at a dosage based on the subject's body weight as specified below.

	During the double blind, placebo controlled phase, subjects received tofacitinib oral tablets/oral solution or matching placebo oral tablets/oral solution, twice daily based on body weight. Body Weight (Dosage in tablet [twice daily] or solution [twice daily]): 5<7kg (2mg or 2mL); 7<10kg (2.5mg or 2. mL); 10 <15kg (3mg or 3mL); 15<25kg (3.5mg or 3.5mL); 25<40kg (4mg or 4mL); 40kg (5 mg or 5 ml). Oral solution (1 mg/mL) is used for subjects <40 kg. Oral tablets (5 mg) are used for subjects >=40 kg.
Follow-up	The duration of subject participation among those who complete the study (without discontinuation) was expected to be approximately 44 weeks.
Primary Outcomes	• Occurrence of disease flare (according to PRCSG/PRINTO Disease Flare criteria) at week 26 of the double blind phase (e.g., week 44 of the study period) [Time frame: week 44]
Secondary Outcomes	• Occurrence of disease flare (according to PRCSG/PRINTO Disease Flare criteria) [Time frame: 26- week double blind phase] • Time to disease flare [Time frame: 26-week double blind phase] • JIA ACR 30 50 70 90 100 response [Time frame: 18-week open label run in and 26-week double blind phase] • Change from baseline in JADAS 27 CRP [Time frame: 18-week open label run in and 26-week double blind phase] • Presence of JIA ACR inactive disease and clinical remission [Time frame: 26-week double blind phase] • Change from baseline in each JIA ACR core set variable [Time Frame: 18-week open label run in and 26-week double blind phase] • Change from baseline in CHQ responses [Time frame: 18-week open label run in and 26-week double blind phase] • Change from baseline in CHAQ responses [Time frame: 18-week open label run in and 26-week double blind phase] • Occurrence of active uveitis (according to SUN criteria) [Time frame: 18- week open label run in and 26-week double blind phase] • In subjects with ERA: Change from baseline in the Tender Entheseal Assessment [Time frame: 26-week double blind phase] • Taste acceptability of tofacitinib oral solution [Time frame: on day 14 of the open label run in phase] • Safety during the study, with focus on serious infections, cytopenias, malignancies, cardiovascular diseases, and validated assessments of growth and pubertal development [Time frame: 44-week study period] • In subjects with ERA: change from baseline in Schober's test response [Time frame: 26-week double blind phase] • In subjects with ERA: change from baseline in overall Back Pain [Time frame: 26-week double blind phase] • In subjects with ERA: change from baseline in Nocturnal Back Pain responses [Time frame: 26-week double blind phase] • PK parameter in first 40 subjects enrolled (excluding subjects with systemic JIA) [Time frame: day 1] • PK parameter in all subjects [Time frame: Day 84] • PK parameter after first 40 subjects enrolled (excluding subjects with systemic JIA), and all subjects with systemic JIA [Time frame: day 14] • PK parameter in first 40 subjects enrolled (excluding subjects with systemic JIA) [Time frame: day 1] • PK parameter in all subjects [Time frame: day 84]

	• PK parameter after first 40 subjects enrolled (excluding subjects with systemic JIA), and all subjects with systemic JIA [Time frame: day 14] • In subjects with PsA, change from baseline in body surface area (BSA) affected by psoriasis [Time frame: 18-week open label run in and 26-week double blind phase] • Change from baseline in JADAS 27 ESR [Time frame: 18-week open label run in and 26-week double blind phase] • Change from baseline in occurrence of JADAS minimum disease activity [Time frame: 18-week open label run in and 26-week double blind phase] • Change from baseline in JADAS inactive disease status [Time frame: 18-week open label run in and 26-week double blind phase] • In subjects with PsA, change from baseline in physician's global assessment (PGA) of psoriasis [Time frame: 18-week open label run in and 26-week double blind phase]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date was in May 2019.

ESTIMATED COST

Tofacitinib is already marketed in the UK. The NHS indicative price for tofacitinib is:[22]

- A pack of 56 x 5 mg tablets costs £690.03
- A pack of 56 x 10 mg tablets costs £1380.06

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.
- 2013/14 NHS Standard Contract Paediatric Medicine: Rheumatology. E03/S/b.

OTHER GUIDANCE

- American College of Rheumatology. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non-Systemic Polyarthritis, Sacroiliitis, and Enthesitis. 2019.[23]
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ADDITIONAL INFORMATION

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