Health Technology Briefing
March 2023

Upadacitinib for treating giant cell arteritis

Company/Developer	AbbVie

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 26984	NICE TSID: 10495	UKPS ID: 655009

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Upadacitinib is currently in clinical development for the treatment of giant cell arteritis (GCA) in adults aged 50 years and older. GCA is a disease of blood vessels where the arteries, particularly those in the neck and at the side of the head (the temples), become inflamed. Common symptoms include headaches with severe pain and tenderness, jaw pain, flu-like fever, and double vision. If left untreated, it can be very serious and cause strokes or blindness. Relapses of GCA are common, and occur in up to 50% of cases, despite appropriate treatment. Currently, there are limited treatment options for GCA, with the main option being steroids (glucocorticoids). However, there are often side effects from the long-term use of glucocorticoids such as skin problems, weight gain, diabetes, and osteoporosis. Also, glucocorticoids are not always effective in many patients, thus there is an unmet need for new treatment options to treat GCA, especially in patients who have relapsed and who are subject to excessive cumulative dosage of glucocorticoids.

Upadacitinib is a targeted immunomodulator which means that it reduces the activity of the immune system. Upadacitinib is administered orally and works by blocking the action of enzymes called Janus kinases. These enzymes are involved in facilitating processes that lead to inflammation, and blocking their effect may bring symptoms of the condition under control. If licensed, upadacitinib will offer an additional treatment option for GCA, and may relieve patients of common side effects of glucocorticoids through a reduced dosage regimen.

Proposed Indication

Giant cell arteritis (GCA) in adults aged 50 years and older.[1]

Technology

Description

Upadacitinib (Rinvoq) is a selective and reversible Janus kinase (JAK) inhibitor. JAKs are intracellular enzymes that transmit cytokine or growth factor signals involved in a broad range of cellular processes including inflammatory responses, haematopoiesis, and immune surveillance, so upadacitinib therefore functions as a targeted immunomodulator.[2] The JAK family of enzymes contains JAK1, JAK2, JAK3 and TYK2 which work in pairs to phosphorylate and activate signal transducers and activators of transcription (STATs). This phosphorylation, in turn, modulates gene expression and cellular function. JAK1 is important in inflammatory cytokine signals while JAK2 is important for red blood cell maturation and JAK3 signals play a role in immune surveillance and lymphocyte function. In human cellular assays, upadacitinib preferentially inhibits signalling by JAK1 or JAK1/3 with functional selectivity over cytokine receptors that signal via pairs of JAK2.[3] Upadacitinib targets JAK, affecting the JAK/STAT pathway inside the cell, which is linked to the signalling of proinflammatory cytokines. By binding to JAK, upadacitinib is thought to block the phosphorylation and activation of STATs, disrupting the proinflammatory cytokine signalling cascade.[4]

Upadacitinib is currently in clinical development for the treatment of GCA. In a phase III clinical trial (NCT03725202), upadacitinib will be administered daily followed with a 26-week corticosteroid taper regimen.[1] The EU Clinical Trials Register entry for this trial (EudraCT 2017-003978-13) indicates that participants will be treated with upadacitinib 7.5mg and 15mg oral film-coated tablets.[5]

Key Innovation

Corticosteroid therapy remains the mainstay treatment for GCA. Despite relieving many of the symptoms, prolonged exposure to corticosteroid therapy can cause unwanted side effects and the underlying inflammation may persist in some patients. Also, people with relapsing or refractory GCA have the highest unmet need, thus, there remains the potential for improved treatment options.[6,7] It has been demonstrated that cytokine signalling dependent on JAK1 and JAK3 is important to the pathogenesis of inflammation in large arteries and that JAK inhibitors show promise in the treatment of large vessel vasculitis diseases such as GCA.[8]

If licensed, upadacitinib would offer an additional treatment option for patients with GCA and may relieve patients of common side effects of glucocorticoids through a reduced dosage regimen.

Regulatory & Development Status

Upadacitinib currently has Marketing Authorisation in the UK for the following indications:[3]

- As a monotherapy or in combination with methotrexate, for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARD)
- As a monotherapy or in combination with methotrexate, for the treatment of active psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more DMARDs
- For the treatment of active non-radiographic axial spondyloarthritis (nr-axSpA) in adult patients with objective signs of inflammation, who have responded inadequately to nonsteroidal anti-inflammatory drugs

- For the treatment of active ankylosing spondylitis in adult patients who have responded inadequately to conventional therapy.
- For the treatment of moderate to severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy.
- For the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent.
- For the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent.

Upadacitinib is also in phase II/III trials for:[9]

- Hidradenitis suppurativa
- Juvenile idiopathic arthritis
- Takayasu arteritis
- Non-segmental vitiligo
- Systemic lupus erythematosus

Patient Group

Disease Area and Clinical Need

GCA, also known as temporal arteritis, is chronic vasculitis characterised by granulomatous inflammation in the walls of medium and large arteries in the scalp, neck, and arms, and it is considered to be a medical emergency.[10] Inflammation causes a narrowing or blockage of the blood vessels, which interrupts blood flow. The disease is commonly associated with polymyalgia rheumatica. Early symptoms of GCA may resemble flu symptoms such as fatigue, loss of appetite and fever. Symptoms specifically related to the inflamed arteries of the head include severe headaches, dizziness or problems with coordination and balance, and temporary or sustained vision loss. The cause of GCA is uncertain but it is believed to be an autoimmune disease in which the body's own immune system attacks the blood vessels, including the temporal arteries, which supply blood to the head and the brain. Genetic and environmental factors (such as infections) are thought to play important roles. As it is rare in people under age 50, its development could be linked to the ageing process.[11]

The incidence rate for GCA in the UK is approximately 2.2 per 10,000 person years, with relapses being common and occurring in up to 50% of cases.[10] Caucasian women over the age of 50 – most commonly between the ages of 70 and 80 years – have the highest risk of developing GCA. Although women are more likely than men to develop GCA, research suggests that men are more likely to suffer potentially blinding eye involvement.[11] In England (2021-22), there were 4,305 finished consultant episodes (FCE) and 3,416 admissions for GCA with polymyalgia rheumatica (IDC-10 code M31.5) and other GCA (ICD-10 code M31.6). This resulted in 5,822 FCE bed days and 1,655 day cases.[12]

Recommended Treatment Options

GCA is usually treated with a high dose of glucocorticoids, which is gradually reduced over time.[7] NICE recommend tocilizumab when used with a tapering course of glucocorticoids (and when used alone after glucocorticoids) for treating GCA in adults, only if they have relapsing or refractory disease, they have not already had tocilizumab, and that tocilizumab administration is stopped after one year of uninterrupted treatment at most.[7]

Clinical Trial Information

Trial	**SELECT-GCA; NCT03725202, EudraCT 2017-003978-13;** A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Upadacitinib in Subjects With Giant Cell Arteritis **Phase III** – recruiting **Location(s)**: 14 EU countries, UK, USA, and other countries **Primary completion date**: October 2024
Trial Design	Randomised, double-blind, placebo-controlled, parallel assignment
Population	N=420 (estimate); patients diagnosed with GCA aged 50 years and older
Intervention(s)	Upadacitinib oral tablet administered daily at a dose of 7.5mg or 15mg
Comparator(s)	Placebo (oral)
Outcome(s)	**Primary outcome measure:** • Percentage of Participants Achieving Sustained Remission [time frame: at week 52]. Sustained remission is defined as having achieved absence of GCA signs and symptoms from week 12 through week 52, and adherence to the protocol-defined corticosteroid (CS) taper regimen. See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Upadacitinib is already licensed for several indications in the UK. The NHS hospital indicative prices for upadacitinib are: 28 x 15mg tablets are £805.56, 28 x 30mg tablets are £1,281.54 and 28 x 45mg tablets are £2087.10.[13]

Relevant Guidance

NICE Guidance

- NICE clinical knowledge summary. Giant cell arteritis. March 2022.
- NICE technology appraisal guidance. Tocilizumab for treating giant cell arteritis (TA518). April 2018.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy Proposition: Tocilizumab for Giant cell arteritis (adults). A13X12/01. March 2016.
- NHS England. 2013/14 NHS Standard Contract for Specialised Rheumatology Services (Adult). A13/S/a.

Other Guidance

- American College of Rheumatology. Foundation Guideline for the Management of Giant Cell Arteritis and Takayasu Arteritis. August 2021.[14]

- British Society for Rheumatology guideline on diagnosis and treatment of giant cell arteritis: executive summary. March 2020.[15]
- Royal College of Physicians. Diagnosis and management of giant cell arteritis. August 2010.[16]

Additional Information

References

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