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HEALTH TECHNOLOGY BRIEFING
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Upadacitinib for non-radiographic axial spondyloarthritis

NIHRIO ID	28721	**NICE ID**	10565
Developer/Company	AbbVie Ltd	**UKPS ID**	Not available

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

SUMMARY

Upadacitinib is in clinical development for the treatment of adults with non-radiographic axial spondyloarthritis (nr-axSpA). This condition affects patients predominantly in the spine and other areas of the body and is caused by inflammation. The inflammation can lead to back pain, fatigue and in serious cases to severe disability as the bones of the spine fuse into a fixed position or joints become progressively damaged. It is characterised by an absence of radiographic sacroilitis which is usually seen in patients with axSpA. Some patients with nr-axSpA do not respond well to current treatment options, resulting in a clear unmet medical need.

Upadacitinib acts by selectively blocking a protein called Janus-Associated Kinase 1 (JAK1 and JAK1/3). JAKs contribute to the processes within the cell to produce an immune or inflammatory response. There is an emerging body of evidence establishing that JAK dependent enzymes are major contributors to the progression of immune-mediated diseases such as nr-axSpA and that blocking such enzymes can be beneficial. Upadacitinib is taken orally and will offer patients a less invasive option of therapy as currently approved therapies for nr-axSpA are administered either by injections or intravenous infusions.

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 adults patients with active non-radiographic axial spondyloarthritis (nr-axSpA).[1]

TECHNOLOGY

DESCRIPTION

Upadacitinib (Rinvoq, ABT-494) is a selective and reversible JAK1 inhibitor.[2] Upadacitinib preferentially inhibits signalling by JAK1 or JAK1/3 with functional selectivity over cytokine receptors that signal via pairs of JAK2 in human cellular assays.[3] JAKs are intracellular enzymes that transmit growth factor or cytokine signals involved in a wide range of cellular processes that include haematopoiesis, inflammatory responses and immune surveillance. JAK1, JAK2, JAK3 and TYK2 make up the four member of the JAK family of enzymes. These enzymes work in pairs to phosphorylate and activate signal transducers and activators of transcription (STATs). The modulation of gene expression and cellular function is through this phosphorylation.[3] JAK1 plays an important role 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.[2,3]

Upadacitinib is currently in phase III clinical development for adults with both active axial spondyloarthritis (axSpA) and nr-axSpA. In the phase III clinical trial (NCT04169373; SELECT AXIS 2), participants will receive 15 mg upadacitinib orally once daily for 104 weeks.[1]

INNOVATION AND/OR ADVANTAGES

Aside from biologic disease-modifying anti-rheumatic drugs (DMARDs), there are limited options available for axial spondyloarthritis (AS) patients who have an inadequate response or contraindication to nonsteroidal antiinflammatory drugs (NSAIDs).[4] Upadacitinib could provide an option for this unmet need.

Currently approved therapies for nr-axSpA patients when NSAIDs are insufficient in controlling the disease are administered either by injections or intravenous infusions. Upadacitinib is administered orally which will give patients a non invasive option of therapy.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Currently, upadacitinib is licensed in the EU/UK. It is licensed as a monotherapy or combination therapy with methotrexate for the treatment of moderate to severe active rheumatoid arthritis in adults who with inadequate response to or intolerance to one or more DMARDs. It is also currently licenced in the EU/UK as a treatment for patients with radiographic axial spondyloarthritis (axSpA) and as a second line treatment for patients with moderate to severe psoriatic arthritis.[3,5]

The most common advese event (≥10%) among patients receiving upadacitinib was upper respiratory tract infections.[3]

Upadacitinib is currently in phase II and phase III clinical development for the treatment of patients with moderate to severe hidradenitis suppurativa, moderate to severe atopic dermatitis, ulceratice colitis, giant cell arthritis, takayasu arteritis and Crohn's disease.[6]

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PATIENT GROUP

DISEASE BACKGROUND

Axial spondyloarthritis (axSpA) is an arthritis caused by the inflammation of the spine and the sacroiliac (SI) joints. There are two forms of axSpA; the most studied form of axSpA is radiographic axSpA also known as ankylosing spondylitis (AS) which according to the modified New York criteria is characterised by sacroiliitis on radiographs. The second form of axSpA is known as non radiographic axSpA (nr-axSpA) which is characterised by a visible inflammation on magnetic resonance imaging (MRI) of the SI joints but an absence of radiographic sacroiliitis.[7]

The main clinical manifestations include back pain and progressive spinal rigidity as well as inflammation of the hips, shoulders, peripheral joints and fingers/toes and fatigue.[8,9] The cause of nr-axSpA is still unclear, research has shown that a majority of people with nr-axSpA have a particular gene known as the HLA-B27. Microbial infection can act as a triggering factor of the host innate immune system and AS development.[9,10] Research has shown that many people with axSpA will progress to the radiographic form of axSpA after years of disease meanwhile, others suffer from the disease for decades, sometimes for the duration of their lifetime, without any evidence of radiographic damage.[11]

CLINICAL NEED AND BURDEN OF DISEASE

The prevalence of axSpA in the UK is believed to range between 0.05% - 0.23%.[12] Applying these figures to population estimates in 2020, it can be estimated there are between 28,141 and 129,450 adults with axSpA in England.[13] The prevalence of nr-axial SpA in comparison to AS is thought to be a ratio of 1:1. This condition is known to affect young people with symptoms starting from the late teens to early twenties, and the average age of onset being 24. The average current delay to diagnosis from the onset of symptoms is 8.5 years, by which time damage to the spine which can be irreversible may have occurred.[14]

Hospital Episode Statistics show that in 2019-20 there were 3,892 Finished Consultant Episodes (FCE), 3,822 admissions and 1,406 FCE bed days with the primary diagnosis ankylosing spondylitis (ICD10 code M45) in England.[15]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

There is currently no cure for nr-axSpA but there are treatments available to help alleviate the symptoms patients experience. Treatment involves physiotherapy and exercise, painkillers including NSAIDs, biological treatments, corticosteroids and DMARDs. Some patients with AS may need joint replacement surgery and regular follow up is recommend as symptoms tend to come and go.[10,16]

CURRENT TREATMENT OPTIONS

For patients with nr-axSpA, NICE recommends:[16,17]

- The lowest effective dose of NSAIDs. Monitoring of risk factors, clinical assessments and the use of gastroprotective treatment should be considered. If adequate pain relief is not reached after the use of an NSAID taken at the maximum tolerated dose for 2–4 weeks, consider switching to a different NSAID.

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- Adalimumab, certolizumab pegol and etanercept are also recommended options for treating severe nr-axSpA in patients who are intolerant of, or whose disease has responded inadequately to NSAIDs.

PLACE OF TECHNOLOGY

If licensed, upadacitinib will provide an additional targeted treatment option for adults with nr-axSpA.

CLINICAL TRIAL INFORMATION

Trial	**SELECT AXIS 2 (STUDY 2);** NCT04169373**;** 2019-003229-12**;** A Phase 3 Randomized, Placebo-Controlled, Double-Blind Program to Evaluate Efficacy and Safety of Upadacitinib in Adult Subjects With Axial Spondyloarthritis **Phase III –** Recruiting **Location:** Europe (incl UK), USA, Canada, and other countries. **Primary completion date:** February, 2023
Trial design	Randomised, quadruple-blind (participant, care provider, investigator, and outcome assessor) parallel assignment.
Population	N= 690 (planned for Study 1 + Study 2); 18 years and older participant (Study 2) with a clinical diagnosis of nr-axSpA fulfilling the 2009 ASAS classification criteria for axSpA but not meeting the radiologic criterion of the modified New York criteria for AS and have objective signs of active inflammation on magnetic resonance imaging (MRI) or based on high sensitivity C-reactive protein (CRP). Participant must have a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score ≥ 4 and a Patient's Assessment of Total Back Pain score ≥ 4 based on a 0 - 10 numerical rating scale at the Screening and Baseline Visits. Participant who have received prior treatment with bDMARD-therapy are allowed.
Intervention(s)	Participants will receive upadacitinib, 15mg to be taken orally once daily for 104 weeks.
Comparator(s)	Participants will receive placebo for 52 weeks followed by upadacitinib to be taken orally for 52 weeks.
Outcome(s)	Percentage of Participants Achieving Assessment of SpondyloArthritis International Society (ASAS) 40 Response [Time Frame: Week 14/Week 52] For full list of outcomes, see trial registry
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

Upadacitinib is already marketed in the UK for the treatment of Rheumatoid arthritis (RA) with inadequate response to or intolerance to one or more DMARD; the NHS indicative price is £805.56 for a pack of 28x15mg tablets.[5]

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RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Secukinumab for treating non-radiographical axial spondloarthritis. (GID-TA1047). Expected publication date: July 2021.
- NICE technology appraisal. TNF-alpha inhibitors for ankylosing spondylitis and nonradiographic axial spondyloarthritis (TA383). February 2016.
- NICE guidance. Golimumab for treating non-radiographical axial spondyloarthritis. (TA497). January 2018.
- NICE guideline. COVID-19 rapid guideline: rheumatological autoimmune, inflammatory and metabolic bone disorders (NG167). April 2020. Last updated March 2021.
- NICE guideline. Spondyloarthritis in over 16s: diagnosis and management (NG65). February 2017. Last updated June 2017.
- NICE quality standard. Spondyloarthritis (QS170). June 2018.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Specialised Rheumatology Services (Adult). A13/S/a.

OTHER GUIDANCE

- Assessment of SpondyloArthritis international Society and European League Against Rheumatism. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. 2017[18]
- British Society of Rheumatology and British Health Professionals in Rheumatology. Guideline for the treatment of axial spondyloarthritis (including ankylosing spondylitis) with biologics. 2017.[19]

ADDITIONAL INFORMATION

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