Health Technology Briefing October 2021

Upadacitinib for moderate to severe active Crohn's disease

Company/Developer	AbbVie Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 10943	NICE ID: 10611	UKPS ID: 655013

Licensing and Market Availability Plans

Currently in phase III clinical trials

Summary

Upadacitinib is in clinical development as a treatment option for moderate to severe Crohn's disease (CD). CD is a type of inflammatory bowel disease which can affect any part of the digestive system. CD causes inflammation and ulceration, which affects food digestion, nutrient absorption, and waste elimination. Symptoms include abdominal pain, diarrhoea, weight loss and fatigue. There is no cure for CD so treatment options focus on managing and relieving symptoms. Patients may have periods of time when they are not suffering from symptoms (remission) or have flare-ups of symptoms (relapses). Additional treatments are required for CD, as some patients do not respond well to some of the current therapy options.

Upadacitinib is an oral medicine in the class of a selective and reversible Janus Kinase (JAK) inhibitor. It acts by inhibiting signalling associated with certain proteins called cytokines involved in the inflammatory process caused by CD. In doing so, upadacitinib limits the inflammation that underpins the pathogenesis of CD and brings the inflammation in the bowel under control. If licensed, upadacitinib will offer an additional treatment option for adult patients with moderate to severe CD.

Proposed Indication

Upadacitinib is indicated for the treatment of adult patients with moderate to severe active Crohn's disease (CD).[1-3]

Technology

Description

Upadacitinib (Rinvoq, ABT-494) is a selective and reversible Janus Kinase (JAK) inhibitor. 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. 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. The JAK family of enzymes contains four members, JAK1, JAK2, JAK3 and tyrosine kinase 2 (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.[4]

Upadacitinib is clinical development for the treatment of adult patients with moderately to severe CD. In the phase II/III trials (NCT03345823, NCT03345836, NCT03345849), upadacitinib was administered orally, one/twice daily for up to 36 weeks.[1-3]

Key Innovation

Currently approved therapies, including corticosteroids, immunosuppressants, and biologic agents, are not effective in some patients and may be associated with adverse effects that limit their use.[5,6] There remains an unmet need for additional targeted therapies for CD that provide short- and long-term benefits as measured by both patients' symptoms and endoscopic outcomes.[7]

Upadacitinib is one of a number of JAK inhibitors with different selectivity which have been studied for treatment of CD.[7-10] Upadacitinib is an oral JAK1 inhibitor with increased selectivity for JAK1 compared with JAK2, JAK3, and TYK2.[11] If licensed, upadacitinib will offer an additional treatment option for adult patients with moderate to severe CD.

Regulatory & Development Status

Upadacitinib is licensed in the UK:[4]

- as 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 (DMARDs)
- as 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 ankylosing spondylitis in adult patients who have responded inadequately to conventional therapy.
- as a monotherapy for the treatment of moderate to severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systematic therapy.

Upadacitinib is in phase II/III clinical trials for:[12]

- various skin conditions (such as atopic dermatitis, hidradenitis suppurativa and non-segmental vitiligo)

- systemic lupus erythematosus
- spondylarthritis, rheumatoid arthritis and psoriatic arthritis
- Takayasu's arteritis
- ulcerative colitis
- giant cell arteritis

Patient Group

Disease Area and Clinical Need

Crohn's disease (CD) can affect any part of the digestive system[13], and causes inflammation and ulceration, which affects food digestion, nutrient absorption, and waste elimination. Main symptoms of CD are abdominal pain, diarrhea, weight loss and fatigue.[14,15] CD is more common in urban areas, and in northern, developed countries such as Northern Europe, particularly amongst white people of European descent. The exact cause of CD is unknown but there are several factors that could contribute to its development, including: inheritance, immune response issues, smoking, gut viruses, abnormal balance of gut bacteria, and stress.[14,16]

It is estimated that CD affects about one in every 650 people in the UK.[17] In England, 2020-21, there were 122,027 hospital admissions, 131,413 finished consultant episodes (FCE) for patients with a primary diagnosis of CD (ICD-10 code K50) resulting in 73,384 FCE bed days and 109,000 day cases.[18] In the UK, in 2017, the prevalence of CD was 400 per 100,000. CD has increased over the past two decades at a rate of 2-3% per annum and is predicted to reach a prevalence of 487.2 per 100,000 by 2025. CD is also associated with an increased risk of all-cause mortality.[19]

Recommended Treatment Options

NICE recommended pharmacological treatment options for CD are as follows:[20]

- Monotherapy with a glucocorticosteroid (prednisolone, methylprednisolone or intravenous hydrocortisone) to induce remission.
- The use of budesonide or aminosalicylate treatment if glucocorticosteroids are contraindicated for patients who have one or more of distal ileal, ileocecal or right-sided colonic disease
- The use of azathioprine or mercaptopurine as an add-on treatment to a glucocorticosteroid or budesonide if there are two or more inflammatory exacerbations in a 12 month period, or the glucocorticosteroid dose cannot be tapered (methotrexate should be used instead if patients cannot tolerate azathioprine or mercaptopurine).
- Biological therapy with infliximab or adalimumab.

Surgery may also be an option for patients whose disease is limited to the distal ileum.[20]

Clinical Trial Information

Trial	NCT03345823; 2017-001225-41; **M14-430; A Multicentre, Randomized, Double-Blind, Placebo-Controlled Maintenance and Long-Term Extension Study of the Efficacy and Safety of Upadacitinib (ABT-494) in Subjects With Crohn's Disease Who Completed the Studies M14-431 or M14-433** **Phase III:** enrolling by invitation **Locations(s):** EU, UK, USA, Canada and other countries **Primary completion date:** August 2027

Trial Design	Randomised, parallel assignment, quadruple blinded
Population	N=747 (estimated); participated in M14-431 or M14-433, aged 18 years to 75 years
Intervention(s)	Group A – Arm A: This is a maintenance group with 52 weeks which includes participants who achieved clinical response to upadacitinib dose A in studies M14-431 and M14-433 and will receive dose B. Group A - Arm B: This is a maintenance group with 52 weeks which includes participants who achieved clinical response to upadacitinib dose A in studies M14-431 and M14-433 and will receive dose C. Group B – Arm A: This is a long-term extension group with 240 weeks which includes participants who complete group A and will receive dose B. Group B – Arm B: This is a long-term extension group with 240 weeks which includes participants who complete group A and will receive dose C.
Comparator(s)	Group A – Arm C: This is a maintenance group with 52 weeks which includes participants who achieved clinical response to upadacitinib dose A in studies M14-431 and M14-433 and will receive placebo. Group B – Arm C: This is a long-term extension group with 240 weeks which includes participants who complete group A.
Outcome(s)	Sub-study 1 [Primary outcomes]: 1. Percentage of participants with clinical remission per Crohn's Disease Activity Index i.e. <150 by CDAI [Time frame: week 52] 2. Percentage of participants with endoscopic response [Time frame: week 52] Sub-study 2 [Primary outcomes]: 3. Number of participants with adverse events [Time frame: through Week 240] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information

Trial	NCT03345836; 2017-001226-18; **M14-431; A Multicentre, Randomized, Double-Blind, Placebo-Controlled Induction Study of the Efficacy and Safety of Upadacitinib (ABT-494) in Subjects With Moderately to Severely Active Crohn's Disease Who Have Inadequately Responded to or Are Intolerant to Biologic Therapy** **Phase III:** completed **Locations(s):** EU, UK, USA, Canada and other countries **Study completion date:** August 2021

Trial Design	Randomised, parallel assignment, quadruple blinded
Population	N=625; adults aged 18-75 years; confirmed diagnosis of moderate to severe CD; demonstrated an inadequate response or intolerance to any biologic therapy for infliximab, adalimumab, certolizumab pegol, vedolizumab, and ustekinumab.
Intervention(s)	Arm A: Upadacitinib (dose A) taken orally once daily for 12 weeks Arm C: Open-label upadacitinib (dose A) taken orally once daily for 12 weeks
Comparator(s)	Arm C: Placebo (taken orally for 12 weeks)
Outcome(s)	Primary outcomes: 1. Percentage of participants with clinical remission per Crohn's Disease Activity Index i.e. <150 by CDAI [Time frame: week 12] 2. Percentage of participants with endoscopic response [Time frame: week 12] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information	
Trial	NCT03345849; 2017-001240-35; **M14-433; A Multicentre, Randomized, Double-Blind, Placebo-Controlled Induction Study of the Efficacy and Safety of Upadacitinib (ABT-494) in Subjects With Moderately to Severely Active Crohn's Disease Who Have Inadequately Responded to or Are Intolerant to Conventional and/or Biologic Therapies** **Phase III**: active, not recruiting **Locations(s):** EU, UK, USA, Canada and other countries **Study completion date:** February 2022
Trial Design	Randomised, parallel assignment, quadruple blinded
Population	N=501 (estimated); adults aged 18-75 years; confirmed diagnosis of moderate to severe CD; demonstrated an inadequate response or intolerance to one or more conventional and/or biologic therapies (Oral locally acting steroids, Intravenous or oral corticosteroids, Immunosuppressants).
Intervention(s)	Arm A: Participants will receive Upadacitinib dose A for 12 weeks. Non-responders will receive Upadacitinib dose B for 12 weeks
Comparator(s)	Arm B: Participants will receive placebo for 12 weeks. Non-responders will receive Upadacitinib dose A for 12 weeks.
Outcome(s)	Primary outcomes 1. Percentage of participants with clinical remission per Crohn's Disease Activity Index i.e. <150 by CDAI [Time frame: week 12] 2. Percentage of participants with endoscopic response [Time frame: week 12] See trial record for full list of other outcomes.

Results (efficacy)	-
Results (safety)	-

Estimated Cost

Upadacitinib (as Upadacitinib hemihydrate) is already marketed in the UK. The NHS indicative price is £805.56 for a pack of 28 x 15 mg tablets.[21]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Etrolizumab for previously treated moderately to severely active Crohn's disease (GID-TA10870). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Risankizumab for previously treated moderately to severely active Crohn's disease in people 16 years and over (GID-TA10884). Expected date of issue to be confirmed.
- NICE technology appraisal. Ustekinumab for moderately to severely active Crohn's disease after previous treatment (TA456). July 2017.
- NICE technology appraisal. Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy (TA352). August 2015.
- NICE technology appraisal. Infliximab and adalimumab for the treatment of Crohn's disease (TA187). May 2010.
- NICE guideline. Crohn's disease: management (NG129). May 2019.
- NICE interventional procedure guidance. Extracorporeal photopheresis for Crohn's disease (IPG288). February 2009.

NHS England (Policy/Commissioning) Guidance

NHS England. 2013/14 NHS Standard Contract for Colorectal: Complex Inflammatory Bowel Disease (Adult). A08/S/c.

Other Guidance

- Lamb CA, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. 2019.[22]
- NICE Clinical Knowledge Summary. Crohn's disease. January 2019.[23]
- Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG Clinical Guideline: Management of Crohn's Disease in Adults. 2018.[6]

Additional Information

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