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HEALTH TECHNOLOGY BRIEFING
APRIL 2021

Upadacitinib for ulcerative colitis

NIHRIO ID	12922	**NICE ID**	10470
Developer/Company	AbbVie	**UKPS ID**	655012

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

*COMMERCIAL IN CONFIDENCE

SUMMARY

Upadacitinib is currently in clinical development for patients with ulcerative colitis (UC). UC is a long-term condition where parts of the large bowel become inflamed, causing urgent bloody diarrhoea and abdominal pain. The symptoms of UC often follow a pattern where individuals with the condition have periods of no symptoms or mild symptoms (remission) followed by periods where their symptoms are particularly troublesome (flare-ups or relapses). There are therapeutic options available for UC, however these are not effective in more than one third of patients and can be associated with adverse effects that limit their use.

Upadacitinib is an oral medicine that reduces the activity of the immune system. Upadacitinib works by blocking the action of enzymes called Janus kinases. These enzymes are involved in setting up processes that lead to inflammation, and blocking their effect brings inflammation in the bowel under control. If licensed, upadacitinib will offer an additional treatment option for patients with moderately to severely active UC.

PROPOSED INDICATION

Treatment of moderately to severely active ulcerative colitis.[1,2]

TECHNOLOGY

DESCRIPTION

Upadacitinib 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, hematopoiesis and immune surveillance. The JAK family of enzymes contains four members, 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.[3]

In phase IIb (NCT02819635) clinical trials patients were randomly assigned to groups that received placebo or induction therapy with upadacitinib (7.5 mg, 15 mg, 30 mg, or 45 mg, extended release) once daily for 8 weeks.[4]

INNOVATION AND/OR ADVANTAGES

Current therapeutic options include mesalamine, glucocorticoids, immunosuppressive agents, and biologics. However, these available treatments are not effective in more than one third of patients and can be associated with adverse effects that limit their use.[4] Since 2018, NICE has recommended the use of a pan-JAK inhibitor in patients with moderately to severely active UC.[5] It is hypothesized that upadacitinib's JAK selectivity will have a more favourable benefit-risk profile over the pan-JAK inhibitors.[4]

In a phase IIb trial, 8 weeks of treatment with upadacitinib was more effective than placebo for inducing remission in patients with moderately to severely active UC.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Upadacitinib is licensed in the UK:[3]

- 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.

The very common (⩾ 1/10) adverse reactions with upadacitinib are upper respiratory tract infections.[3]

Upadacitinib is in phase III clinical trials for:[6]

- atopic dermatitis
- spondyloarthritis

- Crohn's disease
- giant cell arteritis

Upadacitinib is also in phase II clinical trials for systemic lupus erythematosus and hidradenitis suppurativa.[6]

PATIENT GROUP

DISEASE BACKGROUND

Ulcerative colitis (UC), one of the two main forms of Inflammatory Bowel Disease (IBD), is a chronic, relapsing-remitting, non-infectious inflammatory disease of the gastrointestinal tract that causes inflammation and ulceration of the inner lining of the colon and rectum.[7,8] It is characterized by diffuse, continuous, superficial inflammation of the large bowel limited to the intestinal mucosa, and usually affects the rectum with a variable length of the colon involved proximally.[8] The exact pathophysiology of UC is unknown but it is thought to be multifactorial involving epithelial barrier defects, dysregulated immune responses and environmental factors in genetically susceptible people.[8,9] UC tends to run in families with 8-14% of patients with the disease having a family history of IBDs and first degree relatives have four times the risk of developing the disease.[9]

The main symptoms of UC are recurring diarrhoea which may contain blood, mucus or pus, abdominal pain and frequently needing to empty bowels. Patients may also experience extreme tiredness, loss of appetite and weight loss.[10] Extra-intestinal manifestations (symptoms outside of the bowel) such as arthritis, mouth ulcers, uveitis and primary sclerosing cholangitis may also be present during a flare-up of UC.[10,11] These extra-intestinal manifestations can have a severe impact on the patient's quality of life with significant mental health problems, including depression. Patients can develop professional and social constraints that interfere with their work and recreational activities. [12]

The severity of the symptoms will depend on how much of the rectum and colon is inflamed and how severe the inflammation is.[10] Patients often follow a remission then relapse cycle where they go for weeks or months experiencing none or very mild symptoms (remission) before they experience a flare-up where their symptoms are particularly troublesome (relapse).[10]

UC is a lifelong disease associated with significant morbidity, and the potential for social and psychological sequelae particularly if poorly controlled.[13]

CLINICAL NEED AND BURDEN OF DISEASE

It is estimated that 1 in every 420 people living in the UK is affected by UC which amounts to around 146,000 people with a diagnosis.[14] It has been estimated that around 106,000 people in England have ulcerative colitis, of whom about 52% have moderate to severe disease.[15]

The condition can develop at any age, but is most often diagnosed in people aged from 15 to 25 and between 55 and 65 years.[13] It affects both men and women equally. UC is more common in white people of European descent, especially those of Ashkenazi Jewish descent, and black people.[7,10] Although UC usually has a mild to moderate course, approximately 20%-25% of patients suffer at least one severe acute attack, requiring hospitalisation.[16] An estimated 30-60% of people with UC will have at least one relapse per year, with 80% of these classified as mild to moderate and 20% classified as severe.[5]

According to hospital episode statistics for England in 2019-20 there were a total of 115,867 finished consultant episodes for ulcerative colitis (ICD-10 code K51) recorded as primary diagnosis of which 103,524 were recorded as admissions with a total of 91,831 day cases.[17]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

There are no curative therapies for inflammatory and autoimmune diseases like UC.[10] The British Society of Gastroenterology (BSG) guideline states that people with IBD should be cared for by a defined multidisciplinary team including gastroenterologists, colorectal surgeons, nurse specialists, a dietitian, pharmacist, and gastrointestinal radiologist. This should allow for early initiation of appropriate therapy and ongoing assessment of disease progress and any adverse effects of treatment.[18,19]

For those with moderate to severe UC, most treatment options are pharmacological. Colectomy (with the creation of either an ileostomy or an ileo-anal pouch) is a surgical treatment option for some patients, to improve the quality of life in chronic or treatment-refractory active disease or to treat cancer or pre-cancerous changes.[20]

CURRENT TREATMENT OPTIONS

Initial management may include corticosteroids, or topical or oral aminosalicylates (sulfasalazine, mesalazine, balsalazide or olsalazine). If the disease does not adequately respond to oral corticosteroids (beclometasone, budesonide, hydrocortisone or prednisolone) then an immunosuppressant (such as mercaptopurine or azathioprine) may be considered.[20]

The recommended treatment for adults with moderately to severely active UC includes:[21]

Ustekinumab

- Ustekinumab is recommended, when conventional therapy or a biological agent cannot be tolerated, or the disease has responded inadequately or lost response to treatment, only if: a tumour necrosis factor-alpha inhibitor has failed (that is the disease has responded inadequately or has lost response to treatment) or a tumour necrosis factor-alpha inhibitor cannot be tolerated or is not suitable.

Tofacitinib

- Tofacitinib is recommended, within its marketing authorisation, as an option for treating moderately to severely active ulcerative colitis in adults when conventional therapy or a biological agent cannot be tolerated or the disease has responded inadequately or lost response to treatment. It is recommended only if the company provides tofacitinib with the discount agreed in the commercial arrangement.

Vedolizumab

- Vedolizumab is recommended, within its marketing authorisation, as an option for treating moderately to severely active ulcerative colitis in adults only if the company provides vedolizumab with the discount agreed in the patient access scheme.
- Vedolizumab should be given until it stops working or surgery is needed. At 12 months after the start of treatment, people should be reassessed to see whether treatment should continue. Treatment should only continue if there is clear evidence of ongoing clinical benefit. For people in complete remission at 12 months, consider stopping vedolizumab, then resuming treatment if there is a relapse. People who continue vedolizumab should be reassessed at least every 12 months to see whether continued treatment is justified.

Infliximab, adalimumab and golimumab

- Infliximab, adalimumab and golimumab are recommended, within their marketing authorisations, as options for treating moderately to severely active ulcerative colitis in adults whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who cannot tolerate, or have medical contraindications for, such therapies.
- Golimumab is recommended only if the company provides the 100 mg dose of golimumab at the same cost as the 50 mg dose, as agreed in the patient access scheme.
- The choice of treatment between infliximab, adalimumab or golimumab should be made on an individual basis after discussion between the responsible clinician and the patient about the advantages and disadvantages of the treatments available. This should take into consideration therapeutic need and whether or not the patient is likely to adhere to treatment. If more than 1 treatment is suitable, the least expensive should be chosen (taking into account administration costs, dosage and price per dose).
- Infliximab is recommended, within its marketing authorisation, as an option for treating severely active ulcerative colitis in children and young people aged 6–17 years whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who cannot tolerate, or have medical contraindications for, such therapies.
- Infliximab, adalimumab or golimumab should be given as a planned course of treatment until treatment fails (including the need for surgery) or until 12 months after starting treatment, whichever is shorter. Specialists should then discuss the risks and benefits of continued treatment with the patient, and their parent or carer if appropriate:
  - They should continue treatment only if there is clear evidence of response as determined by clinical symptoms, biological markers and investigation, including endoscopy if necessary. People who continue treatment should be reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate.
  - They should consider a trial withdrawal from treatment for all patients who are in stable clinical remission. People whose disease relapses after treatment is stopped should have the option to start treatment again.

NICE has also published evidence summaries on the use of these medicines for the treatment of UC:[21]

- Budesonide multimatrix
- Remsima (infliximab biosimilar)

PLACE OF TECHNOLOGY

If licensed, upadacitinib will offer an additional treatment option for moderately to severely active ulcerative colitis.

CLINICAL TRIAL INFORMATION

Trial	**U-Accomplish, M14-675,** NCT03653026, 2016-000642-62**;** A Multicenter, Randomized, Double-Blind, Placebo-Controlled Induction Study to Evaluate the Efficacy and Safety of Upadacitinib (ABT-494) in Subjects With Moderately to Severely Active Ulcerative Colitis **Phase III** - Completed **Location(s):** EU countries (inc UK), United States, Canada and other countries **Study completion date:** Jan 2021

Trial design	Parallel assignment, randomised, double-blind
Population	N=522, diagnosis of UC, demonstrated an inadequate response, loss of response, or intolerance to at least one of the following treatments including, oral aminosalicylates, corticosteroids, immunosuppressants, and/or biologic therapies, aged 16 years to 75 years.
Intervention(s)	Upadacitinib oral tablet once daily
Comparator(s)	Placebo
Outcome(s)	Primary outcome(s); • Percentage of Participants who Achieve Clinical Remission per Adapted Mayo Score [Time Frame: At Week 8] It is defined by Stool Frequency Subscore (SFS), Rectal Bleeding Subscore (RBS), and endoscopic subscore. See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**U-Accomplish, M14-234,** NCT02819635, 2016-000641-31; A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Upadacitinib (ABT-494) for Induction and Maintenance Therapy in Subjects With Moderately to Severely Active Ulcerative Colitis **Phase III** - ongoing **Location(s):** EU countries (inc UK), United States, Canada and other countries **Study completion date:** Feb 2022
Trial design	Parallel assignment, randomised, double-blind
Population	N= 1267, diagnosis of active ulcerative colitis for 90 days or greater prior to baseline, with exclusion of current infection, colonic dysplasia and/or malignancy, with an Adapted Mayo score of 5 to 9 points and endoscopic sub score of 2 to 3 and have demonstrated an inadequate response to, loss of response to, or intolerance to at least one of the following treatments including: oral aminosalicylates, corticosteroids, immunosuppressants, and/or biologic therapies in the opinion of the investigator, aged 16 years to 75 years.
Intervention(s)	Upadacitinib oral tablet once daily at 4 different doses
Comparator(s)	Placebo
Outcome(s)	Primary outcome(s); - Substudy 1/Substudy 2: Percentage Of Participants Who Achieve Clinical Remission Per Adapted Mayo Score [Time Frame: At Week 8] - Substudy 3: Percentage Of Participants Who Achieve Clinical Remission Per Adapted Mayo Score [Time Frame: At Week 52] See trial record for full list of other outcomes
Results (efficacy)	Substudy 1: At week 8, 8.5%, 14.3%, 13.5%, and 19.6% of patients receiving 7.5 mg, 15 mg, 30 mg, or 45 mg

	upadacitinib, respectively, achieved clinical remission compared with none of the patients receiving placebo (P = .052, P = .013, P = .011, and P = .002 compared with placebo, respectively).[4]
Results (safety)	Substudy 1: One event of herpes zoster and 1 participant with pulmonary embolism and deep venous thrombosis (diagnosed 26 days after treatment discontinuation) were reported in the group that received upadacitinib 45 mg once daily. Increases in serum lipid levels and creatine phosphokinase with upadacitinib were observed.[4]

Trial	**U-Activate, M14-533,** NCT03006068, 2016-000674-38; A Phase 3 Multicenter, Long-Term Extension Study to Evaluate the Safety and Efficacy of Upadacitinib (ABT-494) in Subjects With Ulcerative Colitis **Phase III** - Enrolling by invitation **Location(s):** EU countries (inc UK), United States, Canada and other countries **Study completion date:** Aug 2024
Trial design	Parallel assignment, non-randomised, double-blind
Population	N= 950, participants have not achieved clinical response at the end of the induction period (Week 8) in Study M14-234 Substudy 1, has had loss of response during the maintenance period of Study M14-234 Substudy 3, or has successfully completed Study M14-234 Substudy 3. During the COVID-19 pandemic, for participants with missing endoscopy at Week 8, Week 16 or Week 52 due to the COVID-19 pandemic in Studies M14-234 Substudy 2, M14-234 Substudy 3 and M14-675, participants may be enrolled if certain criteria are met, aged 16 years to 75 years.
Intervention(s)	Upadacitinib oral tablet once daily at 3 different doses
Comparator(s)	Placebo
Outcome(s)	Primary outcome(s); - Assessing Treatment-Emergent Adverse Events [Time Frame: Up to 288 Weeks] 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.[22]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal proposed. Filgotinib for treating moderately to severely active ulcerative colitis (ID3736). Expected publication date: December 2021

- NICE technology appraisal in development. Ustekinumab for treating moderately to severely active ulcerative colitis (TA633). June 2020.
- NICE technology appraisal. Tofacitinib for moderately to severely active ulcerative colitis (TA547). November 2018.
- NICE technology appraisal. Vedolizumab for treating moderately to severely active ulcerative colitis (TA342). June 2015.
- NICE technology appraisal. Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (TA329). February 2015.
- NICE technology appraisal. Adalimumab for the treatment of moderate to severe ulcerative colitis (TA262). July 2012.
- NICE technology appraisal guidance. Infliximab for acute exacerbations of ulcerative colitis (TA163). December 2008.
- NICE clinical guideline. Ulcerative colitis: management (NG130). May 2019.
- NICE quality standard. Inflammatory bowel disease (QS81). February 2015.
- NICE diagnostics guidance. Faecal calprotectin diagnostic tests for inflammatory diseases of the bowel (DG11). October 2013.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

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

OTHER GUIDANCE

- NICE Clinical Knowledge Summaries. Ulcerative colitis. 2020.[23]
- British Society of Gastroenterology. Consensus guidelines on the management of inflammatory bowel diseases in adults. 2019. [19]
- European Federation of Crohn's and Ulcerative Colitis Association (EFCCA). ECCO-EFCCA Patient Guidelines on Ulcerative Colitis (UC). 2014. [24]

ADDITIONAL INFORMATION

REFERENCES

1 clinicaltrials.gov. A Multicenter, Randomized, Double-Blind, Placebo-Controlled Induction Study to Evaluate the Efficacy and Safety of Upadacitinib (ABT-494) in Subjects With Moderately to Severely Active Ulcerative Colitis. *Trial ID: NCT03653026*. 2018;Status: Completed. Available from: https://clinicaltrials.gov/ct2/show/NCT03653026?term=Upadacitinib&phase=2&draw=2&rank=9.

2 clinicaltrials.gov. A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Upadacitinib (ABT-494) for Induction and Maintenance Therapy in Subjects With Moderately to Severely Active Ulcerative Colitis. *Trial ID: NCT02819635*. 2016;Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT02819635.

3 electronic Medicines Compendium (eMC). *RINVOQ 15mg prolonged-release tablets.* 2019. Available from: https://www.medicines.org.uk/emc/product/10972 [Accessed 19 March 2021].

4 Sandborn WJ, Ghosh S, Panes J, Schreiber S, D'Haens G, Tanida S, et al. Efficacy of Upadacitinib in a Randomized Trial of Patients With Active Ulcerative Colitis. *Gastroenterology*. 2020 Jun;158(8):2139-49.e14. Available from: https://doi.org/10.1053/j.gastro.2020.02.030.

5 National Institute for Health and Care Excellence (NICE). *Tofacitinib for moderately to severely active ulcerative colitis: Final scope* Last Update Date: Available from: https://www.nice.org.uk/guidance/ta547/documents/final-scope [Accessed 11 March 2021].
6 clinicaltrials.gov. *Studies found for: Upadacitinib | Phase 2, 3.* 2021. Available from: https://clinicaltrials.gov/ct2/results?term=Upadacitinib&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 19 March 2021].
7 Crohn's and Colitis UK. *Ulcerative Colitis.* 2017. Available from: https://www.crohnsandcolitis.org.uk/about-crohns-and-colitis/publications/ulcerative-colitis [Accessed 11 March 2021].
8 NICE Clinical Knowledge Summaries (CKS). *NICE CKS: Ulcerative colitis.* 2020. Available from: https://cks.nice.org.uk/ulcerative-colitis#!backgroundSub [Accessed 11 March 2021].
9 Ungaro R, Mehandru S, Allen P, Peyrin-Biroulet, Colombel J. Ulcerative colitis. *The Lancet*. 2016;389(10080):1756-70. Available from: https://doi.org/10.1016/S0140-6736(16)32126-2.
10 NHS. *Ulcerative colitis.* 2019. Available from: https://www.nhs.uk/conditions/ulcerative-colitis/ [Accessed 11 March 2021].
11 Vavricka S, Schoepfer A, Scharl M, Lakatos P, Navarini A, Rogler G. Extraintestinal Manifestations of Inflammatory Bowel Disease. *Inflammatory Bowel Diseases*. 2015;21(8):1982-92. Available from: https://doi.org/10.1097/MIB.0000000000000392.
12 Nobrega V, Silva I, Brito B, Silva J, Silva M, Santana G. The onset of clinical manifestations in inflammatory bowel disease patients. *Arq Gastroenterol*. 2018;55(3). Available from: https://doi.org/10.1590/S0004-2803.201800000-73.
13 National Institute for Health and Care Excellence (NICE). *NICE Clinical guideline and quality standard: ulcerative colitis scope (CG166)*. Last Update Date: Available from: https://www.nice.org.uk/guidance/CG166/documents/ulcerative-colitis-final-scope2 [Accessed 7 March 2021].
14 National Health Service. *Overview-Ulcerative colitis.* 2019. Available from: https://www.nhs.uk/conditions/ulcerative-colitis/ [Accessed 11 March 2021].
15 National Insitute for Health and Care Excellence. *Filgotinib for treating moderately to severely active ulcerative colitis.* 2021 Available from: https://www.nice.org.uk/guidance/gid-ta10600/documents/final-scope [Accessed 7 March 2021].
16 Antonelli E, Villanacci V, Bassotti G. Novel oral-targeted therapies for mucosal healing in ulcerative colitis. *World J Gastroenterol*. 2018;24(47):5322-30. Available from: https://doi.org/10.3748/wjg.v24.i47.5322.
17 NHS Digital. *Hospital Admitted Patient Care Activity, 2019-20: Diagnosis.* 2020. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2019-20 [Accessed 7 March 2021].
18 National Institute for Health and Care Excellence (NICE). *Quality statement 2: Multidisciplinary team support (QS81)*. Last Update Date: Available from: https://www.nice.org.uk/guidance/qs81/chapter/quality-statement-2-multidisciplinary-team-support [Accessed 7 March 2021].
19 The British Society of Gastroenterology (BSG). *British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults* Last Update Date: Available from: https://www.bsg.org.uk/wp-content/uploads/2019/12/BSG-IBD-Guidelines-2019.pdf [Accessed 7 March 2021].
20 National Institute for Health and Care Excellence (NICE). *NICE Proposed Technology Appraisal: Tofacitinib for moderately to severely active ulcerative colitis* Last Update Date: Available from: https://www.nice.org.uk/guidance/ta547/documents/final-scope [Accessed 7 March 2021].
21 National Insitute for Health and Care Excellence. *Further treatment for moderate-to-severe ulcerative colitis.* 2021. Available from: https://pathways.nice.org.uk/pathways/ulcerative-colitis#path=view%3A/pathways/ulcerative-colitis/inducing-remission-in-people-with-ulcerative-colitis.xml&content=view-node%3Anodes-further-treatment-for-moderate-to-severe-ulcerative-colitis [Accessed 7 March 2021].
22 British National Formulary. *UPADACITINIB.* 2021. Available from: https://bnf.nice.org.uk/medicinal-forms/upadacitinib.html [Accessed 11 April 2021].
23 National Institute for Health and Care Excellence (NICE). *Ulcerative colitis: management (NG130)*. Last Update Date: Available from: https://www.nice.org.uk/guidance/ng130/chapter/Recommendations [Accessed 11 April 2021].
24 European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA). *ECCO-EFCCA Patient Guidelines on Ulcerative Colitis (UC)* Last Update Date: Available from:

https://www.efcca.org/sites/default/files/Ulcerative%20Colitis%20Patient%20Guidelines.pdf [Accessed 11 April 2021].

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