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HEALTH TECHNOLOGY BRIEFING NOVEMBER 2019

Filgotinib for moderately to severely active ulcerative colitis

NIHRIO ID	12986	**NICE ID**	10169
Developer/Company	Gilead Sciences Ltd	**UKPS ID**	Not Available

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

SUMMARY

Filgotinib is in clinical development for the treatment of patients with moderately to severely active ulcerative colitis. Ulcerative colitis is a type of inflammatory bowel disease that causes inflammation and ulcers in the bowel and rectum which can cause diarrhoea, abdominal pain and faecal urgency or incontinence. The symptoms of ulcerative colitis often follow a pattern of relapse and remission where they have periods of none or mild symptoms followed by periods of increased symptoms flare-up ('active'). There are no curative therapies for ulcerative colitis and current treatment aims to relieve symptoms during a flare-up and maintain remission by preventing symptoms from returning.

Filgotinib is administered orally in tablet form. It works by binding to and blocking a pathway of the JAK enzymes, which mediates the signalling and activity of many molecules involved in inflammation and immune mediated diseases. Filgotinib is highly selective for JAK1 so it may have fewer adverse effects compared to other non-selective drugs that block all JAK enzymes. If licensed, filgotinib will offer an additional treatment option for the induction and maintenance of remission in adults with moderately to severely active ulcerative colitis.

PROPOSED INDICATION

Adults with moderately to severely active ulcerative colitis.[1]

TECHNOLOGY

DESCRIPTION

Filgotinib (GLP-0634) is an orally bioavailable Janus Kinase (JAK) inhibitor that specifically blocks JAK1.[2,3] JAKs are intracellular non-receptor tyrosine kinases that play a key role in signalling transduction for several extracellular molecules such as cytokines and growth factors. The activation of cell-membrane receptors by circulating cytokines results in the phosphorylation of signal transducers and activators of transcription (STATs) by the JAK family members.[3] Filgotinib specifically targets, binds to and inhibits the phosphorylation of JAK1 which interferes with JAK/STAT dependent signalling. As JAK1 mediates signalling of many pro-inflammatory cytokines, JAK1 inhibition prevents cytokine signalling and activity in many inflammatory and immune-mediated processes and leads to a decrease in inflammation and activation of certain immune cells.[2,4]

Filgotinib is currently in clinical development for the induction and maintenance treatment of moderately to severely active ulcerative colitis. In the phase III clinical trials (NCT02914522; SELECTION1 and NCT02914535; SELECTIONTE) filgotinib is administered orally to patients once daily for 10 weeks and compared to placebo.[1,5]

INNOVATION AND/OR ADVANTAGES

Filgotinib is a highly-selective JAK inhibitor; it is 30 times more selective for JAK1 than JAK2.[6] Recent findings suggest that JAK1 dominates the JAK signalling pathway, suggesting that JAK1 inhibition might be largely responsible for the in-vivo efficacy of JAK inhibitors in immune-inflammatory diseases.[7]

JAK inhibitors are associated with adverse effects such as an increase in herpes zoster infections and potentially other systemic infections, serum lipid disturbances and anaemia.[8] Since filgotinib has such high affinity to JAK1, it has the potential to reduce unwanted adverse effects because it can be given at lower doses without declining clinical efficacy.[9]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Filgotinib does not currently have Marketing Authorisation in the EU/UK for any indication.

Filgotinib is in pre-registration in the UK/EU for the treatment of moderate-to-severe rheumatoid arthritis, and in phase III clinical development for the treatment of Crohn's disease and in phase II for active psoriatic arthritis.[10,11]

PATIENT GROUP

DISEASE BACKGROUND

Ulcerative colitis is one of the two most prevalent forms of inflammatory bowel disease (IBD).[12] Ulcerative colitis is a long-term condition where the colon and rectum become

inflamed and small ulcers can develop on the colon's lining, resulting in bleeding and production of pus.[13] The inflamed colon is less able to absorb liquid and cannot hold as much waste as normal, leading to frequent bowel movements (six or more a day).[12] The exact pathophysiology of ulcerative colitis is unknown but it is thought to be multifactorial involving epithelial barrier defects, dysregulated immune responses and environmental factors in genetically susceptible people.[14,15] Ulcerative colitis tends to run in families with 8-14% of patients with the disease having a family history of inflammatory bowel diseases and first degree relatives have four times the risk of developing the disease.[14]

The main symptoms of ulcerative colitis are recurring diarrhoea which may contain blood, mucus or pus, abdominal cramping and frequently needing to empty bowels. Patients may also experience extreme tiredness, loss of appetite and weight loss.[13] Extra-intestinal manifestations such as arthritis, mouth ulcers, uveitis and primary sclerosing cholangitis may also be present during a flare-up of ulcerative colitis.[16,17] 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.[18]

The severity of the symptoms will depend on how much of the rectum and colon is inflamed and how severe the inflammation is.[13] Severity is classified as mild, moderate or severe by using the Truelove and Witts' severity index, which assesses bowel movements, heart rate, erythrocyte sedimentation rate and the presence of melaena, pyrexia or anaemia.[13,15] 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).

CLINICAL NEED AND BURDEN OF DISEASE

In the UK, it is estimated that around 146,000 people have a diagnosis of ulcerative colitis and the incidence and prevalence of ulcerative colitis has been increasing worldwide.[14, 19] IBD like ulcerative colitis can be painful, disrupt normal activities and reduce quality of life, particularly during periods of active disease.[19]

An estimated 30-60% of people with ulcerative colitis will have at least one relapse per year, with 80% of these classified as mild to moderate and 20% classified as severe.[20]

In England in 2018-19 there were 63,819 finished consultant episodes, 56,741 admissions for ulcerative colitis (ICD-10 code K51.9) which resulted in 45,366 bed days.[21]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

There are no curative therapies for inflammatory and autoimmune diseases like ulcerative colitis although clinical remission has become a realistic target in diseases like IBD.[22] Treatment for ulcerative colitis aims to relieve symptoms during a flare-up and maintain remission by preventing symptoms from returning.[17]

The British Society of Gastroenterology (BSG) guideline states that people with inflammatory bowel disease 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.[23]

The treatment strategy used is mainly based on the severity, distribution, pattern of disease, previous response to treatment and the patient's preference.[15,24] If the patient has frequent flare-ups that have a significant effect on their quality of life or if they are have a particularly severe flare-up that's not responding to medicines, surgery may be an option. Surgery for ulcerative colitis involves permanently removing the colon.[25]

CURRENT TREATMENT OPTIONS

According to NICE clinical knowledge summaries, specialist drug treatment for ulcerative colitis is generally given for induction and maintenance of remission. Detailed treatment recommendations are provided in the NICE clinical guideline[26] but the main classes of drugs used include:

- Aminosalicylates (melsalazine, balsalazide, olsalazine, sulfasalazine) [27,28]
- Corticosteroids (hydrocortisone, methylprednisolone, prednisolone, beclometasone dipropionate) [29]
- Calcineurin inhibitors (ciclosporin, tacrolimus) [30]
- Immunosuppressive therapy (azathioprine, ciclosporin, mercaptopurine, tacrolimus)[20]
- Biologic therapy (adalimumab, golimumab, infliximab, vedolizumab, tofacitinib)[25]

PLACE OF TECHNOLOGY

If licensed, filgotinib will offer an additional treatment option for the induction and maintenance of remission in adults with moderately to severely active ulcerative colitis.

CLINICAL TRIAL INFORMATION

Trial	**SELECTION1, NCT02914522, EudraCT-2016-001392-78, GS-US-418-3898; adults aged 18 to 75 years old; filgotinib vs placebo; phase III**
Sponsor	Gilead Sciences
Status	Ongoing
Source of Information	Trial Registry[1,31]
Location	19 EU countries (incl UK), USA, Canada and other countries
Design	Randomised, double-blind, placebo-controlled study
Participants	n=1351; aged 18-75; males and non-pregnant, non-lactating females; documented diagnosis of ulcerative colitis (UC) of Crohn's disease (CD) of at least 6 months; moderately to severely active UC or CD.
Schedule	There are 4 treatment arms. • Arm 1: filgotinib (dose A) for 10 weeks • Arm 2: filgotinib (dose B) for 10 weeks • Arm 3: placebo 10 weeks • Arm 4: participants who meet response or remission criteria at week 10 will continue into maintenance study and will receive filgotinib and/or placebo for 48 weeks

Follow-up	Treatment duration for the induction study is 10 weeks and for the maintenance study is 48 weeks. Follow up duration: 58 weeks
Primary Outcomes	• Proportion of participants achieving remission based on components of Mayo Clinic Score (MCS) at Week 10. [Time Frame : Week 10] • Proportion of participants achieving remission based on components of MCS at week 58
Secondary Outcomes	Time Frame : Week 10 • Proportion of patients achieving MCS remission • Proportion of participants achieving endoscopic subscore of 0 • Proportion of participants achieving histologic remission • Proportion of participants achieving MCS remission (alternative definition) at week 10. Time Frame: Week 58 • Proportion of patients achieving MCS remission • Proportion of participants achieving histologic remission • Proportion of participants achieving MCS remission (alternative definition) • Proportion of patients achieving 6-month corticosteroid-free remission based on components of MCS • Proportion of participants achieving endoscopic subscore of 0 • Pharmacokinetic plasma concentrations of filgotinib and its metabolite GS-829845 [Time frame : week 4 post dose and week 10 predose] • Pharmacokinetic plasma concentrations of filgotinib and its metabolite GS-829845 [Time Frame : Week 26 (predose or postdose) and Week 58 predose]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study primary completion date reported as Apr 2020

Trial	**SELECTIONTE**, NCT02914535, EudraCT-2016-002765-58, **GS-US-418-3899; adults aged 18 to 75 years old; filgotinib vs placebo; phase III extension**
Sponsor	Gilead Sciences
Status	Ongoing
Source of Information	Trial Registry[5,31]
Location	19 EU countries (incl UK), USA, Canada and other countries
Design	Randomised, double-blind, placebo-controlled study

Participants	n=1000 (planned); aged 18 years and older; males and non-pregnant, females; willingness to refrain from live or attenuated vaccines during the study and for 12 weeks after last dose of study drug
Schedule	5 treatment arms • Arm 1: filgotinib (dose A) for up to 336 weeks (blinded dosing) • Arm 2: filgotinib (dose B) 336 weeks (blinded dosing) • Arm 3: placebo for up to 336 weeks (blinded dosing) • Arm 4: filgotinib (dose A) for up to 336 weeks (open-label) • Arm 5: filgotinib (dose B) for up to 336 weeks (open-label)
Follow-up	Treatment duration for the induction study is 10 weeks and for the maintenance study is 48 weeks. Follow up duration: 58 weeks
Primary Outcomes	• Overall safety profile of filgotinib evaluated by proportion of participants experiencing adverse events and abnormal clinical laboratory tests [Time Frame: Up to 336 weeks plus 30 days]
Secondary Outcomes	• Change from baseline in components of mayo clinic score (MCS) [Time Frame: Baseline and up to 336 weeks]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study primary completion date reported as Nov 2026

Trial	**MANTA**, NCT03201445, EudraCT-2017-000402-38, **GS-US-418-4279; males aged 21 to 65 years; filgotinib vs placebo or standard of care; phase II**
Sponsor	Gilead Sciences
Status	Ongoing
Source of Information	Trial Registry[32,33]
Location	11 EU countries (incl UK), USA, Canada and other countries
Design	Randomised, double-blind, placebo-controlled study
Participants	n=250 (planned); aged 21-65; males; documented diagnosis of ulcerative colitis (UC) of Crohn's disease (CD) of at least 4 months; moderately to severely active UC or CD.
Schedule	4 treatment arms: Arm 1: 200mg filgotinib tablet or placebo tablet once daily for 13 weeks in part A and then a further 13 weeks in part B if they meet specified parameters. Arm 2: 200mg filgotinib tablet for up to 13 weeks Arm 3: Standard of care therapy Arm 4: 200mg filgotinib tablet or placebo tablet administered orally once daily for up to 195 weeks.
Follow-up	26 weeks

Primary Outcomes	• Proportion of participants with a >50% decrease from baseline in sperm concentration at week 13 [Time Frame : week 13]
Secondary Outcomes	Time Frame : week 13 • Change from baseline in percent motile sperm • Change from baseline in total sperm count • Change from baseline in sperm concentration • Change from baseline in ejaculate volume • Change from baseline in percent normal sperm morphology Time Frame : week 26 • Proportion of participants with a ⩾ 50% decrease from baseline in sperm concentration • Chance from baseline in percent motile sperm • Change from baseline in total sperm count • Change from baseline in sperm concentration • Change from baseline in ejaculate volume • Change from baseline in percent normal sperm morphology
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study primary completion date reported as Jan 2021

ESTIMATED COST

The cost of filgotinib is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Ustekinumab for treating moderately to severely active ulcerative colitis (ID1511). Expected March 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

- British Society of Gastroenterology. Consensus guidelines on the management of inflammatory bowel diseases in adults. 2019.[34]
- European Crohn's and Colitis Organisation. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative colitis. Part 2: Current Management. 2017.[24]

ADDITIONAL INFORMATION

Gilead Sciences Ltd did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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