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HEALTH TECHNOLOGY BRIEFING
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Etrolizumab for treating moderately to severely active ulcerative colitis in adults

NIHRIO ID	7164	**NICE ID**	10347
Developer/Company	Roche Products Ltd	**UKPS ID**	645041

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Etrolizumab is in clinical development for the treatment of adult patients with moderately to severely active ulcerative colitis. Ulcerative colitis is a long-term condition where the colon and rectum (parts of the bowel), become inflamed. Small ulcers can develop on the colon's lining, which can cause rectal bleeding and recurring diarrhoea. The symptoms of ulcerative colitis 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).

Etrolizumab is a new monoclonal antibody (an immune protein) delivered by subcutaneous injection. The treatment works by targeting molecules called integrins to control the immune response and prevent the accumulation of immune molecules, which cause inflammation in individuals with a form of ulcerative colitis where inflammation is not mediated by a signalling protein called tumour necrosis factors (TNF) alpha ('non-TNF-α') and who are therefore intolerant to TNF blockers. This represents a new target group as current therapies focus mainly on anti-TNF inflammation. In one study, etrolizumab showed a greater reduction of intestinal lymphocyte infiltration in comparison to standard treatment.

PROPOSED INDICATION

Treatment of moderate to severe active ulcerative colitis in adult patients.[a]

TECHNOLOGY

DESCRIPTION

Etrolizumab (PRO145223, RG7413, rhuMAb beta7) is a humanised, monoclonal antibody targeting β7 subunit of the heterodimeric integrins α4β7 and αEβ7. Cell accumulation in the gut is controlled by cell trafficking processes including gut homing and intestinal retention. Adhesion of lymphocytes dependent on activated α4β7 integrin to mucosal vascular address in cell adhesion molecule (MAdCAM)-1 expressed on high-endothelial venules in the gut has been identified as an important mechanism of gut homing. In addition to α4, the β7 integrin monomer also pairs with αE to form the αEβ7 heterodimer, which has been shown to control epithelial retention of homed lymphocytes in intestinal inflammation. Etrolizumab, the anti-β7 antibody, blocks both α4β7-mediated gut homing as well as αEβ7-controlled retention.[1,2,3]

Etrolizumab is currently in clinical development for the treatment of moderate to severe ulcerative colitis. In the phase III clinical trials, HICKORY (NCT02100696), COTTONWOOD (NCT02118584), HIBISCUS I/II (NCT02163759, NCT0217142) and GARDENIA (NCT02136069), participants receive 105mg of etrolizumab through a subcutaneous injection, once every 4 weeks.[4,5,6,7,8]

INNOVATION AND/OR ADVANTAGES

Etrolizumab is a new biological entity. Anti-integrin therapy offers a different mechanistic target than anti-tumour necrosis factor (TNF) therapy, affording the opportunity to modulate inflammation in patients who may suffer from 'non-TNF-α' mediated inflammation. By targeting integrins, it is possible that symptoms can be improved and inflammation reduced in patients who are primary non-responders to anti-TNF therapy as well as those who lose response to anti-TNF therapy over time. Etrolizumab is designed as a dual-action anti-integrin; by specifically targeting the β7 integrin subunit, etrolizumab may inhibit both the α4β7 integrin and the αEβ7 integrin.[2,3]
In vivo research comparing vedolizumab and etrolizumab found that etrolizumab seems to offer superior reduction of intestinal lymphocyte infiltration especially concerning CD8+ and Th9 cells.[9]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

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

Etrolizumab is currently in phase III trials for the treatment of Crohn's disease.[10,11]

[a] Information provided by Roche Products Ltd on UK PharmaScan

PATIENT GROUP

DISEASE BACKGROUND

Ulcerative colitis (UC) is one of the two major forms of Inflammatory Bowel Disease (IBD): the other being Crohn's disease. It is a chronic inflammatory disease of the colon and the rectum characterised by ulceration, rectal bleeding and recurring diarrhoea.[12] Although it is described as chronic, there are often periods where a patient will have no symptoms; sustained remission of ulcerative colitis is around 20-30% with current available treatments.[13]

The cause of UC is not clear, however, it is believed to be caused by a combination of genetic and environmental factors and an abnormal reaction of the immune system. UC is thought to be an autoimmune disease where the body recognises normal gut bacteria as foreign and produces an immune response against them causing redness and severe inflammation in an attempt to protect the body. Genetic factors may play a role in UC as studies have shown that 1 in 4 people who have UC have a family history of the disease.[14] Genes such as *ABCB1* and *IL23R* are thought to be implicated in the disease pathway.[15] Viruses, bacteria, diet and stress have all been suggested as environmental triggers, but there is no definite evidence that any one of these factors is the cause of UC.[16]

The most common symptoms of UC include abdominal pain, cramping and frequency diarrhoea often with blood, pus or mucus. Nausea, loss of appetite, fever and fatigue are also common symptoms. As UC can cause bleeding, anaemia is often seen in patients and people can experience significant weight loss due to an inability to absorb fluids and nutrients. Those who suffer the most severe symptoms may need to be hospitalised.[16]

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

UC is the most common inflammatory bowel disease and it is estimated that UC affects around 1 in 420 people in the UK.[16] UC has an incidence of 10 per 100,000 annually and a prevalence of 243 per 100,000.[13] This totals around 146,000 UC patients in the UK with a diagnosis.

UC can present at any age but tends to have highest incidence in a bimodal distribution, with peaks between the ages of 15 and 25 years and between 55 and 65 years.[13] Around 30-60% will have at least one relapse per year with 20% of these being classified as severe.[13]

According to hospital episode statistics for England in 2018-19 there were a total of 103,050 finished consultant episodes for ulcerative colitis (ICD-10 code K51) recorded as primary diagnosis of which 91,021 were recorded as admissions with a total of 79,830 day cases.[17]

The company has provided an estimated eligible patient population of 71,000.[b]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The aim of treatment in active disease is to address symptoms of urgency, frequency and rectal bleeding, and thereafter to maintain remission.[18]

[b] Information provided by Roche Products Ltd on UK PharmaScan

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.[18]

CURRENT TREATMENT OPTIONS

In the UK, NICE currently recommends the following treatment options for moderate to severe UC:[19]

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.

Budesonide multimatrix

- NICE has published an evidence summary on the use of budesonide multimatrix for the treatment of UC.

PLACE OF TECHNOLOGY

If licensed, etrolizumab will offer an additional treatment option for patients who have had an inadequate response with, lost response to, or were intolerant to immunosuppressants or corticosteroids, or a TNF-blocker.[c]

CLINICAL TRIAL SUMMARY INFORMATION

Trial	**HICKORY;** NCT02100696, 2013-004278-88 (EudraCT Number); Phase III, Double-blind, Placebo-Controlled, Multicenter Study of the Efficacy and Safety of Etrolizumab During Induction and Maintenance in Patients With Moderate to Severe Active Ulcerative Colitis Who Have Been Previously Exposed to Tumour Necrosis Factor (TNF) Inhibitors **Phase III** **Locations: EU (incl UK), USA, Canada and other countries**
Trial design	Randomized, parallel assignment, double blind, placebo-controlled study
Population	N=609; aged 18 to 80 years; diagnosis of ulcerative colitis (UC) established at least 3 months before day 1, moderate to severe UC determined by the Mayo Clinic Score (MCS); treatment within 5 years prior to screening with one or two induction regimens that contain TNF inhibitors See trial record for full list of inclusion and exclusion criteria
Intervention(s)	105mg etrolizumab, subcutaneous injection every 4 weeks (Q4W) up to week 14 during the induction phase. Clinical responders re-randomised to the experimental arm will receive 105mg, subcutaneous injection Q4W from weeks 16 to 66 during the maintenance phase
Comparator(s)	Matched placebo
Outcome(s)	• Induction Phase: Percentage of Participants with Remission at Week 14, as Determined by the MCS (Time Frame: Week 14) • Maintenance Phase: Percentage of Participants with Remission at Week 66 Among Participants Who Had Achieved a Clinical Response at Week 14, as Determined by the MCS (Time Frame: Week 66) See trial record for full list of other outcomes
Results (efficacy)	• At week 14, 22% (21/97), 23% (22/97), and 8% (8/97) of patients achieved resolution of neutrophilic inflammation based on either NHI or RHI/Geboes,

[c] Information provided by Roche Products Ltd on UK PharmaScan

	endoscopic improvement (ES ≤ 1), and endoscopic remission (ES = 0), respectively • Among patients with endoscopic improvement and endoscopic remission, neutrophilic resolution was achieved in 55% (12/22) and 75% (6/8) of patients, respectively • There was weak to no association between ΔNHI/ΔRHI/ΔES and Δfecal calprotectin (ρ = −0.02 to 0.38), ΔC-reactive protein (ρ = 0.03 to 0.07), Δalbumin (ρ = −0.19 to −0.10), Δhemoglobin (ρ = −0.22 to −0.19), and Δsegmented neutrophils in the blood (ρ = −0.06 to 0.01) • Weak correlations were observed between ΔNHI/ΔRHI and ΔES (ρ = 0.26–0.27), Δrectal bleeding (ρ = 0.24–0.28), and Δstool frequency (ρ = 0.40–0.42). • Correlations between NHI, RHI/Geboes, and ES with symptomatic outcomes were weak (κ = 0.28–0.45). • Difference in the mean grouped by achievement of ΔMCS ≥3 suggests MCIDs in ΔNHI and ΔRHI of 1.2 and 8.6, respectively[20]
Results (safety)	-

Trial	**COTTONWOOD;** NCT02118584; 2013-004435-72 (EudraCT Number); An Open-Label Extension and Safety Monitoring Study of Moderate to Severe Ulcerative Colitis Patients Previously Enrolled in Etrolizumab Phase II/III Studies **Phase III** **Locations: EU (incl UK), USA, Canada and other countries**
Trial design	Single Group Assignment; Open Label
Population	N= ~2100 (planned); 18 years and older; Open-label Extension (OLE): participants previously enrolled in the Phase II OLE study or Phase III controlled studies who meet the eligibility criteria for open-label etrolizumab for those studies; Safety Monitoring: participants who participated in one of the etrolizumab Phase III studies and are not eligible or willing to enter Part 1 (OLE), participants who transfer from Part 1 (OLE).
Intervention(s)	105mg etrolizumab, subcutaneously every 4 weeks for up to 9 years
Comparator(s)	No comparator
Outcome(s)	• Percentage of Participants With Clinical Remission as Determined by the Partial Mayo Clinic Score (pMCS) - Part 1 [Time Frame: Baseline up to 9 years (assessed at Baseline, Week 4, 8, 12 thereafter every 12 weeks up to 9 years after the first participant is enrolled or until commercial availability, whichever is earlier, or until sponsor's decision to terminate the study)] • Percentage of Participants With Remission as Determined by the Mayo Clinic Score (MCS) - Part 1 [Time Frame: Week 108]

	• Percentage of Participants With Endoscopic Remission [Time Frame: Week 108] • Percentage of Participants With Anti-therapeutic Antibodies to Etrolizumab - Part 1 [Time Frame: Baseline, Week 12, every 48 weeks, week 108, at early withdrawal from treatment up to 9 years after first participant enrolled or until commercial availability, whichever is earlier, or until sponsor's decision to terminate the study)] • Percentage of Participants With Adverse Events - Part 1 [Time Frame: Baseline up to 9 years after the first participant is enrolled or until commercial availability, whichever is earlier, or until the Sponsor's decision to terminate the study] • Percentage of Participants With Progressive Multifocal Leukoencephalopathy (PML) - Part 2 [Time Frame: 104 weeks] • Change From Baseline in pMCS at Year 9 [Time Frame: Baseline, Year 9]
Results (efficacy)	-
Results (safety)	-

Trial	**HIBISCUS I;** NCT02163759; 2013-004279-11 (EudraCT Number); Phase III, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy (Induction of Remission) and Safety of Etrolizumab Compared With Adalimumab and Placebo in Patients With Moderate to Severe Ulcerative Colitis Who Are Naive to TNF Inhibitors **Phase III** **Locations: EU (incl UK), USA, Canada and other countries**
Trial design	Randomized, parallel assignment, double blind, active comparator and placebo-controlled study
Population	N=358; aged 18 to 80; diagnosis of UC established at least 3 months before day 1, moderate to severe UC determined by the Mayo Clinic Score; naïve to treatment with TNF inhibitor therapy; an inadequate response, loss of response or intolerance to prior corticosteroid and/or immunosuppressant treatment
Intervention(s)	• Etrolizumab, subcutaneously, 105mg Q4W
Comparator(s)	• Adalimumab, subcutaneously, 160mg at week 0. 80mg at week 2, 40mg at weeks 4, 6 and 8. • Etrolizumab placebo, subcutaneously, (vs Adalimumab), Q4W matched to etrolizumab • Adalimumab placebo, subcutaneously, matched to adaliumamab at weeks 0, 2, 4, 6 and 8.
Outcome(s)	• Percentage of participants with induction of remission with Etrolizumab compared with placebo at Week 10, as determined by the MCS See trial record for full list of other outcomes
Results (efficacy)	-

Results (safety)	-

Trial	**HIBISCUS II;** NCT02171429; 2013-004277-27 (Eudra CT Number); Phase III, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy (Induction of Remission) and Safety of Etrolizumab Compared With Adalimumab and Placebo in Patients With Moderate to Severe Ulcerative Colitis Who Are Naive to TNF Inhibitors **Phase III** **Locations: EU (incl UK), USA, Canada and other countries**
Trial design	Randomized, parallel assignment, double blinded, active comparator and placebo controlled
Population	N=358; aged 18-80 years; diagnosis of UC established at least 3 months before day 1, moderate to severe UC determined by the Mayo Clinic Score (MCS); naïve to treatment with TNF inhibitor therapy; an inadequate response, loss of response or intolerance to prior corticosteroid and/or immunosuppressant treatment
Intervention(s)	• Etrolizumab, subcutaneously, 105mg Q4W
Comparator(s)	• Adalimumab, subcutaneously, 160mg at week 0. 80mg at week 2, 40mg at weeks 4, 6 and 8 • Etrolizumab placebo, subcutaneously, (vs Adalimumab) Q4W • Adalimumab placebo, subcutaneously, (vs Etrolizumab), matched to adalimumab at weeks 0, 2 , 4 ,6 and 8
Outcome(s)	• Percentage of Participants With Induction of Remission With Etrolizumab Compared With Placebo at Week 10, as Determined by the Mayo Clinic Score (MCS) See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**GARDENIA;** NCT02136069; 2013-004282-14 (EudraCT Number); Phase III, Randomized, Multicenter Double-Blind, Double Dummy Study to Evaluate the Efficacy and Safety of Etrolizumab Compared With Infliximab in Patients With Moderate to Severe Active Ulcerative Colitis Who Are Naive to TNF Inhibitors **Phase III** **Locations: EU (incl UK), USA, Canada and other countries**
Trial design	Randomized, double blind, double dummy, parallel group study and active comparator
Population	N=397; 18-80; moderate to severe UC determined by the Mayo Clinic Score; naïve to treatment with any anti-TNF inhibitor therapy; inadequate response to or intolerance of prior corticosteroid and/or immunosuppressant treatment

Intervention(s)	• Etrolizumab, 105mg, subcutaneously Q4W until week 52
Comparator(s)	• Infliximab, 5mg/kg, intravenously at weeks 0, 2 and 6 then every 8 weeks until week 46 • Intravenous placebo (vs Etrolizumab) administered at weeks 0, 2 and 6 then every 8 weeks until week 46 • Subcutaneous placebo (vs Infliximab) administered Q4W until week 52
Outcome(s)	• Percentage of participants with both clinical response at week 10 and clinical remission at week 54 See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The estimated cost of etrolizumab is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Ustekinumab for treating moderately to severely active ulcerative colitis. (GID-TA10434). Expected June 2020.
- NICE technology appraisal guidance. Tofacitinib for moderately to severely active ulcerative colitis. (TA547). November 2018
- NICE technology appraisal guidance. Vedolizumab for treating moderately to severely active ulcerative colitis. (TA342). June 2015
- NICE technology appraisal guidance. Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy. (TA329). February 2015
- NICE technology appraisal guidance. Infliximab for acute exacerbations of ulcerative colitis. (TA163). December 2008
- NICE guidance. Ulcerative colitis: management. (NG130). May 2019.
- NICE quality standard. Inflammatory bowel disease (QS81). February 2015.
- NICE diagnostic guidance. Faecal calprotectin diagnostic tests for inflammatory diseases of the bowel (DG11). October 2013.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

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

OTHER GUIDANCE

- NICE Clinical Knowledge Summary. Ulcerative colitis. April 2019.[21]

- British Society of Gastroenterology. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. 2019.[22]
- European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA). ECCO-EFCCA Patient Guidelines on Ulcerative Colitis (UC). 2014.[23]

ADDITIONAL INFORMATION

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