NIHR | Innovation Observatory

HEALTH TECHNOLOGY BRIEFING
MAY 2021

Etrolizumab for Crohn's Disease

NIHRIO ID	11482	**NICE ID**	10349
Developer/Company	Roche Products Ltd	**UKPS ID**	645040

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

SUMMARY

Etrolizumab is being developed for adults with moderate to severe Crohn's disease (CD). CD is an inflammatory bowel disease (IBD) that can affect any part of the digestive system. It causes inflammation, which results in difficulty absorbing nutrients from food. Symptoms of moderate to severe CD include vomiting, abdominal pain, loss of weight, frequent diarrhoea, and digestive system obstruction. There is no cure for CD and current treatments focus on lessening and managing symptoms of the condition.

Etrolizumab is a new biological entity which is given as an under the skin injection. This treatment prevents cell death caused by inflammation. It does so be blocking two receptors that are thought to have a role in IBD. If licenced, etrolizumab would offer an additional treatment option for patients with moderate to severe CD that cannot have other current treatments, or where treatments have stopped working.

PROPOSED INDICATION

Etrolizumab is indicated for the treatment of moderately to severely active Crohn's disease (CD) in adults.[a]

TECHNOLOGY

DESCRIPTION

Etrolizumab (PRO145223[1], RG7413, rhuMAb Beta7) is a humanised monoclonal antibody (IgG1 MAb) targeting the β7 integrin subunit on gut-selective inflammatory cells. It is a next-generation anti-integrin with dual action, binding to two integrin receptors, α4β7 and αEβ7. These receptors are required for trafficking and retention in lymphocytes in the gastrointestinal tract and appear to play a role in inflammatory bowel diseases.[2-4] Anti-integrins are considered an effective treatment for CD, even for patients refractory to other therapies.[4]

Etrolizumab is in clinical development for moderate to severe CD following an intolerance, loss of response or failure to respond to treatment with either corticosteroids, immunosuppressants, or anti-TNF therapy.[a] In the phase III clinical trial (BERGAMOT; NCT02403323) patients receive either 105mg etrolizumab every four weeks or 210mg etrolizumab at Weeks 0, 2, 4, 8 and 12 within a 14-week induction phase, by subcutaneous injection, before progressing to the maintenance phase. Maintenance phase is 105mg etrolizumab, administered subcutaneously every four weeks.[b]

INNOVATION AND/OR ADVANTAGES

Etrolizumab is a new biological entity.[1] 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.[5]

Anti-integrin therapy offers a different mechanistic target than anti-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.[4]

For patients with moderate-severe ulcerative colitis (UC) that are anti-tumour necrosis factor (TNF) intolerant or refractory, which falls under the same umbrella of inflammatory bowel disease (IBD) as CD, there were clinically significant signs of improvement for patients when treated with etrolizumab.[3,6,7]

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

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 II and III clinical development for UC.[8]

PATIENT GROUP

DISEASE BACKGROUND

Inflammatory bowel disease (IBD) is an umbrella term for describing long-term conditions that involve inflammation of the digestive system: UC and CD. These two conditions are separated in terms of the location of inflammation, with UC only affecting the colon (large intestine), whereas CD can affect any part of the digestive system.[7]

CD causes inflammation and ulceration, which affects food digestion, nutrient absorption, and waste elimination. CD most often develops in the ileum (the end of the small intestine) or the colon, and can produce inflamed patches with healthy gut in between.[9] There is no cure for CD so treatment options focus on managing and relieving symptoms.[9,10] Patients may have periods of time when they are not suffering from symptoms (remission), or have flare-ups of symptoms (relapses).[9]

Main symptoms of CD are abdominal pain, diarrhoea, weight loss and fatigue. Other symptoms include high temperatures and feverishness, mouth ulcers, anaemia (reduced red blood cells), generally feeling unwell, vomiting, joint pains, sore eyes, and patches of painful, red and swollen skin.[9,11] CD can sometimes cause other associated issues such as strictures (healing and scarring that narrows the tract), perforations (holes in the tract wall) and fistulas (a tunnel between the gut and skin/another organ).[9] Mild to moderate CD symptoms are characterised by diarrhoea and abdominal pain, whereas moderate to severe include intermitted vomiting, abdominal pain, >10% weight loss and abdominal mass without overt obstruction. Very severe CD includes persistent symptoms despite appropriate treatment, high fever, persistent vomiting and evidence of intestinal obstruction or abscesses.[12]

CD can occur in all age groups however it usually develops between the ages of 10 and 40 years old. CD is more common in urban areas, and in northern, developed countries such as Northern Europe, particularly amongst white people of European descent. CD is more common in smokers, and slightly more common in women than men.[13] The exact cause of CD is unknown but there are several factors that could contribute to its development, including: inheritance (people are more likely to get CD if a close family member has it), immune response issues, smoking, gut viruses, abnormal balance of gut bacteria, and stress.[9,10]

CLINICAL NEED AND BURDEN OF DISEASE

It is estimated that CD affects about one in every 650 people in the UK.[13] The annual estimated cost for a relapsed patient with mild-to-moderate CD is £2,903.24, and for those with acute severe disease relapse is it £10,760.23.[14]

In England, 2019-20, there were 139,303 finished consultant episodes (FCE) for patients with a primary diagnosis of CD (ICD-10 code K50) resulting in 90,148 FCE bed days and 114,365 day cases.[15]

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.[16]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The aims of CD treatment are to achieve remission, maintain remission and control inflammation.[17] Options include steroids, liquid diet, antibiotics, immunosuppressants, anti-inflammatories, biological medicines and surgery.[17,18]

CURRENT TREATMENT OPTIONS

Pharmacological treatment options for CD are as follows:[17,18]

- Anti-inflammatories, such as sulfasalazine, mesalamine and olsalazine
- Steroids, such as prednisolone
- Immunosuppressants, such as azathioprine, mercaptopurine and methotrexate
- Biological medicines, such as adalimumab, infliximab, vedolizumab and ustekinumab
- Antibiotics, such as metronidazole and ciprofloxacin

PLACE OF TECHNOLOGY

If licenced, 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 INFORMATION

Trial	**BERGAMOT; NCT02394028; EudraCT 2014-003824-36; A Phase III, Randomized, Double-Blind, Placebo-Controlled,**	**JUNIPER; NCT02403323; EudraCT 2014-003855-76; An Open-Label Extension and Safety Monitoring Study of Patients**

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

	Multicenter Study to Evaluate the Efficacy and Safety of Etrolizumab as an Induction And Maintenance Treatment For Patients With Moderately to Severely Active Crohn's Disease **Phase III – Recruiting** **Location(s):** EU (including UK), USA, Canada and other countries **Primary completion date:** July 2021	**With Moderately to Severely Active Crohn's Disease Previously Enrolled in the Etrolizumab Phase III Protocol GA29144** **Phase III – Recruiting** **Location(s):** EU (including UK), USA, Canada and other countries **Primary completion date:** May 2026
Trial design	Randomised, double-blind, parallel assignment	Open label, single group assignment
Population	N=1,150 (estimated); aged 18 to 80 years old; moderately to severely active CD; intolerance, refractory disease, or not response to corticosteroids (CS), immunosuppressants (IS), or anti-TNF therapy within 5 years from screening	N=900 (estimated); aged 18 years and older; patients previously enrolled in etrolizumab Phase III study GA29144 (NCT02394028) who meet the eligibility criteria for open-label etrolizumab as described in the protocol
Intervention(s)	105mg or 210mg of etrolizumab will be administered, by subcutaneous (SC) injection, as per regimen specified in individual arms. See trial record for full list of interventions.	105 mg etrolizumab subcutaneous administration once every 4 weeks.
Comparator(s)	Matched placebo	No comparator
Outcome(s)	• Induction Phase: Percentage of Participants with Clinical Remission at Week 14 [Time Frame: Baseline and Week 14] Clinical remission is defined as liquid/soft stool frequency (SF) mean daily score less than or equal (≤)3 and abdominal pain mean daily score ≤1, with no worsening in either subscore compared to baseline, averaged over the 7 days prior to visit. • Induction Phase: Percentage of Participants with Endoscopic Improvement at Week 14 [Time Frame: Baseline and Week 14] Endoscopic improvement is defined as 50 percent (%) reduction from baseline in	Number of Participants with Crohn's Disease Activity Index (CDAI) Remission Over Time [Time Frame: Weeks 0, 12, 24, and every 12 weeks thereafter until study completion or early withdrawal, commercial availability of etrolizumab, or study termination, whichever is earliest (up to approximately 10 years)]. See trial record for full list of other outcomes.

	Simplified Endoscopic Index for Crohn's Disease (SES-CD) score. • Maintenance Phase: Percentage of Participants with Clinical Remission at Week 66 [Time Frame: Baseline and Week 66] Clinical remission is defined as SF mean daily score ≤3 and abdominal pain mean daily score ≤1, with no worsening in either subscore compared to baseline, averaged over the 7 days prior to visit. • Maintenance Phase: Percentage of Participants with Endoscopic Improvement at Week 66 [Time Frame: Baseline and Week 66] Endoscopic improvement is defined as 50% reduction from baseline in SES-CD score. See trial record for full list of other outcomes.	
Results (efficacy)	-	-
Results (safety)	-	-

ESTIMATED COST

The estimated cost etrolizumab is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- 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.[19]
- NICE Clinical Knowledge Summary. Crohn's disease. January 2019.[20]
- ACG Clinical Guideline: Management of Crohn's Disease in Adults. 2018.[21]

ADDITIONAL INFORMATION

REFERENCES

1 AdisInsight. *Etrolizumab.* 2021. Available from: https://adisinsight.springer.com/drugs/800026082 [Accessed 05 May 2021].

2 Roche. *Product Development Portfolio - RG7413 etrolizumab.* 2021. Available from: https://www.roche.com/research_and_development/who_we_are_how_we_work/pipeline.htm [Accessed 28 Apr 2021].

3 Sandborn WJ, Vermeire S, Tyrrell H, Hassanali A, Lacey S, Tole S, et al. Etrolizumab for the Treatment of Ulcerative Colitis and Crohn's Disease: An Overview of the Phase 3 Clinical Program. *Advances in therapy*. 2020;37(7):3417-31. Available from: https://doi.org/10.1007/s12325-020-01366-2.

4 McLean LP, Cross RK. Integrin antagonists as potential therapeutic options for the treatment of Crohn's disease. *Expert opinion on investigational drugs*. 2016;25(3):263-73. Available from: https://doi.org/10.1517/13543784.2016.1148137.

5 Zundler S, Schillinger D, Fischer A, Atreya R, López-Posadas R, Watson A, et al. Su1966 - Differential Effects of Vedolizumab and Etrolizumab-S on UC CD4+ and CD8+ T Cell Trafficking in the Inflamed gut in vivo. *Gastroenterology*. 2017 Apr;152(5):Supp. 1, S614. Available from: http://dx.doi.org/10.1016/S0016-5085(17)32181-9.

6 Hayee Bh, Rubin D, Feagan B, Oh YS, Arulmani U, Tyrrell H, et al. PWE-071 Etrolizumab induction in moderate/severe anti-TNF intolerant/refractory (IR) UC: the hickory open-label induction (OLI) trial. *Gut*. 2018;67(Suppl 1):A102-A3. Available from: http://dx.doi.org/10.1136/gutjnl-2018-BSGAbstracts.203.

7 NHS. *Inflammatory Bowel Disease.* 2020. Available from: https://www.nhs.uk/conditions/inflammatory-bowel-disease/ [Accessed 29 Apr 2021].

8 Clinicaltrials.gov. *Phase II and III clinical trials for etrolizumab.* Available from: https://clinicaltrials.gov/ct2/results?term=etrolizumab&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 28 Apr 2021].

9 Crohn's & Colitis UK. *Crohn's Disease.* 2016. Available from: https://www.crohnsandcolitis.org.uk/about-crohns-and-colitis/publications/crohns-disease [Accessed 29 Apr 2021].

10 NHS. *Crohn's Disease - Overview.* 2018. Available from: https://www.nhs.uk/conditions/crohns-disease/ [Accessed 28 Apr 2021].
11 NHS. *Crohn's Disease - Symptoms.* 2018. Available from: https://www.nhs.uk/conditions/crohns-disease/symptoms/ [Accessed 29 Apr 2021].
12 Crohn's & Colitis. *What are the symptoms of Crohn's disease?* 2020. Available from: https://www.crohnsandcolitis.com/crohns/disease-symptoms [Accessed 29 Apr 2021].
13 Crohn's & Colitis UK. *How common is Crohn's Disease?* 2016. Available from: https://www.crohnsandcolitis.org.uk/about-crohns-and-colitis/publications/crohns-disease#:~:text=How%20common%20is%20Crohn's%20Disease,650%20people%20in%20the%20UK [Accessed 28 Apr 2021].
14 Ghosh N, Premchand P. A UK cost of care model for inflammatory bowel disease. *Frontline gastroenterology*. 2015;6(3):169-74. Available from: https://doi.org/10.1136/flgastro-2014-100514.
15 NHS Digital. *Hospital Episode Statistics for England. Admitted Patient Care statistics, 2019-20.* Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2019-20 [Accessed 25 Mar 2021].
16 King D, Reulen RC, Thomas T, Chandan JS, Thayakaran R, Subramanian A, et al. Changing patterns in the epidemiology and outcomes of inflammatory bowel disease in the United Kingdom: 2000-2018. *Alimentary Pharmacology & Therapeutics*. 2020;51(10):922-34. Available from: https://doi.org/10.1111/apt.15701.
17 Crohn's & Colitis. *Crohn's disease treatment.* 2020. Available from: https://www.crohnsandcolitis.com/crohns/disease-treatment [Accessed 29 Apr 2021].
18 NHS. *Crohn's Disease - Treatment.* 2018. Available from: https://www.nhs.uk/conditions/crohns-disease/treatment/ [Accessed 29 Apr 2021].
19 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. *Gut*. 2019;68(Suppl 3):s1-s106. Available from: https://doi.org/10.1136/gutjnl-2019-318484.
20 National Institute for Health and Care Excellence (NICE). *Crohn's disease.* 2020. Available from: https://cks.nice.org.uk/topics/crohns-disease/#!topicSummary [Accessed 29 Apr 2021].
21 Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG Clinical Guideline: Management of Crohn's Disease in Adults. *Official journal of the American College of Gastroenterology | ACG*. 2018;113(4):481-517. Available from: https://doi.org/10.1038/ajg.2018.27.

NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.