NIHR | Innovation Observatory

HEALTH TECHNOLOGY BRIEFING
JUNE 2021

Mirikizumab for the treatment of moderately to severely active ulcerative colitis

NIHRIO ID	24192	**NICE ID**	10393
Developer/Company	Eli Lilly and Company Ltd.	**UKPS ID**	652450

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Mirikizumab is in clinical development for the treatment of adult patients with moderately to severely active ulcerative colitis (UC). UC 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). Additional therapies are required as some therapies do no induce remission in some patients.

Mirikizumab, which is administered intravenously (IV), is a new type of antibody that binds to an inflammatory protein called interleukin 23, inhibiting its activity which prevents the triggering of inflammation. Therefore, if licensed, mirikizumab would offer an additional treatment option for patients with moderately to severely active UC.

PROPOSED INDICATION

Treatment of adult patients with moderate to severe active UC who have had an inadequate response to, loss of response, or intolerant to conventional or biologic therapy for UC.[1,2]

TECHNOLOGY

DESCRIPTION

Mirikizumab (LY3074828) is a humanised immunoglobulin G4–variant monoclonal antibody that binds to the p19 subunit of interleukin (IL)-23, preventing its binding to IL-23R, thus inhibiting its activity. IL-23 is composed of two submits; p40 (which is also found in IL 12) and p19 (specific for IL 23). IL-23 plays a key role in the maintenance and amplification of T helper 17 (Th17) cells and the stimulation of many innate immune cells, which are important in the pathogenesis of chronic inflammatory diseases, including UC.[3]

Mirikizumab is currently in phase III clinical development for the treatment of moderate to severe UC.[1,2] Mirikizumab treatment will be split into an induction and maintenance phase; induction IV mirikizumab and maintenance with subcutaneous (SC) mirikizumab.

INNOVATION AND/OR ADVANTAGES

Mirikizumab is a new chemical entity. There are currently no monoclonal p19-directed antibodies recommended by the National Institute for Health and Care Excellence (NICE) for the treatment of moderately to severely active UC. It is thought that more selective targeting of the p19 subunit of IL-23 can provide better outcomes for patients with moderate to severe UC.[3,4]

Results from the phase II clinical study, NCT02589665, showed mirikizumab to have a favourable benefit-vs-risk profile for treatment of UC.[3] Results from the phase III study, NCT03518086, demonstrate that mirikizumab reduces bowel urgency.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Mirikizumab is not currently licensed for any other indications in the EU/UK.

Mirikizumab is currently in phase II/III trials for the treatment of ulcerative colitis in children, crohn's disease and plaque psoriasis.[6]

PATIENT GROUP

DISEASE BACKGROUND

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.[7] 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.[8]

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.[9] Genes including ATP-binding cassette sub-family B member 1 (ABCB1) and IL23R are thought to be implicated in the disease pathway.[10] 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.[11]

The most common symptoms of UC include abdominal pain, cramping and frequent 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.[11]

UC is a lifelong disease associated with significant morbidity, and the potential for social and psychological sequelae particularly if poorly controlled.[8]

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.[11] UC has an incidence of 10 per 100,000 annually and a prevalence of 243 per 100,000.[8] This totals around 146,000 UC patients in the UK with a diagnosis with about 52% of these patients having moderate to severe cases.[12]

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. Around 30-60% will have at least one relapse per year with 20% of these being classified as severe.[8]

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.[13]

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.[12]

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.[12]

CURRENT TREATMENT OPTIONS

In the UK, NICE currently recommends the following treatment options for moderate to severe UC:[14]

- Ustekinumab
- Tofacitinib
- Vedolizumab
- Infliximab, adalimumab and golimumab

PLACE OF TECHNOLOGY

If licensed, mirikizumab will provide an additional treatment option for patients with moderately to severely active ulcerative colitis who have failed prior therapy.

CLINICAL TRIAL INFORMATION

Trial	**LUCENT 1;** NCT03518086; 2017-003229-14; Phase 3, Multicentre, Randomised, Double-Blind, Parallel, Placebo-Controlled Induction Study of Mirikizumab in Conventional-Failed and Biologic-Failed Patients With Moderately to Severely Active Ulcerative Colitis **Phase III** - ongoing **Location(s):** 17 EU countries, UK, US, Canada and other countries **Study completion date:** January 2021
Trial design	Randomised, parallel assignment, double-blinded, placebo-controlled
Population	N = 1160; 18-80 years old; diagnosis of UC for at least 3 months prior to baseline; demonstrated an inadequate response to, a loss of response to, or an intolerance to conventional or to biologic therapy for UC.
Intervention(s)	Mirikizumab IV
Comparator(s)	Matched placebo
Outcome(s)	Percentage of Participants in Clinical Remission [Time Frame: Week 12]. Clinical remission based on the modified Mayo Score (MMS). See trial record for full list of other outcomes
Results (efficacy)	• Mirikizumab met the primary endpoint of clinical remission at Week 12 compared to placebo ($p<0.0001$). Clinical remission is met when inflammation of the colon is controlled or resolved, leading to normalization or near-normalization of symptoms such as stool frequency and bleeding. • Mirikizumab also achieved all key secondary endpoints compared to placebo at Week 12 in patients with UC with highly statistically significant p-values, including reduced bowel urgency, clinical response, endoscopic remission, symptomatic remission, and improvement in endoscopic histologic inflammation. In addition, mirikizumab demonstrated rapid improvement in patient symptoms as early as four weeks after initiating treatment. Mirikizumab also reduced symptoms among patients who had previously not responded to or stopped responding to biologic and/or Janus kinase (JAK) inhibitor therapies.[5]
Results (safety)	• The incidence of treatment-emergent adverse events (AEs) and serious AEs among patients treated with

	mirikizumab was consistent with that of the previous Phase 2 mirikizumab study in UC and studies with the anti-IL-23p19 antibody class. • The most common AEs included nasopharyngitis, anaemia and headache for both placebo and mirikizumab-treated patients.[5]

Trial	**LUCENT 2;** NCT03524092; 2017-003238-96; Phase 3, Multicentre, Randomised, Double-Blind, Parallel-Arm, Placebo-Controlled Maintenance Study of Mirikizumab in Patients With Moderately to Severely Active Ulcerative Colitis **Phase III** - ongoing **Location(s):** 16 EU countries, UK, US, Canada and other countries **Primary completion date:** November 2021
Trial design	Randomised, parallel assignment, double-blinded, placebo-controlled
Population	N = 1044; 18 to 80 years old; have completed Study AMAN (NCT03518086), with at least 1 study drug administration and without early termination of study
Intervention(s)	- Mirikizumab Subcutaneously (SC) - Mirikizumab IV
Comparator(s)	Placebo (SC)
Outcome(s)	Percentage of Participants in Clinical Remission [Time Frame: Week 40]; clinical remission based on modified Mayo Score (MMS). See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**LUCENT 3;** NCT03519945; 2017-004092-31; A Phase 3, Multicentre, Open-Label Extension Study to Evaluate the Long Term Efficacy and Safety of Mirikizumab in Patients With Moderately to Severely Active Ulcerative Colitis **Phase III** - ongoing **Location(s):** 16 EU countries, UK, US, Canada and other countries **Primary completion date:** August 2023
Trial design	Single group assignment, open label
Population	N = 960; 18-80 years old; participants from Study AMAC (NCT02589665) or AMBG (NCT03524092) who have had at least one study drug administration and have not had early termination of study drug.
Intervention(s)	Mirikizumab (SC)
Comparator(s)	No comparator

Outcome(s)	Percentage of Participants in Clinical Remission [Time Frame: Week 52]; clinical remission based on the modified Mayo Score (MMS). See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	NCT02589665; 2015-003123-57; A Phase 2, Multicentre, Randomized, Double-Blind, Parallel, Placebo-Controlled Study of LY3074828 in Subjects With Moderate to Severe Ulcerative Colitis **Phase II** - Completed **Location(s):** 9 EU countries, UK, US, Canada and other countries **Study completion date:** May 2019
Trial design	Randomized, double-blind, Parallel assignment, placebo-controlled
Population	N=249; 18-75 years old; have moderate to severe active UC as defined by a Mayo score of 6 to 12 with an endoscopic subscore ≥2 within 14 days before the first dose of study treatment
Intervention(s)	• 50m or 200mg or 600mg mirikizumab administered every 4 weeks intravenously (IV) during the induction period. • This is followed by 200mg mirikizumab either every 4 weeks or every 12 weeks subcutaneously (SC) during the maintenance period • Open label extension: 600mg or 1000mg mirikizumab IV or 200mg mirikizumab SC every 4 weeks
Comparator(s)	Matched placebo
Outcome(s)	Induction Period: Percentage of Participants With Clinical Remission at Week 12 [time frame: Week 12]. Clinical remission at week 12 is a defined as achieving a 9-pt Mayo subscore for rectal bleeding=0, stool frequency=0 or 1 with ≥ 1-point decrease from baseline, and endoscopy=0 or 1, excluding Physician's Global Assessment (PGA). See trial record for full list of other outcomes
Results (efficacy)	• At week 12, 15.9% (*P* = .066), 22.6% (*P* = .004), and 11.5% (*P* = .142) of patients in the 50-mg, 200-mg, and 600-mg groups achieved clinical remission, respectively, compared with 4.8% of patients given placebo. The primary endpoint was not significant (comparison to 600 mg, *P* > .05). • Clinical responses occurred in 41.3% (*P* = .014), 59.7% (*P* < .001), and 49.2% (*P* = .001) of patients in the 50-mg, 200-mg, and 600-mg groups, respectively, compared with 20.6% of patients given placebo. • At week 52, 46.8% of patients given subcutaneous mirikizumab 200 mg every 4 weeks and 37.0% given

	subcutaneous mirikizumab 200 mg every 12 weeks were in clinical remission.[3]
Results (safety)	• The most frequent treatment-emergent AEs (≥5% in any treatment group) included nasopharyngitis, worsening of UC, anaemia, headache, nausea, cough, and worsening of gastroenteritis during induction and worsening of UC, nasopharyngitis, headache, upper respiratory tract infection, arthralgia, hypertension, and influenza during maintenance. • Serious AEs (SAE) occurred in 7 patients during the induction period (2 each in the placebo and 200-mg groups and 3 in the 600-mg group) and 5 patients during the maintenance period.[3]

ESTIMATED COST

The cost of mirikizumab is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Etrolizumab for treating moderately to severely active ulcerative colitis. (GID-TA10717). Expected publication date TBC.
- NICE technology appraisal in development. Ozanimod for treating moderately to severely active ulcerative colitis. (GID-TA10732). Expected publication date TBC.
- NICE technology appraisal in development. Filgotinib for treating moderately to severely active ulcerative colitis. (GID-TA10600). Expected publication date: December 2021.
- NICE technology appraisal. Ustekinumab for treating moderately to severely active ulcerative colitis. (TA633). 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.

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.[15]
- British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. 2019.[16]
- European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA). ECCO-EFCCA Patient Guidelines on Ulcerative Colitis (UC). 2014.[17]

ADDITIONAL INFORMATION

REFERENCES

1 ClinicalTrials.gov. *An Induction Study of Mirikizumab in Participants With Moderately to Severely Active Ulcerative Colitis (LUCENT 1). Trial ID: NCT03518086*. Status: Recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT03518086 [Accessed 16 April 2021].

2 ClinicalTrials.gov. *A Maintenance Study of Mirikizumab in Participants With Moderately to Severely Active Ulcerative Colitis (LUCENT 2). Trial ID: NCT03524092*. Status: Recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT03524092 [Accessed 16 April 2021].

3 Sandborn W, Ferrante M, Bhandari B, Berliba E, Feagan B, Hibi T, et al. Efficacy and Safety of Mirikizumab in a Randomized Phase 2 Study of Patients With Ulcerative Colitis. *Gastroenterology*. 2019;158(3):537-49. Available from: https://doi.org/10.1053/j.gastro.2019.08.043.

4 National Institute for Health and Care Excellence (NICE). *Treatment Summary: Ulcerative colitis* Last Update Date: 2020. Available from: https://bnf.nice.org.uk/treatment-summary/ulcerative-colitis.html [Accessed 16 April 2021].

5 Eli Lilly and Company. *Lilly's Mirikizumab Helps Patients Achieve Clinical Remission and Improves Symptoms in Adults with Ulcerative Colitis in 12-Week Phase 3 Induction Study*. Available from: https://investor.lilly.com/news-releases/news-release-details/lillys-mirikizumab-helps-patients-achieve-clinical-remission-and [Accessed 16 April 2021].

6 ClinicalTrials.gov. *14 Studies found for: Mirikizumab | Phase 2, 3*. Available from: https://clinicaltrials.gov/ct2/results?term=Mirikizumab&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 16 April 2021].

7 National Health Service. *Overview: Ulcerative Colitis*. Available from: https://www.nhs.uk/conditions/ulcerative-colitis/ [Accessed 16 April 2021].

8 National Institute for Health and Care Excellence (NICE) Guidance. *Ulcerative colitis: management (NG130)*. Last Update Date: 2019. Available from: https://www.nice.org.uk/guidance/ng130/resources/ulcerative-colitis-management-pdf-66141712632517 [Accessed 16 April 2021].

9 National Health Service. *Causes: Ulcerative Colitis*. Available from: https://www.nhs.uk/conditions/ulcerative-colitis/causes/ [Accessed 16 April 2021].

10 National Institutes of Health. *Ulcerative Colitis: causes*. Available from: https://ghr.nlm.nih.gov/condition/ulcerative-colitis# [Accessed 16 April 2021].

11 Crohn's & Colitis UK. *Ulcerative Colitis Your Guide*. Available from: http://s3-eu-west-1.amazonaws.com/files.crohnsandcolitis.org.uk/Publications/ulcerative-colitis.pdf [Accessed 16 April 2021].

12 National Institute for Health and Care Excellence. *Tofacitinib for moderately to severely active ulcerative colitis* Last Update Date: November 2018. Available from: https://www.nice.org.uk/guidance/ta547/documents/final-scope [Accessed 16 April 2021].

13 NHS Digital. *Hospital Admitted Patient Care Activity, 2019-20: Diagnosis*. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2019-20 [Downloaded 21 June 2021].

14 National Institute for Health and Care Excellence (NICE). *Inducing remission in people with ulcerative colitis: further treatment for moderate to severe ulcerative colitis.* . 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-index [Accessed 14 April 2021].
15 National Institute for Health and Care Excellence (NICE) Clinical Knowledge Summary. *Ulcerative Colitis.* 2019. Available from: https://cks.nice.org.uk/ulcerative-colitis#!management [Accessed 16 April 2021].
16 Lamb C, Kennedy N, Raine T, Hendy P, Smith P, Limdi J, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *British Medical Journal*. 2019;68. Available from: https://gut.bmj.com/content/gutjnl/68/Suppl_3/s1.full.pdf.
17 European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA). *ECCO-EFCCA Patient Guidelines on Ulcerative Colitis (UC)* Last Update Date: 2020. Available from: https://www.efcca.org/sites/default/files/Ulcerative%20Colitis%20Patient%20Guidelines.pdf [Accessed 16 April 2021].

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.