NIHR | Innovation Observatory

Newcastle University

# Health Technology Briefing
# December 2022

# Mirikizumab for treating moderately to severely active Crohn's disease

| Company/Developer | Eli Lilly and Company Limited |
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☒ New Active Substance ☐ Significant Licence Extension (SLE)

| NIHRIO ID: 13188 | NICE ID: 11826 | UKPS ID: 666049 |
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## Licensing and Market Availability Plans

Currently in phase II and III clinical trials.

## Summary

Mirikizumab is in clinical development for the treatment of moderately to severely active Crohn's disease in adults who have had intolerance, loss of response or inadequate response to previous therapy. Crohn's disease is an inflammatory disease of the gastrointestinal tract. Genetics, immune system irregularities, smoking, a stomach bug and abnormal gut bacteria balance are thought to play a role in the cause of Crohn's disease. There's no cure for Crohn's disease, but treatment can help reduce or control symptoms. The effectiveness of current available treatments is limited as some patients may have an inadequate response to, or may not tolerate a drug, thus resulting in discontinuation of therapy or suboptimal treatment. As such, a significant unmet need remains as suboptimal treatment is associated with higher rates of surgery, hospitalisation, and/or prolonged steroid use as well as impaired quality of life.

Mirikizumab is a human monoclonal antibody that binds specifically to a portion of a cytokine (protein) called interleukin (IL) 23. IL23 plays a key role in the maintenance, amplification and stimulation of many immune cells which are important in the development of Crohn's disease. Mirikizumab would be administered intravenously (IV) or subcutaneously (SC). If licensed, mirikizumab would offer an additional treatment option for adult patients with moderately to severely active Crohn's disease after prior therapy.

## Proposed Indication

Treatment of moderately to severely active Crohn's disease in adults who have had intolerance, loss of response or inadequate response to prior conventional or biologic therapy.[1-3]

## Technology

### Description

Mirikizumab (LY3074828) is a humanised immunoglobulin G4 (IgG4)–variant monoclonal antibody that binds specifically to the p19 subunit of interleukin (IL) 23. IL23 is a cytokine that plays a key role in the maintenance and amplification of T helper 17 cells and stimulation of many innate immune cells, which are important in the pathogenesis of chronic inflammatory diseases including Crohn's disease.[4]

Mirikizumab is in clinical development for the treatment of moderately to severely active Crohn's disease in adults who have had an inadequate response with, lost response to, or were intolerant to prior systemic therapy. In the phase III trial (VIVID-1; NCT03926130), mirikizumab will be administered intravenously (IV) and subcutaneously (SC).[2]

### Key Innovation

For more than a decade, tumour necrosis factor–α (TNF-alpha) inhibitors were the only biologics available. More recently, other biologics with different mechanisms of action have been approved. However, the efficacy of these biologics is limited in that some patients may have an inadequate response or lose response over time, or may not tolerate a given drug, thus resulting in discontinuation of therapy or suboptimal treatment. As such, a significant unmet need remains as suboptimal treatment is associated with higher rates of surgery, hospitalisation, and/or prolonged corticosteroid use as well as impaired quality of life.[4] In the phase II clinical trial (NCT02891226), mirikizumab effectively induced endoscopic response after 12 weeks in patients with moderate to severe active Crohn's disease and demonstrated durable efficacy to week 52.[4] These improvements in patients' disease severity and symptom severity were sustained or improved with continued maintenance treatment.[5]

If approved, mirikizumab will provide an additional treatment option for patients with moderately to severely active Crohn's disease who have few well-tolerated effective therapies available.

### Regulatory & Development Status

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

Mirikizumab is also in phase II and III clinical development for ulcerative colitis.[6]

## Patient Group

### Disease Area and Clinical Need

Crohn's disease is a chronic, disabling, and progressive inflammatory disease of the gastrointestinal tract.[4] It is one type of a condition called inflammatory bowel disease (IBD). The symptoms usually start in childhood or early adulthood. Symptoms include diarrhoea, stomach aches and cramps, blood in your poo, tiredness (fatigue) and weight loss. The exact cause of Crohn's disease is unknown, however, several factors could play a role, including genetics, a problem with the immune system that causes it to attack the digestive system, smoking, a previous stomach bug and an abnormal balance of gut bacteria. Crohn's

disease affects people of all ages.[7] The median age at diagnosis is about 30 years; and about 20–30% of cases present before the age of 20 years. Crohn's disease occurs in men and women at approximately equal rates.[8]

At least 1 in every 323 people in the UK are living with Crohn's Disease.[9] In England (2021-22), there were 151,340 finished consultant episodes (FCEs) and 140,775 admissions for a primary diagnosis of Crohn's disease (ICD-10 code K50), which resulted in 126,981 day cases and 85,964 FCE bed days for all ages.[10] In the UK, in 2017, the prevalence of Crohn's Disease was 400 per 100,000. Crohn's Disease 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.[11]

## Recommended Treatment Options

NICE recommends the following treatment options for moderately to severely active Crohn's disease after prior systemic treatment: [12-14]

- Infliximab and adalimumab for adults with severe active Crohn's disease whose disease has not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments), or who are intolerant of or have contraindications to conventional therapy.
- Ustekinumab for treating moderately to severely active Crohn's disease for adults who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNF-alpha inhibitor or have medical contraindications to such therapies.
- Vedolizumab for treating moderately to severely active Crohn's disease only if: a TNF-alpha inhibitor has failed (that is, the disease has responded inadequately or has lost response to treatment), or a TNF-alpha inhibitor cannot be tolerated or is contraindicated.

## Clinical Trial Information

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| Trial | **VIVID-2; NCT04232553; EudraCT-2019-002687-27;** A Phase 3, Multicenter, Open-Label, Long-Term Extension Study to Evaluate the Long-Term Efficacy and Safety of Mirikizumab in Patients With Crohn's Disease<br>**Phase III –** Recruiting<br>**Location(s) –** 17 countries in EU, UK, USA, Canada and other countries<br>**Primary completion date –** January 2025 |
| Trial Design | Non-randomised, single group assignment, open label |
| Population | N=778 (estimated); aged 18 years and older; subjects with Crohn's disease who must have completed study I6T-MC-AMAG (NCT02891226) or study I6T-MC-AMAM (NCT03926130) |
| Intervention(s) | Mirikizumab IV and SC |
| Comparator(s) | No comparator. |
| Outcome(s) | Primary outcome measures:<br>• Percentage of Participants Achieving Endoscopic Response [Time frame: Week 52]<br>• Percentage of Participants Achieving Clinical Remission [Time frame: Week 52] |

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| | See trial record for full list of other outcomes. |
| Results (efficacy) | - |
| Results (safety) | - |

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| Trial | **VIVID-1**; NCT03926130; EudraCT-2018-004614-18; A Phase 3, Multicenter, Randomized, Double-Blind, Placebo- and Active- Controlled, Treat-Through Study to Evaluate the Efficacy and Safety of Mirikizumab in Patients With Moderately to Severely Active Crohn's Disease<br>**Phase III –** Active, not recruiting<br>**Location(s) -** 17 countries in EU, UK, USA, Canada and other countries<br>**Primary completion date –** August 2023 |
| Trial Design | Randomised, parallel assignment, triple-masked, placebo- and active-controlled |
| Population | N=1100 (estimated); aged 15 years to 80 years; subjects with a confirmed diagnosis of moderately to severely Crohn's disease; demonstrated intolerance, loss of response or inadequate response to conventional or to biologic therapy for Crohn's disease |
| Intervention(s) | Mirikizumab IV and SC |
| Comparator(s) | Ustekinumab IV and SC |
| Outcome(s) | Primary outcome measures:<br>• Percentage of Participants Achieving Clinical Response at Week 12 and Endoscopic Response at Week 52 [Time frame: Baseline to Week 52]<br>• Percentage of Participants Achieving Clinical Response at Week 12 and Clinical Remission at Week 52 [Time frame: Baseline to Week 52]<br>See trial record for full list of other outcomes |
| Results (efficacy) | - |
| Results (safety) | - |

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| Trial | **SERENITY**; NCT02891226; EudraCT- 2016-002204-84; A Phase 2, Multicenter, Randomized, Parallel-Arm, Placebo-Controlled Study of LY3074828 in Subjects With Active Crohn's Disease (SERENITY)<br>**Phase II –** Completed<br>**Location(s) –** 7 countries in EU, UK, USA, Canada, and other countries<br>**Study completion date –** December 2018 |
| Trial Design | Randomised, parallel assignment, double-masked, placebo-controlled |
| Population | N=191 (actual); aged 18 years to 75 years; subjects with active Crohn's disease; inadequate response or failure to tolerate at least one of the following: aminosalicylates; budesonide; systemic corticosteroids; immunosuppressants (e.g., azathioprine, 6-mercaptopurine, or methotrexate); or prior exposure to biologics for the treatment of Crohn's disease |

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| Intervention(s) | Mirikizumab IV and SC<br><br>See trial record for full dosage |
| Comparator(s) | Matched placebo (IV) every 4 weeks (weeks 0 – 12) |
| Outcome(s) | Primary outcome measure:<br><br>• Percentage of Participants Achieving Endoscopic Response at Week 12 [Time frame: Week 12]<br><br>See trial record for full list of other outcomes. |
| Results (efficacy) | At week 12, endoscopic response was significantly higher by the predefined 2-sided significance level of 0.1 for all mirikizumab groups compared with placebo (200 mg: 25.8%, 8/31, 95% confidence interval [CI], 10.4–41.2, P = 0.079; 600 mg: 37.5%, 12/32, 95% CI, 20.7–54.3, P = 0.003; 1000 mg: 43.8%, 28/64, 95% CI, 31.6–55.9, P < 0.001; Placebo: 10.9 %, 7/64, 95% CI, 3.3–18.6). Endoscopic response at week 52 was 58.5% (24/41) and 58.7% (27/46) in the IV-C and SC groups, respectively.[4] |
| Results (safety) | Frequencies of adverse events (AE) in the mirikizumab groups were similar to placebo. Through week 52, frequencies of treatment-emergent AEs were similar across all groups. Frequencies of serious AE and discontinuations due to AE were higher in the nonrandomized maintenance cohort.[4] |

## Estimated Cost

The cost of mirikizumab is not yet known.

## Relevant Guidance

### NICE Guidance

- NICE technology appraisal guidance in development. Etrolizumab for previously treated moderately to severely active Crohn's disease (GID-TA10870). Expected publication date to be confirmed.
- NICE technology appraisal guidance in development. Upadacitinib for previously treated moderately to severely active Crohn's disease (GID-TA10997). Expected publication date June 2023.
- NICE technology appraisal guidance in development. Risankizumab for previously treated moderately to severely active Crohn's disease (GID-TA10884). Expected publication date March 2023.
- NICE technology appraisal guideline. Ustekinumab for moderately to severely active Crohn's disease after previous treatment (TA456). July 2017.
- NICE technology appraisal guideline. Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy (TA352). August 2015.
- NICE technology appraisal guidance. Infliximab and adalimumab for the treatment of Crohn's disease (TA187). May 2010.
- NICE clinical guideline. Crohn's disease: management (NG129). May 2019.
- NICE quality standard. Inflammatory bowel disease (QS81). February 2015.

### NHS England (Policy/Commissioning) Guidance

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

Other Guidance

- The European Crohn's and Colitis Organisation [ECCO]. ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment. January 2020.[15]
- British Society of Gastroenterology. BSG consensus guidelines on the management of Inflammatory Bowel Disease in adults. 2019.[16]
- American College of Gastroenterology. ACG Clinical Guideline: Management of Crohn's Disease in Adults. April 2018.[17]

## Additional Information

## References

1 ClinicalTrials.gov. *A Study of Mirikizumab (LY3074828) in Participants With Active Crohn's Disease (SERENITY). Trial ID: NCT02891226*. 2016. Available from: https://clinicaltrials.gov/ct2/show/NCT02891226 [Accessed 15th November 2022].

2 ClinicalTrials.gov. *A Study of Mirikizumab (LY3074828) in Participants With Crohn's Disease (VIVID-1). Trial ID: NCT03926130*. 2019. Available from: https://clinicaltrials.gov/ct2/show/NCT03926130 [Accessed 15th November 2022].

3 ClinicalTrials.gov. *A Long-term Extension Study of Mirikizumab (LY3074828) in Participants With Crohn's Disease (VIVID-2). Trial ID: NCT04232553*. 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT04232553 [Accessed 15th November 2022].

4 Sands BE, Peyrin-Biroulet L, Kierkus J, Higgins PDR, Fischer M, Jairath V, et al. Efficacy and Safety of Mirikizumab in a Randomized Phase 2 Study of Patients With Crohn's Disease. *Gastroenterology*. 2022;162(2):495-508. Available from: https://doi.org/10.1053/j.gastro.2021.10.050.

5 Healio. *Mirikizumab reduces disease severity in Crohn's, ulcerative colitis.* 2022. Available from: https://www.healio.com/news/gastroenterology/20220122/mirikizumab-reduces-disease-severity-in-crohns-ulcerative-colitis [Accessed 17th November 2022].

6 ClinicalTrials.gov. *Mirikizumab, LY3074828 | Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | Phase 2, 3.* 2022. Available from: https://www.clinicaltrials.gov/ct2/results?term=Mirikizumab%2C+LY3074828&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 15th November 2022].

7 National Health Serivce (NHS). *Overview-Crohn's disease.* 2021. Available from: https://www.nhs.uk/conditions/crohns-disease/ [Accessed 17th November 2022].

8 National Institute for Health and Care Excellence. *Crohn's disease: How common is it?* 2020. Available from: https://cks.nice.org.uk/topics/crohns-disease/background-information/prevalence/ [Accessed 17th November 2022].

9 Crohn's and Colitis. *Crohn's disease: Your guide.* 2021. Available from: https://crohnsandcolitis.org.uk/media/ol1niezn/crohns-ed-8-final.pdf [Accessed 7th December 2022].

10 NHS Digital. *Hospital Admitted Patient Care Activity 2021-22: Diagnosis.* 2022. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2021-22 [Accessed 18th November 2022].
11 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.
12 National Institute for Health and Care Excellence. *Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy*. 2015. Available from: https://www.nice.org.uk/guidance/ta352/chapter/1-Guidance [Accessed 15th November 2022].
13 National Institute for Health and Care Excellence. *Ustekinumab for moderately to severely active Crohn's disease after previous treatment*. 2017. Available from: https://www.nice.org.uk/guidance/ta456/chapter/1-Recommendations [Accessed 15th November 2022].
14 National Institute for Health and Care Excellence. *Crohn's disease: management*. 2019. Available from: https://www.nice.org.uk/guidance/ng129/chapter/Recommendations [Accessed 15th November 2022].
15 Torres J, Bonovas S, Doherty G, Kucharzik T, Gisbert JP, Raine T, et al. ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment. *Journal of Crohn's and Colitis*. 2020;14(1):4-22. Available from: https://doi.org/10.1093/ecco-jcc/jjz180.
16 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. Available from: https://doi.org/10.1136/gutjnl-2019-318484.
17 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). Available from: https://doi.org/10.1038/ajg.2018.27.

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