Study title: **Mirikizumab Investigation of Real-world Assessment of Clinical and Long-term Effectiveness and Adverse Events in patients with Ulcerative Colitis**

Study Acronym: **MIRACLE-UC**

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AUTHORIZATIONS AND SIGNATURES

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AGREEMENT

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The Principal Investigator's signature below confirms his agreement to this protocol and provides the necessary guarantees that:

1.This study will be conducted following all the clauses of the protocol and in accordance with the Helsinki declaration (Edinburgh 2000 with Explanatory note paragraph 29 from Washington 2002 and paragraph 30 from Tokyo 2004) and current legislation regarding clinical studies.

2. No partial or final data (written or verbal) will be published without prior agreement between the Investigator and the IgIBD

PRINCIPAL INVESTIGATOR SIGNATURE

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Signature _____ Date_____

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Abstract

Ulcerative colitis (UC) significantly impacts patient quality of life, with disease progression and complications often leading to long-term disability. Recent advancements in treatment, including biologics like mirikizumab, have expanded therapeutic options. Mirikizumab, a humanized monoclonal antibody targeting IL-23, has shown promise in recent LUCENT trials, which demonstrated its efficacy in achieving clinical and endoscopic remission. This study aims to evaluate the effectiveness of mirikizumab in real-world settings, addressing this knowledge gap. The primary objective is to assess the percentage of UC patients achieving steroid-free clinical remission after 12 months of treatment. Secondary objectives include evaluating clinical, endoscopic, and histologic outcomes at multiple time points and determining predictors of deep remission. This multicenter, prospective, observational study will include patients who have previously failed at least one prior therapy and will track their response to mirikizumab over 12 months. By analyzing real-world data, this study seeks to enhance understanding of mirikizumab's role in UC treatment and support informed clinical decision-making. The findings will provide valuable insights into optimizing treatment strategies and improving patient care in chronic inflammatory bowel diseases.

State of the Art and Scientific Rationale

Ulcerative colitis (UC), a type of inflammatory bowel disease (IBD), can profoundly affect a patient's life and lead to long-term, burdensome complications [1]. Patients may experience disease progression, such as proximal disease extension to pancolitis, or structural and functional changes, resulting in a reduced quality of life and disability [2].

Over the past decade, treatment options for UC have significantly expanded with the introduction of biologics and small molecules: the recent emergence of various new mechanisms of action and individual therapies for treating UC offers significant potential for personalized patient care, but it also complicates the decision-making process [3].

Mirikizumab is a humanized immunoglobulin G4 monoclonal antibody that selectively targets the p19 subunit of interleukin (IL)-23, distinguishing itself by its lack of binding to IL-12 [4,5]. This specificity makes mirikizumab a pioneering agent in its class, recently authorized by the European Medicines Agency for treating UC. The clinical development of

mirikizumab incorporates innovative aspects, such as novel assessments of bowel urgency and histologic outcomes, including the absence of mucosal neutrophils [6,7].

The dosing regimen for mirikizumab was established through the Phase 3 LUCENT trial program, which involved an intravenous (IV) administration of 300 mg every 4 weeks for the initial 12 weeks, followed by subcutaneous (SC) administration of 200 mg every 4 weeks for up to 40 weeks [7]. In the clinical trials, an extended induction protocol was implemented for patients who did not respond to the initial treatment and for patients who initially responded to the treatment by week 12 but later experienced a loss of response, a reinduction protocol was available [8].

The efficacy of mirikizumab has been rigorously evaluated through the LUCENT-1, LUCENT-2 AND LUCENT-3 trials. The LUCENT-1 study, a 12-week induction trial, demonstrated that mirikizumab significantly outperformed placebo in achieving clinical remission and response. Notably, mirikizumab also showed superior outcomes in endoscopic and histologic improvements compared to placebo [7]. The subsequent LUCENT-2 maintenance study confirmed the long-term benefits of mirikizumab. Patients who achieved clinical response during induction and continued with mirikizumab maintenance therapy had significantly higher rates of clinical remission at 40 weeks [7]. In a post hoc analysis, mirikizumab showed significant clinical benefits for both induction and maintenance phases, regardless of prior biologic or small-molecule therapy exposures and in patients with previously failed one anti-TNF treatment [7,9,10].

The ongoing LUCENT-3 study (NCT03519945) aims to further assess the long-term safety and efficacy of mirikizumab, extending the evaluation period to 3 and 4 years. Preliminary findings indicate that mirikizumab continues to demonstrate a robust efficacy and safety profile, with notable improvements in symptom scores and quality of life for patients who remain on treatment for up to 104 weeks [11]. These data will offer valuable insights into the sustained benefits and long-term impact of mirikizumab therapy [12].

Safety is a critical aspect of evaluating any new therapy. Although the safety of IL-23 inhibitors is largely informed by experiences in other disease states [13], the LUCENT trials indicated that the safety profile of mirikizumab is consistent with other IL-23 inhibitors, showing a comparable incidence of treatment-emergent adverse events (TEAEs) to placebo. Common TEAEs included nasopharyngitis and headache, with no unexpected safety signals reported [7]. However, the trials also noted a slightly higher incidence of elevated liver enzymes and opportunistic infections [7].

While clinical trials provide rigorous data on efficacy and safety, real-world data (RWD) offer crucial insights into how therapies perform outside the controlled conditions of trials. RWD can highlight how treatments are used in diverse patient populations, including those with comorbidities or those on multiple therapies, thus offering a more comprehensive view of their effectiveness and safety. Current literature provides limited RWD on the use of Mirikizumab in treating UC [14]. This study seeks to fill existing gaps by evaluating the effectiveness of mirikizumab in a prospective cohort of UC patients at multiple secondary and tertiary IBD centers throughout Italy. The goal is to assess clinical, endoscopic, and histologic outcomes of mirikizumab in real-world settings, thereby providing supplementary data to enhance and contextualize current and future trial results.

Objectives and Specific Working Hypotheses

Primary Outcome Measures:

1. Clinical Remission at Month 12:

To evaluate the percentage of patients achieving clinical remission by month 12, as defined by achieving a 9-point modified Mayo score (MMS) for rectal bleeding = 0, stool frequency = 0 or 1 with a ≥ 1 point decrease from baseline, and endoscopy = 0 or 1 (excluding friability).

Secondary Outcome Measures:

1. Endoscopic Remission at Month 3, 6, and 12:

To assess the percentage of patients achieving endoscopic remission at 3,6 and 12 months. Endoscopic remission is defined as achieving a Mayo endoscopic subscore of 0 or 1 (excluding friability).

2. Histologic Remission at Month 3, 6, and 12:

To assess the percentage of patients achieving histologic remission at 3,6 and 12 months, assessed using the Geboes histologic or Nancy scoring system. Remission is defined as a Geboes histological subscore of 0 for grades: 2b (lamina propria neutrophils), 3 (neutrophils in epithelium), 4 (crypt destruction), and 5 (erosion or ulceration).

Remission is defined as a Nancy histological score of 0.

3. Symptomatic Remission at Month 3, 6, and 12:

To assess the percentage of patients achieving symptomatic remission at 3,6 and 12 months. Symptomatic remission is defined as achieving a Mayo score with rectal bleeding = 0, and stool frequency = 0 or 1 with a ≥ 1 point decrease from baseline.

4. Endoscopic Response at Month 3, 6, and 12:

To assess the percentage of patients achieving endoscopic response at 3,6 and 12 months. Endoscopic response is defined as achieving at least a 1-point decrease from baseline in the Mayo endoscopic subscore.

5. Clinical Response at Month 3, 6, and 12:

To assess the percentage of patients achieving clinical response at 3,6 or 12 months. Clinical response is defined as a decrease in the 9-point MMS by at least 2 points and 30% from baseline, with either a decrease of rectal bleeding subscore by ≥1 or a rectal bleeding subscore of 0 or 1.

6. Clinical Remission at Month 3 and 6:

To assess the percentage of patients achieving clinical remission at month 3 and 6. Clinical remission is defined as achieving a 9-point MMS for rectal bleeding = 0, stool frequency = 0 or 1 with a ≥ 1 point decrease from baseline, and endoscopy = 0 or 1 (excluding friability).

7. Change in Fecal Calprotectin from Baseline to Month 3, 6, and 12:

To assess changes in faecal calprotectin levels from baseline to 3,6 and 12 months.

8. Change in Bowel Urgency Based on the Urgency NRS from Baseline to Month 3, 6, and 12:

To assess changes in bowel urgency severity, measured by the Urgency NRS, from baseline to 3,6 and 12 months.

9. Hospitalization for UC by Month 12:

To assess the percentage of patients hospitalized for UC, with only hospitalizations associated with an adverse event with a stay of at least 24 hours recorded.

10. Safety

To evaluate the safety of Mirikizumab throughout the study period.

11. Predictors of Deep Remission by Month 12:

To identify clinical, endoscopic, or radiologic predictors of deep remission in UC at 12 months.

12. EIMS at Month 3,6 and 12

To assess the percentage of patients achieving control of extraintestinal manifestations present at baseline at 3, 6 and 12 of Mirikizumab treatment.

13. Comparing the Efficacy in Different Treatment lines by Month 12:

To compare the efficacy of Mirikizumab, based on the primary endpoint of the study, when used as a second, third, or fourth line of biological treatment.

14. CRP levels from Baseline to Month 3, 6, and 12:

To assess changes in C-reactive protein (CRP) levels after 3, 6, and 12 months of Mirikizumab treatment in UC patients.

15. BWT normalization at Month 3, 6, and 12

To evaluate the percentage of patients showing normalization of bowel wall thickness (BWT) at intestinal ultrasound (IUS) in UC, with sigmoid colon ≤4.0 mm, descending colon ≤3.0 mm, transverse colon ≤3.0 mm, and ascending colon ≤3.0 mm after 3, 6, and 12 months of Mirikizumab treatment. This will be evaluated only in patients with increased BWT at baseline.

15. Ultrasound remission at Month 3, 6, and 12

To evaluate the percentage of patients having a Milano Ultrasound Criteria (MUC) score ≤ 6.2 after 3, 6, and 12 months of Mirikizumab treatment. This will be evaluated only in patients with Milano Ultrasound Criteria (MUC) score > 6.2 at baseline.

16. Deep Remission at Month 3, 6 and 12

To assess the percentage of patients achieving deep remission at month 3, 6 and 12. Deep remission is defined as a combination of a rectal bleeding score of 0, a stool frequency score of 0, and an eMayo score ≤1.

17. Disease clearance at Month 3, 6 and 12

To assess the percentage of patients achieving clinical remission, endoscopic remission and histologic remission at month 3 and 6.

18. Quality of Life

To assess changes in the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) and FACIT–Fatigue questionnaire after 3, 6, and 12 months of Mirikizumab treatment in UC patients

Methodology

Study design

Overall study design

This multicentre, prospective and retrospective observational study will include patients who meet the specified inclusion and exclusion criteria and have data available as required by the protocol. We will enrol consecutive patients with UC who have started treatment with Mirikizumab, starting from December 2024.

Study duration

The study will last 12 months from the first patient enrolled, for patient recruitment. Each subject will participate for a maximum of 12 months. Therefore, the duration of the study is overall of 24 months.

Methods: Participants, interventions and outcomes

Eligibility criteria

Inclusion criteria

The participants must fulfill the following criteria for participating in the study:

- **Age:** At least 18 years old.
- **Diagnosis:** A confirmed diagnosis of UC according to the ECCO guidelines, established at least 3 months [26] prior to study enrollment.
- **Current Treatment:** Initiation of Mirikizumab therapy for UC based on clinical practice indications (primary loss of response, secondary loss of response, or intolerance to previous therapy).
- **Informed Consent:** Willingness to provide written informed consent to participate in the study.

Exclusion criteria

1. Age < 18 years.
2. Patients with diagnosis of Crohn disease or indeterminate IBD.
3. Refusal to sign written informed consent certifying the willingness of the subject to participate to the study.

Treatment dosage:

Mirikizumab Treatment:

- Induction Phase:
  - Dosage: 300 mg administered IV every 4 weeks.
  - Duration: Initial 12 weeks (0-4-8 weeks).
- Maintenance Phase:
  - Dosage: 200 mg administered SC every 4 weeks.
  - Duration: Up to 40 weeks.
- Extended Induction (if needed):
  - Dosage: Additional 300 mg IV every 4 weeks for three doses.
  - Indication: If the patient does not achieve a clinical response after the initial 12 weeks.
- Reinduction (if needed):
  - Dosage: Additional 300 mg IV every 4 weeks for three doses.
  - Indication: If the patient loses response after initial treatment.

b. Criteria for Modifying or Discontinuing Treatment

- Modification Criteria:
  - Adverse Events (AEs): Dose adjustments or discontinuation may be considered if the patient experiences significant AEs, such as severe infections or liver enzyme elevations.
  - Disease Progression: Treatment may be modified if there's a significant worsening of UC symptoms or complications.
- Discontinuation Criteria:
  - Lack of Efficacy: If the patient does not achieve clinical response after the extended induction phase or during maintenance.
  - Severe AEs: If the patient experiences severe or life-threatening adverse effects.
  - Patient Withdrawal: If the patient decides to withdraw from the study.

c. Strategies to Improve Adherence

- Patient Education: Detailed counseling on the importance of adherence and potential benefits of Mirikizumab.
- Monitoring Adherence:

- Biological Markers: Regular assessments of CRP and fecal calprotectin levels to monitor disease activity and adherence.

Participant timeline

- Enrollment: December 2024 to December 2025.
- Treatment Period: Maximum of 12 months for each participant.
- Assessments:
  - Baseline: At enrollment.
  - Follow-up Visits: At 3, 6 and 12 months.
  - Data Collection: Regular intervals as specified above, including laboratory tests, endoscopic evaluations, and clinical assessments.

Sample size

Up to now, no real-word data on the efficacy and safety of mirikizuamb are available, therefore we approximate the calculation of the sample size based on the LUCEN trial, where the incidence of the primary outcome for patients receiving mirikizumab was oserved to be 44.9% [7]. The sample size was calculated using a significance level (α) of 0.05 with 80% of beta power, resulting in a sample size of 128 participants.

Data collection and management

Data will be retrieved from the electronic archives of all participating centers. Each patient will be assigned a unique identification number to prevent duplicate entries and ensure data anonymization. Collected data will be entered into an electronic case report form (RedCap) in compliance with all Italian privacy policy requirements.

Standard Data Collection Points:

- **T0 (Week 0):** baseline
- **T1 (Month 3):** 3 months after the beginning of therapy (post-induction)
- **T2 (Month 6):** 6 months after the beginning of therapy
- **T3 (Month 12):** 12 months after the beginning of therapy

At each time point, from baseline to 12 months, the following data will be collected:

- **Clinical Data:** To evaluate the modified Mayo score (MMS), including general well-being, abdominal pain, rectal bleeding, urgency, number of liquid/soft stools, and extraintestinal manifestations of UC.

- **Laboratory Tests:** Faecal calprotectin and CRP levels will be assessed.
- **Endoscopic and Radiological Monitoring:** Disease activity will be evaluated through ileocolonoscopy or rectosigmoidoscopy and intestinal ultrasound.
- **Patient questionnaires:** SIBDQ and FACIT-F will be assessed.

For participants who exit the study or discontinue treatment, we will collect outcome data up to the point of exit. This will include:

- **Reason for Withdrawal:** Documenting the reason for withdrawal to analyse potential impacts on study results.
- **Last Available Data:** Collecting and analyzing the last available data to ensure completeness of the dataset.

This approach will allow us to comprehensively assess the efficacy and safety of the treatment, as well as to track patient outcomes and responses throughout the study period.

Data management and protection

All records identifying the patient will be kept confidential and, to the extent permitted by applicable laws and regulations, will not be made publicly available. The PI, co-investigators, and personnel involved in the trial will comply with the GCP principles regarding the storage, processing, and dissemination of sensitive data. Patient names will be kept confidential. Only the patient number and initials will be recorded in the electronic Case Report Form (eCRF) using the IGIBD RedCap system. Study findings stored on a computer will adhere to local data protection laws. Patients will be informed in writing that representatives of the sponsor, Institutional Ethics Committee (IEC), or Regulatory Authorities may inspect their medical records to verify the collected information. All personal information made available for inspection will be handled with the utmost confidentiality and in accordance with local data protection laws. Patients will also be informed that non-identifiable information regarding the study will be posted on clinicaltrials.gov. If the results of the trial are published, the patient's identity will remain confidential. The investigators will maintain a list to enable the identification of patient records. Data storage will be under the responsibility of the PI.

Description of Statistical Data Analysis

The sample will be described using descriptive statistics. Qualitative data will be presented as absolute and relative frequencies, while quantitative variables will be reported as means with standard deviations (SD) or medians with interquartile ranges (IQR), as appropriate. The normality of quantitative variables will be assessed using the Shapiro-Wilk test. Missing values (if <5%) will be addressed using multiple imputation methods: Lasso Regression for quantitative data and classification trees for qualitative data.

Baseline differences between groups will be assessed using Chi-squared or Fisher-Freeman-Halton's exact test for qualitative variables, and one-way ANOVA or Kruskal-Wallis test for quantitative data. Pairwise comparisons will be performed using Student’s t-test or Mann-Whitney U test, with adjustments for multiple comparisons using the False Discovery Rate method. Adverse events (AEs) and serious adverse events (SAEs) will be described and compared across different therapy lines using the same inferential tests. Differences in steroid-free clinical remission rates at 12 months across various biological sequential therapies in second and third-line treatments will be analysed using Kaplan-Meier survival analysis. The log-rank test will be applied, and cumulative incidence curves will be generated.

Potential predictors of steroid-free clinical remission will be evaluated using Cox proportional hazards regression models. Hazard Ratios (HR) and 95% confidence intervals (CIs) will be reported. The proportionality of hazard functions will be assessed through visual inspection of hazard and Schoenfeld residual plots. If proportionality assumptions are violated, alternative Cox regression models will be fitted.

To evaluate the combined effects of drug and therapy line, multivariable interaction models will be fitted for each predictor, and interaction hazard ratios (IHR) will be reported. Coefficients of main effects will be interpreted as HRs for unit increases in predictors within the reference category (first line) for quantitative predictors, or as changes in hazard compared to the reference group for qualitative data. Interaction parameters (IHR) will reflect differences in HRs due to variations of predictors among different therapy lines, with the first line serving as the reference category. Statistical analyses will be performed using the updated version of R.

Relevance of the Proposed Study for Advancing Knowledge and Improving Clinical Management of Chronic Inflammatory Bowel Diseases

The proposed study is crucial for advancing our understanding and improving the clinical management of UC. UC is challenging due to its unpredictable disease course and significant impact on patients' quality of life. Clinical trials, such as the LUCENT program, offer rigorous efficacy data, but real-world studies are essential to evaluate how these treatments perform across diverse patient populations, including those with comorbidities or who have not responded to previous therapies. This study will contribute to personalized medicine by identifying clinical, endoscopic, and histologic predictors of treatment response and deep remission. Furthermore, by evaluating a range of outcomes—from steroid-free clinical remission to mucosal healing and bowel wall normalization—the study will offer comprehensive data on mirikizumab’s effectiveness.

Addressing the high rate of therapy failure and disease progression in UC, this research will provide valuable information on alternative therapeutic options for patients who have not benefited from conventional treatments.

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