**Study title:** A Multicenter, Prospective Real-life Evaluation of Effectiveness and Safety of Etrasimod in Biologic-Experienced Patients with Moderate-to-Severe Ulcerative Colitis Over One Year

**Study Acronym:** E-PRIME – Etrasimod Prospective Real-world Investigation of Moderate-to-severe Effectiveness

**Protocol version:** v.3.0 Date: MAY2025

**Sponsor:** Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD)

**Confidential**

**AUTHORIZATIONS AND SIGNATURES**

**Study Title**

A Multicenter, Prospective Real-life Evaluation of Effectiveness and Safety of Etrasimod in Biologic-Experienced Patients with Moderate-to-Severe Ulcerative Colitis Over One Year

**AGREEMENT**

This document is confidential and belongs to the Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD). The information is confidential and is to be used only in connection with matters authorized by IG-IBD, and no part of it is to be disclosed to others without prior written permission from the IG-IBD.

The Principal Investigator's signature below confirms agreement to this protocol and guarantees the following:

1. This study will be conducted following all clauses of the protocol and in accordance with the Helsinki declaration (Edinburgh 2000, Washington 2002, and 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 IG-IBD.

**PRINCIPAL INVESTIGATOR SIGNATURE**

Printed name:
Institution:
Signature: _____
Date: _____

**ROLES AND RESPONSIBILITIES**

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**Background** Ulcerative colitis (UC) is a chronic inflammatory bowel disease characterized by relapsing and remitting inflammation of the colon [1]. Despite advancements in therapeutic options, including biologic agents and small molecules, many patients experience inadequate response, loss of response, or intolerance to existing treatments, especially after exposure to multiple biologics [2].

Etrasimod is a once-daily, oral selective sphingosine 1-phosphate (S1P) receptor modulator that primarily targets S1P1,4,5 with no detectable activity on S1P2,3, distinguishing it from first-generation S1P modulators associated with adverse effects [3]. By reversibly sequestering lymphocytes in lymph nodes, Etrasimod reduces peripheral immune cell trafficking to inflamed gastrointestinal tissue, thereby mitigating inflammation while maintaining immune surveillance [3,4]. This mechanism is particularly relevant for UC, as immune-mediated dysregulation contributes significantly to disease pathophysiology [4].

Recent phase 3 trials (ELEVATE UC 52 and ELEVATE UC 12) demonstrated that Etrasimod significantly improves clinical, endoscopic, and histologic outcomes in patients with moderate-to-severe UC, including those who have failed previous therapies [5]. The efficacy and tolerability of Etrasimod make it a promising oral alternative for patients requiring durable disease control without the burdens associated with parenteral biologic administration [5].

This study aims to prospectively evaluate the efficacy and safety of Etrasimod over one year in patients with moderate-to-severe UC who have previously been exposed to biologic therapies, further expanding the evidence for its real-world application and impact on symptom control, including urgency assessment through the validated Urgency Numeric Rating Scale (UNRS).

**Study Design**

- **Type:** Multicenter, Prospective, Open-Label Study
- **Duration:** 54 weeks
- **Population:** Adults diagnosed with moderate-to-severe UC who have failed or are intolerant to at least one prior biologic therapy
- **Timeline:** Enrollment: July 2025 to December 2025; Treatment period: 54± 4 weeks for each participant; Data collection: as follows.

**Objectives**

**Primary Objective:**

- Evaluate the effectiveness of Etrasimod in achieving deep remission at Week 54, defined as the simultaneous presence of clinical and endoscopic remission.

**Secondary Objectives:**

- Assess the safety profile of Etrasimod over 54 weeks.
- Evaluate the proportion of patients achieving clinical response and biochemical response (fecal calprotectin [FC] and C-reactive protein [CRP]) at Weeks 12, 24, and 54.
- Measure improvement in patient-reported outcomes (PROs), including the urgency numeric scale (UNRS), at Weeks 12, 24, and 54.
- Assess mucosal and histological healing at Week 54 using endoscopy and biopsy.
- Evaluate changes in rectal and colonic wall thickness via ultrasound, if feasible[6] .

**Endpoints**

**Composite Endpoint:**

Proportion of patients achieving deep remission at 54 ± 4 weeks, defined as: Mayo rectal bleeding subscore = 0, stool frequency subscore = 0, endoscopic subscore ≤1.

**Secondary Endpoints:**

- Proportion of patients achieving clinical response at Weeks 12, 24, and 54, defined as a decrease from baseline in Mayo Clinic total score of ≥3 points and ≥30%, with a decrease in rectal bleeding subscore of ≥1 or an absolute rectal bleeding subscore of 0 or 1.
- Change from baseline in PRO scores, including the urgency numeric scale (UNRS), at Weeks 12, 24, and 54.
- Proportion of patients achieving biochemical response (normalization or significant reduction in FC and CRP levels) at Weeks 12, 24, and 54.
- Safety outcomes: Incidence and severity of adverse events (AEs), serious adverse events (SAEs), and discontinuations due to AEs throughout the study.

**Outcomes measurement**

**Primary Outcome Measures:**

1. **Clinical Remission at 24 and 54 ± 4 weeks**

    - To assess the proportion of patients achieving clinical remission at 54 ± 4 weeks, defined as a modified Mayo score (MMS) with a rectal bleeding subscore of 0, stool frequency subscore of 0 or 1 with at least a 1-point reduction from baseline, and an endoscopic subscore of 0 or 1 (excluding friability).

**Secondary Outcome Measures:**

1. **Endoscopic Remission at 54 ± 4 weeks**

    - To determine the proportion of patients attaining endoscopic remission at 54 ± 4 weeks, defined as a Mayo endoscopic subscore of 0 or 1 (excluding friability) and UCEIS score.

2. **Histologic Remission at 54 ± 4 weeks**

    - To evaluate histologic remission at 54 ± 4 weeks using the Nancy histological score. Remission is defined as a Nancy histological score of 0.

3. **Symptomatic Remission at 12, 24 e 54 ± 4 weeks**

    - To assess the proportion of patients achieving symptomatic remission at 12, 24 e 54 ± 4 weeks, defined as a Mayo score with a rectal bleeding subscore of 0 and a stool frequency subscore of 0 or 1 with at least a 1-point decrease from baseline.

4. **Endoscopic Response at 54 ± 4 weeks**

    - To evaluate the proportion of patients achieving endoscopic response at 54 ± 4 weeks, defined as at least a 1-point reduction from baseline in the Mayo endoscopic subscore.

5. **Clinical Response at 12, 24 and 54 ± 4 weeks**

    - To determine the proportion of patients achieving clinical response at 12, 24 e 54 ± 4 weeks, defined as a decrease of at least 2 points and 30% from baseline in the 9-point MMS, with either a reduction of rectal bleeding subscore by at least 1 point or an absolute rectal bleeding subscore of 0 or 1.

6. **Change in Fecal Calprotectin and C-Reactive protein from Baseline to 12, 24 e 54 ± 4 weeks**

- Biochemical response will be defined as either normalization (FC < 150 µg/g and CRP < 5 mg/L) or a ≥50% reduction from baseline values in patients with elevated biomarkers at study entry.

7. **Change in Bowel Urgency Based on the Urgency NRS from Baseline to 12, 24 e 54 ± 4 weeks**

    - To evaluate changes in bowel urgency severity using the Urgency Numeric Rating Scale (NRS) at 12, 24 e 54 ± 4 weeks.

8. **Comparing Effectiveness Across Different Treatment Lines by 54 ± 4 weeks**

- To compare the efficacy of Etrasimod in achieving the primary study endpoint when used as a second, third, or fourth-line biological treatment.

9. **Normalization of Bowel Wall Thickness (BWT) at 12, 24 e 54 ± 4 weeks (optional)**

- To determine the proportion of patients exhibiting normalization of bowel wall thickness (BWT) on intestinal ultrasound (IUS), defined as a rectum ≤4.0 mm, sigmoid colon ≤4.0 mm, descending colon ≤3.0 mm, transverse colon ≤3.0 mm, and ascending colon ≤3.0 mm, at 12, 24 e 54 ± 4 weeks. This will be evaluated only in patients with increased BWT at baseline. [7,8]

10. **Ultrasound Remission at 12, 24 e 54 ± 4 weeks (optional)**

- To evaluate the proportion of patients achieving an intestinal ultrasound remission score of ≤6.2 based on the Milano Ultrasound Criteria (MUC) after 12, 24 e 54 ± 4 weeks of Etrasimod treatment. This will be evaluated only in patients with an MUC score >6.2 at baseline.

11. **Deep Remission at 12, 24 e 54 ± 4 weeks**

- To assess the proportion of patients achieving deep remission at 12, 24 e 54 ± 4 weeks, defined as a rectal bleeding subscore of 0, a stool frequency subscore of 0, and an eMayo score ≤1. [9]

12. **Disease Clearance at 12, 24 e 54 ± 4 weeks**

- To evaluate the proportion of patients achieving disease clearance at 12, 24 e 54 ± 4 weeks, defined as simultaneous attainment of deep remission (see above) and histologic remission (Nancy Histological Index = 0, indicating absence of significant inflammatory infiltrate)

13. **Quality of Life Assessment**

- To assess changes in health-related quality of life, measured using the IBD Disability Index (IBD-Disk) and the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT–Fatigue) questionnaire, 12, 24 e 54 ± 4 weeks.

14. **Safety assessment through the 54 weeks**, reporting side effects related to Etrasimod

**Study Population**

**Inclusion Criteria:**

- Adults aged ≥18 years with a confirmed diagnosis of UC for at least 6 months.
- Moderate-to-severe UC defined by a Mayo Clinic total score between 6 and 12 inclusive, with an endoscopic subscore ≥2.
- Inadequate response, loss of response, or intolerance to at least one prior biologic therapy (e.g., anti-TNF agents, vedolizumab, ustekinumab).

**Exclusion Criteria:**

- Diagnosis of Crohn's disease or indeterminate colitis.
- History of colectomy or anticipated need for colectomy during the study period.
- Presence of colonic dysplasia or malignancy.
- Active or latent tuberculosis not adequately treated.
- Serious uncontrolled medical conditions (e.g., severe infection, significant hepatic or renal impairment).
- Known hypersensitivity to Etrasimod or its excipients.

**Intervention**

**Etrasimod Dosing Regimen:**

- **Induction Phase:**
    - Etrasimod 2 mg administered orally once daily.
- **Maintenance Phase:**
    - Etrasimod 2 mg administered orally once daily up to Week 54.

**Study Assessments and Visits**

**Baseline (Week 0):**

- Comprehensive clinical assessment, including 9-point MMS.
- Endoscopic evaluation to assess mucosal appearance (endoscopic MAYO and UCEIS scores).
- Histological assessment via biopsy (Nancy score).
- Baseline PROs, including urgency numeric scale (UNRS).
- Laboratory tests: FC, CRP, complete blood count (CBC), liver and renal function tests.
- Collection of demographic and disease-specific data.
- Ultrasound evaluation of colonic and rectal wall thickness, if feasible (Milan Ultrasound Criteria).

**Week 12, 24, 54 Assessments:**

- Clinical response and remission assessment.
- Laboratory tests: FC, CRP.
- PRO assessments, including UNRS.
- Endoscopic and histological evaluation at Week 54.
- Safety monitoring.
- Ultrasound evaluation (Week 54, if feasible).

**Urgency Numeric Rating Scale (UNRS) Assessment:**

- Urgency severity will be evaluated using the validated UNRS, with scores ranging from 0 (no urgency) to 10 (worst possible urgency).
- Improvement in UNRS scores will be analyzed at Weeks 12, 24, and 54, and correlated with clinical remission and mucosal healing.
- This assessment will provide insights into symptom control and quality of life improvements in Etrasimod-treated patients.

**Safety Monitoring**

- Adverse events will be recorded and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.
- Immediate reporting of any serious adverse events to relevant regulatory bodies.

**Sample Size Determination:**

The required sample size for McNemar's test of paired proportions, based on the asymptotic approximation by Miettinen (1968), with a two-sided alpha level of 0.05, power of 0.8, probabilities of discordant pairs 0–1 and 1–0 equal to 0.35 and 0.10 respectively [10], and a drop-out rate of 5%, is 68 pairs**.** The McNemar test will be used to assess changes in paired proportions, particularly in the context of pre- and post-intervention comparisons of binary outcomes.

**Data Collection**

**Statistical analysis**

Continuous data will be expressed as mean ± standard deviation (SD) or median and interquartile range (25th–75th percentile), while categorical variables will be reported as absolute and relative frequencies. Normality will be assessed using the Kolmogorov–Smirnov test and Levene's test for homogeneity of variance. The primary endpoint is the proportion of patients achieving deep remission at Week 54, defined as a binary variable. To compare paired proportions (e.g., remission status at baseline vs Week 54), McNemar's test will be used. To identify predictors of remission, multivariable logistic regression models will be applied, adjusting for baseline covariates. Repeated measures at Weeks 12, 24, and 54 will be analyzed using generalized estimating equations (GEE) with an appropriate link function (logit for binary outcomes; identity for continuous) to account for within-subject correlations over time. When evaluating continuous outcomes, repeated-measures ANOVA or linear mixed models may be used as appropriate. Between-group comparisons of continuous variables will be conducted using Student's t-test or Mann–Whitney U test, depending on data distribution. Chi-square or Fisher's exact test will be used for categorical comparisons. Associations between variables will be assessed using Spearman's correlation coefficient. Survival outcomes (if any) will be analyzed using the Kaplan–Meier method, with comparisons made using the log-rank test. Hazard ratios (HR) will also be presented using smoothed estimates to visualize changes over time. A two-tailed p-value $< 0.05$ will be considered statistically significant. All analyses will be conducted using SPSS v27.0, R (version 3.4.3), and EZR.

**Ethical Considerations**

- The study will adhere to the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines.
- Written informed consent will be obtained from all participants before any study-related procedures.

**Enrollment Period**

- **Duration:** Enrollment is planned to commence in July 2025 or upon commercial availability of the investigational drug, which is currently accessible exclusively under compassionate use. The enrollment window will extend for 6 months from the date of drug availability. Each participant will be followed for 54 ± 4 weeks from the time of inclusion.
- **Recruitment Strategy:**
    - Patients will be recruited from multiple specialized inflammatory bowel disease (IBD) centers across different geographic regions.
    - Investigators will work closely with referring clinicians to ensure eligible patients are identified promptly.
    - Digital outreach and patient registries may be utilized to enhance recruitment efforts.
- **Enrollment Monitoring:**
    - Monthly updates on enrollment numbers will be provided to participating centers.
    - Interim analyses may be conducted to evaluate the recruitment pace and adjust strategies accordingly.