Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

the Italian Group for the study of Inflammatory Bowel Disease

Study protocol

RESOLVE: Risankizumab Evaluation Study of Outcomes in real Life and Verification of Effectiveness and safety

The "RESOLVE" study

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CLINICAL STUDY PROTOCOL INVESTIGATOR SIGNATURE PAGE

Study Title:	**RESOLVE: Risankizumab Evaluation Study of Outcomes in real Life and Verification of Effictiveness and safety**

The Principal-Investigator has approved the protocol version dated and confirms hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines, ISO 14155 norm and the local legally applicable requirements.

Principal-Investigator: Prof. Franco Scaldaferri

Date Signature

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1. Background

Inflammatory bowel diseases (IBDs), such as Crohn's disease (CD) and ulcerative colitis (UC), are chronic and debilitating conditions which affect the gastrointestinal tract and are characterized by a relapsing-remitting course [1]. Their pathogenesis is multifactorial, likely triggered by a dysregulated immune response to the gut microbiota in genetically susceptible individuals [2,3].

Traditionally, the management of IBD patients involved a broad spectrum of anti-inflammatory drugs, including 5-aminosalicylic acid drugs, steroids, and non-targeted immunosuppressants [4,5]. However, over the past two decades, with an increased understanding of the underlying disease mechanisms, there has been a therapeutic revolution, including biological therapies and small molecules targeting the adaptive immune system [6].

Since the late 1990s, the emergence of TNF inhibitors (such as infliximab and adalimumab) has represented a breakthrough in the treatment and disease control. These inhibitors have demonstrated excellent efficacy in inducing and maintaining remission, preventing disease complications, and achieving mucosal healing [7]. However, date from the literature indicate that up to 30% of patients do not respond to initial therapy with TNF inhibitors, and up to 50% lose response over time, with 10% ultimately requiring surgery [8]. Consequently, there is an urgent need to develop new molecules targeting different molecular targets.

New drugs with different signaling pathways for intestinal inflammation have been developed, targeting molecules such as α4β7 integrin, Janus kinase (JAK), and interleukin 12 and 23 (IL-12/ IL-23). In particular, studies on murine models have highlighted the critical role of IL-12 and IL-23 in promoting various inflammatory conditions, including colitis [9]. This understanding has spurred the development of new molecules targeting this pathway.

IL-12, primarily produced by dendritic cells, macrophages, and neutrophils in response to antigens, plays a pivotal role in guiding T-cell differentiation towards the Th1 interferon-gamma-producing lineage. In contrast, IL-23, formed by a complex of IL-12p40 and IL-23p19 subunits, plays a crucial role in Th17 cell differentiation and activates inflammatory cascades via JAK and STAT pathways [10–12]. Dysregulation of IL-23 may contribute to the development or exacerbation of intestinal inflammation by regulating effector cytokines such as IL-22 [10,13]. In patients with Crohn's disease, elevated levels of IL-23 are typically found in the mucosal lining. Additionally, genome-wide association studies have highlighted a significant link between variations in the IL-23 or IL-23 receptor (IL-23R) gene and the development of inflammatory bowel diseases [14–17]. Finally, variants of the IL-23R gene have been observed to influence the levels of IL-22 in the bloodstream, which in turn have been linked to the severity of the disease.

This understanding marks a turning point in our knowledge of IBD pathogenesis and has led to a growing interest in selectively blocking IL-23 [12,18]. Efforts have been directed towards developing increasingly selective drugs to minimize off-target/side effects and maximize efficacy [19].

The first generation of treatments involves therapy directed at anti-IL-12p40, with efficacy attributed to the inhibition of IL-23 rather than direct blocking of IL-12 [11]. Ustekinumab, a p40 subunit IgG1k inhibitor of IL12/23, has been a notable candidate in this category, demonstrating efficacy and safety for both CD and UC [20–22].

The second generation of selective anti-IL-23 therapies targets IL-23p19 and showed greater effectiveness compared to ustekinumab in other immune-mediated conditions, such as plaque psoriasis [23,24]. The rationale for specifically targeting the p19 subunit of IL-23 is to enhance safety by preserving the normal IL-12-mediated Th1 immune response, crucial for defending against intracellular pathogens [25]. This approach aims to maintain efficacy achieved with p40 antibodies while avoiding potential disruptions to the immune response [22]. Indeed, the IL-12-mediated Th1 response has been suggested to have a more significant impact on susceptibility to certain diseases, such as mycobacterial infections, compared to the IL-23-mediated Th17 response [26]. Similar relationships have been observed with other pathogens. By selectively targeting IL-23p19 while leaving IL-12 intact, host immunity against a variety of pathogens could be preserved [11,22]. However, despite belonging to the same drug category, these therapies have different molecular attributes that may result in differences in clinical efficacy.

Risankizumab, a monoclonal antibody targeting the IL-23 p19 subunit, has recently been approved for the treatment of Crohn's Disease by hindering its interaction with the IL-23R complex. In a randomized, double-blinded, phase 2 trial involving patients with moderate to severe Crohn's disease, intravenous induction therapy with risankizumab proved well-tolerated and effective at doses of 200 mg and 600 mg, regardless of patients' prior exposure to TNF antagonist therapy or vedolizumab [27]. Furthermore, two phase 3 studies, ADVANCE and MOTIVATE, showed that risankizumab was well-tolerated and led to significant early improvements compared to placebo across primary and secondary endpoints, in patients with moderate to severe Crohn's disease, irrespective of prior treatment history. IL-22, serving as a marker of IL-23 activity, decreased at week 12 with risankizumab treatment (600 mg and 1200 mg) but remained unchanged with placebo, Early symptom relief was associated with reductions in CRP and faecal calprotectin. The safety profile of risankizumab in Crohn's disease was consistent with previous studies in other conditions, with no new safety concerns identified [28].

Notably, previous literature revealed different rates of efficacy and effectiveness respectively assessed by randomized clinical trials (RCTs) and real-life studies for previously approved IBD biological drugs. Much of this variability stems from the strict inclusion and exclusion criteria employed in RCTs to select patients, which often exclude a significant portion of real-life patient. As a result, findings from RCTs may not always reflect real-world clinical practice. To address this gap, we established this study to assess the effectiveness of risankizumab in a multicenter, real-world cohort of CD patients.

Our study will encompass a retrospective cohorts of CD patients who is initiating biological treatment with risankizumab across various secondary and tertiary IBD centers in Italy with the objective to assess clinical, endoscopic and radiologic effectiveness of this promising new treatment in real-life CD patients.

2. Study aims

1. Primary aims

To evaluate the percentage of patients achieving the steroid-free clinical-practice deep remission of CD after 12 months from baseline of treatment with risankizumab (defined as the combination of patient reported outcomes (PRO) (patients reported abdominal pain ≤1 and average stool consistency ≤5 on Bristol Stool Scale without use of oral/intravenous steroids (prednisone-equivalent or budesonide) in the last 3 months) with an objective parameter of inflammation.

Faecal calprotectin <150 mcg/g, OR Simple Endoscopic Score for Crohn's Disease (SES-CD) ≤4 and at least a 2-point reduction vs baseline and no subscore >1 in any individual variable, OR transmural healing at MRI/CT scan enterography or intestinal ultrasound, defined as bowel wall thickness (BWT) ≤ 3 mm with no signs of active disease.

2. Secondary aims

1. To evaluate the percentage of patients achieving the steroid-free CPDR of CD after 6 and 24 months of risankizumab.
2. To evaluate the percentage of patients achieving clinical remission of CD (defined as HBI < 5) after 3 months, 12 months and 24 months of risankizumab. This aim will be evaluated only in patients with an HBI> 5 at baseline.
3. To evaluate the percentage of patients showing clinical response of CD (defined as a reduction of the HBI of at least 3 points from baseline) after 3 months, 6 months, 12 months and 24 months of risankizumab.
4. To evaluate the percentage of patients achieving endoscopic remission of CD (defined as SES-CD ≤4 and at least a 2-point reduction vs baseline and no subscore >1 in any individual variable) after 3 months, 6 months, 12 months and 24 months of risankizumab.
5. To evaluate the percentage of patients showing endoscopic response of CD (defined as a greater than 50% decrease in SES-CD from baseline (or for isolated ileal disease and a baseline SES-CD of 4, at least a 2-point reduction from baseline) after 3 months, 6 months, 12 months and 24 months of risankizumab.

6. To evaluate the percentage of patients achieving the steroid-free "deep remission" of CD, defined as the combination of clinical remission and endoscopic remission according to the above mentioned criteria (PMID: 26303131) after 6 months, 12 months and 24 months of risankizumab.
7. To evaluate the percentage of CD patients achieving transmural healing at CT-scan or MRI enterography or at intestinal ultrasound (defined as a BWT ≤ 3 and normal parietal contrast enhancement or color Doppler signal (CDS) or absence of hyperemia) after 3 months, 6 months, 12 months and 24 months of risankizumab.
8. To evaluate the percentage of patients showing response of CD at radiological exams, including CT-scan or MRI enterography and intestinal ultrasound (defined as a decrease in BWT by 25% from baseline or 2.0 mm, or greater than 1.0 mm with a decrease in parietal contrast enhancement or in CDS assessed by the modified Limberg score of one grade) after 3 months, 6 months, 12 months and 24 months of risankizumab.
9. To assess the variation of C-reactive protein (CRP) after 3 months, 6 months, 12 months and 24 months of treatment with risankizumab in CD patients.
10. To identify clinical, endoscopic or radiologic predictors of deep remission in CD at 12 months and 24 months.
11. To evaluate the percentage of patients achieving control of extraintestinal manifestation at 3 months, 6 months, 12 months and 24 months.
12. To compare the efficacy of risannkizumab, as assessed according to the primary endpoint of the study, when used as second, third or fourth line of biological treatment.
13. To assess the safety of risankizumab during the entire study period.

2. Study endpoints

2.1. Primary endpoint

Primary endpoint of the study is the proportion of CD patients achieving steroid-free clinical-practice-deep remission (CPDR) after 12 months from baseline of treatment with Risankizumab, defined as the combination of:

patient reported outcomes (PRO) (patients reported abdominal pain ≤1 and average stool consistency ≤5 on Bristol Stool Scale without use of oral/intravenous steroids (prednisone-equivalent or budesonide) in the last 3 months)

AND an objective parameter of inflammation:

Faecal calprotectin <150 mcg/g, OR SES-CD ≤4 and at least a 2-point reduction vs baseline and no subscore >1 in any individual variable, OR transmural healing at MRI/CT scan enterography or intestinal ultrasound, defined as BWT ≤ 3 mm with no signs of active disease.

2.2. Secondary endpoints

1. Percentage of patients achieving the CPDR of CD after 6 and 24 months of risankizumab.
2. Percentage of patients achieving clinical remission of CD (defined as HBI < 5) after 3 months, 6 months, 12 months and 24 months of risankizumab.
3. Percentage of patients showing clinical response of CD (defined as a reduction of the HBI of at least 3 points from baseline) after 3 months, 6 months, 12 months and 24 months of risankizumab. This endpoint will be assessed only in patients with an HBI> 5 at baseline.
4. Percentage of patients achieving endoscopic remission of CD (defined as SES-CD ≤4 and at least a 2-point reduction vs baseline and no subscore >1 in any individual variable) after 3 months, 6 months, 12 months and 24 months of risankizumab.
5. Percentage of patients showing endoscopic response of CD (defined as a greater than 50% decrease in SES-CD from baseline (or for isolated ileal disease and a baseline SES-CD of 4, at least a 2-point reduction from baseline) after 3 months, 6 months, 12 months and 24 months of risankizumab.
6. Percentage of patients achieving the steroid-free "deep remission" of CD, defined as the combination of clinical remission and endoscopic remission according to the above-mentioned criteria (PMID: 26303131) after 6 months, 12 months and 24 months of risankizumab.
7. Percentage of CD patients achieving transmural healing at CT-scan or MRI enterography or at intestinal ultrasound (defined as a BWT ≤ 3 and normal parietal contrast enhancement or color Doppler signal (CDS) or absence of hyperemia) after 3 months, 6 months, 12 months and 24 months of risankizumab.
8. Percentage of patients showing response of CD at radiological exams, including CT-scan or MRI enterography and intestinal ultrasound (defined as a decrease in BWT by 25% from baseline or 2.0 mm, or greater than 1.0 mm with a decrease in parietal contrast enhancement or in CDS assessed by the modified Limberg score of one grade) after 3 months, 6 months, 12 months and 24 months of risankizumab.

9. Variation of C-reactive protein (CRP) after 3 months, 6 months, 12 months and 24 months of treatment with risankizumab in CD patients.
10. Identification of clinical, endoscopic or radiologic predictors of deep remission in CD at 12 months and 24 months.
11. Percentage of patients achieving control of extraintestinal manifestation at 3 months, 6 months, 12 months and 24 months.
12. Comparison between the efficacy of risankizumab, as assessed according to the primary endpoint of the study, when used as second, third or fourth line of biological treatment.
13. Assessment of the safety of risankizumab during the entire study period.

3. Study design and investigational plan

3.1. Overall study design

This is a multicenter, retrospective observational study with drug, including patients fulfilling inclusion and exclusion criteria, whom data required for the protocol are available.

We will include consecutive patients affected by CD, who have initiated Risankizumab and failed (already exposed) at least one mechanism of action (for anti TNF-alpha several molecules are allowed), until January 2024.

3.2. Study duration and milestones

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

4. Study population

4.1. Recruitment

Suitable subjects will be identified from patients referred to the IBD Unit of the Digestive Disease Center (CEMAD) of Fondazione Policlinico Universitario Agostino Gemelli IRCCS in Rome Italy and to all others IBD Unit of all centres involves. Based on the number of patients that are referred to the clinics, we estimate that 30 patients per month, time for recruitment is 24 months. The potential study participants will receive oral and written information of the study. Patients that agree to participate in the study will be asked to sign a written informed consent according to GCP.

4.2. Inclusion criteria

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

1. Age of at least 18 years.
2. Patients with a previous diagnosis of CD at least 3 months before baseline.
3. Patients who have failed at least one advanced (biological or small molecule) therapy for CD and who have experienced failure to at least one mechanism of action (failure is defined as primary failure, secondary failure, or intolerance).
4. Patients, with any grade of clinical or endoscopic disease activity who have started a therapy with risankizumab for CD based on clinical practice indication (primary loss of response, secondary loss of response, intolerance to the previo us drug).
5. Written informed consent certifying the willingness of the subject to participate to the study.

4.3. Exclusion criteria

1. Age < 18 years.
2. Patients with diagnosis of indeterminate IBD.
3. Patients naive to advanced (biological or small molecule) therapy for IBD.
4. Refusal to sign written informed consent certifying the willingness of the subject to participate to the study.

4.4. Sample size evaluation and statistical analysis

Based on the real-life study design and on the primary endpoint, which foresees a descriptive evaluation of remission rates according to each therapy line considered, we present diverse scenarios of potential sample size (from 50 till 300 by 25), and related confidence intervals in order to detect a CPDR at 12 months of 50-55 and 60% according to the evidence available from the current literature on the drugs under investigation. All scenarios are assessed according to a single group study design with a two-sided 95% confidence interval for a single proportion. A table with all potential scenarios will be provided as attachment.

As an example, such single-group design to obtain a two-sided 95% confidence interval for a single proportion, assuming a sample proportion of 0.5, with a sample size of 50, would produce a confidence

interval width of 0.28945, i.e., 0.5 ±0.145. The confidence interval widths were computed using PASS 2022, version 22.0.4 [29].

Based on the data available to the participating centers (for the retrospective phase) and the recruitment capabilities of the centers during the enrollment period, we expect to enroll 200 subjects with Crohn disease in this retrospective study.

The sample will be described in its clinical and demographic characteristics by descriptive statistics techniques. In depth, qualitative data will be expressed as absolute and relative percentage frequency, whilst quantitative variables either by mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate. To verify the Gaussian distribution of quantitative variables, the Shapiro-Wilk test will be applied. Eventual missing values (if <5%) will be treated by imputeR package, using multiple imputation with Lasso Regression methods centered on the mean for quantitative data, whilst classification trees for imputation by "rpartC" function, centered on the mode, i.e. most represented class object, will be applied on qualitative data [30]. The sample will be described in its clinical and demographic characteristics by descriptive statistics techniques. In depth, qualitative data will be expressed as absolute and relative percentage frequency, whilst quantitative variables either by mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate. To verify the Gaussian distribution of quantitative variables, the Shapiro-Wilk test will be applied. Eventual missing values (if <5%) will be treated by *imputeR* package, using multiple imputation with Lasso Regression methods centered on the mean for quantitative data, whilst classification trees for imputation by "rpartC" function, centered on the mode, i.e., most represented class object, will be applied on qualitative data [30].

Between-group differences at baseline will be assessed by either the Chi-squared or the Fisher-Freeman-Halton's exact test for qualitative variables, whilst with either one-way ANOVA or non-parametric Kruskal Wallis will be applied to quantitative data. Pairwise comparisons will be performed by either Student's t test or Mann-Withney U test, as appropriate, with "False Discovery rate" correction for multiple comparisons. AEs and SAEs will be assessed by descriptive statistics and compared among the different lines with the aforementioned inferential tests.

The evaluation of the difference in terms of CPDR at 12 months and 24 months, respectively, according to the different biological sequential therapies at II and III lines will be evaluated by Kaplan-Meier survival analysis. In particular, the log-rank test will be applied and appropriate cumulative incidence curves will be drawn. The analysis will be performed using the R packages "*ggplot2*" and "*survminer*" [31,32].

Potential predictors of CPDR will be assessed by Cox regression models. In detail, the potential predictors of the outcome will be evaluated by means of ordinary proportional hazards Cox regression models, and the Hazard Ratios (HR) and the 95% confidence intervals (CIs) will be reported. The proportionality of the hazard functions will be evaluated by visual inspection of the hazards and Schoenfeld residual plots. In case of doubtful proportionality, Cox weighted regression models will be

fitted. The analysis will be performed with "*survival*" and "*coxphw*" R packages [33-37]. Whether possible due to the different sample sizes of each therapeutic line and sequential strategy, to evaluate the combined effects between drug and line of administration, multivariable interaction models will be fitted, one per each predictor, and the interaction hazard ratios (IHR) reported. In summary, the coefficients of the main effects (in exponential terms) will be interpreted as HRs of the outcome by considering a unit increase of the predictor in the reference category (first line) (HRpredictor) as for quantitative predictors, whilst as increase in the hazard of the outcome occurring, as compared with the (arbitrarily) chosen reference group for qualitative data. The interaction parameters (IHR) will be interpreted as difference (in HR terms) of variations of the predictors among the different lines (first line as reference category).

5. Study procedures

5.1. Experimental procedures

Data will be retrieved from the electronic archives of all participating center. Each patient will be identified by a number who will avoid double insertion of the same patient and will ensure the anonymization of data. Collected data will be entered in an electronic case report form (RedCap) and will follow all the requirements of Italian privacy policy.

In depth, the standard points will be: induction of therapy (T0 - week 0); 12 weeks after the beginning of therapy (T1), 6 months after the beginning of therapy (T2), 12 months after the beginning of therapy (T3), and 24 months after the beginning of therapy (T4).

The following clinical data at each time-point will be collected, to calculate Harvey Bradshaw Index – general well-being, abdominal pain, number of liquid/soft stools, abdominal mass and extraintestinal manifestations for CD.

Endoscopic or radiologic monitoring of disease activity respectively by ileocolonoscopy or intestinal ultrasound or CT-scan or MRI-enterography will be collected at baseline and at 12 and 24 months after the start of therapy. Endoscopic disease activity will be assessed according to the SES-CD.

Steroid-free clinical practice deep remission (CPDR) will be defined based on patient reported outcomes (PRO) combined with an objective parameter of inflammation:

- patients reported abdominal pain ≤1 and average stool consistency ≤5 on Bristol Stool Scale without use of oral/intravenous steroids (prednisone-equivalent or budesonide) in the last 3 months;

AND

- Faecal calprotectin <150 mcg/g, OR SES-CD ≤4 and at least a 2-point reduction vs baseline and no subscore >1 in any individual variable, OR transmural healing at MRI/CT scan enterography or intestinal ultrasound, defined as BWT ≤ 3 mm with no signs of active disease.

6. Ethical aspects

6.1. Study performance

The study will be conducted in concordance with the principles of the "Declaration of Helsinki" and according to Good Clinical Practice (GCP) guidelines.

6.2. Institutional Review Board/Institutional Ethics Committee (IRB/IEC)

Documented approval from the appropriate Institutional Review Board /Ethics Committee (IRB/IEC) will be obtained prior to study start, according to ICH GCP, local laws, regulations, and organization. When necessary, an extension, amendment, or renewal of the IEC approval must be obtained. The IEC must supply to the sponsor a list of the IRB/IEC membership and a statement to confirm that the IEC is organized and operates according to GCP and applicable laws and regulations.

6.3. Patient Informed Consent

A core information and consent form will be provided. Prior to the beginning of the study, the investigator must have the IEC written approval/favorable opinion of the written patient informed consent and any other written information to be provided to patients. The written approval of the IEC together with the approved patient information/patient informed consent must be filed in the study files. The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s),and must adhere to GCP principles and to the ethical principles originating in the Declaration of Helsinki. Participation in the trial and date of informed consent given by the patient should be documented appropriately in the patient files.

6.4. Data protection and patient's privacy

All records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. The PI, the co-investigators and the personnel involved in the trial will comply with the GCP principles about storage, elaboration and divulgation of sensitive data.

Patient names will be kept confidential. Only the patient number and initials will be recorded in the eCRF (IGIBD RedCap). Study findings stored on a computer will be stored in accordance with local data protection laws. The patients will be informed in writing that representatives of the sponsor, IEC or Regulatory Authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. Patients will also be informed that information regarding the study that does not include patient identifiers 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 patients' records to be identified. Data storage will be under the responsibility of the PI.

7. Publication Policy

Upon publication of the results, the list of Authors will be outlined as follows:

1. The first two Authors will be the investigators from the Coordinating Centre responsible for writing the manuscript and analysing the data
2. The last Author will be the Principal Investigator from the Centre with the largest number of patients enrolled.
3. The other Authors will be listed in descending order according to the number of patients enrolled and included in the final analysis, up to a maximum of 20 Authors. If a Centre has included more than 5 patients in the study, an additional Author from that Centre will be considered for inclusion in the list."

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