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ORIGINAL ARTICLE

Real-World Effectiveness of Risankizumab in Refractory Crohn's Disease: The RISANCROHN Study From the ENEIDA Registry

Manuel Barreiro-de Acosta[1] | Yamile Zabana[2] | Laura Nieto-García[1] | Marta Poncela[3] | Mariam Aguas[4] | Cristina Martínez-Cuevas[5] | Federico Argüelles-Arias[6] | Marta Calvo[7] | Carla J. Gargallo-Puyuelo[8] | Lucía Zabalza[9] | Pilar Varela Trastoy[10] | Maia M. Boscá-Watts[11] | Daniel Ceballos[12] | Cristina Martínez Pascual[13] | Francisco Rodríguez-Moranta[14] | María Luisa de Castro Parga[15] | Patricia Suárez[16] | Blau Camps[17] | Vanesa Royo[18] | Iria Baston-Rey[1] | Ruth de Francisco[19] | Santiago García-Lopez[20] | María Dolores Martín-Arranz[21] | Fernando Bermejo[22] | Inmaculada Alonso-Abreu[23] | Javier P. Gisbert[24] | Montserrat Rivero[25] | Beatriz Sicilia[26] | Isabel Nicolás[27] | Marta Teller[28] | Ángel Ponferrada Díaz[29] | Elena Ricart[30] | María Algara[31] | Paola Fradejas[32] | Pilar Robledo[33] | Lucía Madero[34] | Ainara Elorza[35] | Marta Piqueras[36] | Mari Fe Garcia-Sepulcre[37] | Eva Sesé[38] | Alejandro Hernandez-Camba[39] | Sandra Izquierdo[40] | Ana M. Trapero[41] | Eva Iglesias[42] | María Teresa Diz-Lois Palomares[43] | Eduard Brunet-Mas[44] | Jesús Castro Poceiro[45] | David Busquets[46] | Miriam Manosa[47] | Ramón Pajares[48] | Juan A. Ferrer[49] | Daniel Carpio[50] | Francisco Mesonero[51] | Luis Bujanda[52] | Rufo Lorente[53] | Javier Santos[54] | Carlos Martínez Flores[55] | Carlos González-Muñoza[56] | Daniel Martín[57] | Margarita Menacho[58] | Nuria Maroto[59] | Martín Irabien[60] | Sol Porto-Silva[1] | Eugeni Domènech[47] | Rocío Ferreiro-Iglesias[1] | on behalf of the ENEIDA Project of GETECCU

Correspondence: Manuel Barreiro-de Acosta (manubarreiro@hotmail.com)

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ABSTRACT

Background and Aims: Risankizumab, a selective interleukin-23 p19 inhibitor, has demonstrated efficacy in clinical trials for moderate-to-severe Crohn's disease, but real-world data in highly refractory populations are limited. We evaluated the short-term effectiveness and outcomes at last follow-up of risankizumab and the impact of prior advanced therapy exposure.

Methods: This multicentre observational study included adult patients with predominantly refractory Crohn's disease treated with risankizumab and registered in the ENEIDA registry. Steroid-free clinical remission, defined as a Harvey–Bradshaw Index ≤ 4 without systemic corticosteroids, was assessed at weeks 8–12 and at the last available follow-up visit. Multivariable logistic regression was used to identify factors associated with remission at last follow-up.

Results: A total of 857 patients with predominantly refractory Crohn's disease were included. Steroid-free clinical remission was achieved in 56% of patients at weeks 8–12 and in 61% at last follow-up (mean follow-up: 7.4 months). Remission rates were higher in patients previously exposed to ≤ 2 biologic therapies than in those exposed to > 2 biologic therapies at both time points ($p < 0.001$). Prior ustekinumab exposure was associated with lower remission rates in unadjusted analyses but was not independently associated with remission at last follow-up. Treatment-related adverse events occurred in 8% of patients, with no serious adverse events.

Abbreviations: **CD**, Crohn's disease; **CI**, confidence interval; **HBI**, Harvey–Bradshaw Index; **3IL-23**, interleukin-23; **OR**, odds ratio; **RWE**, real-world evidence; **RZB**, risankizumab; **TNF**, tumour necrosis factor; **UST**, ustekinumab.

For affiliations refer to page 9.

Conclusions: In this large real-world cohort of patients with refractory Crohn's disease, risankizumab achieved clinically meaningful steroid-free clinical remission, both at early assessment and at last follow-up, with effectiveness primarily influenced by cumulative biologic exposure and demonstrating a favourable safety profile.

1 | Introduction

Crohn's disease (CD) is a chronic, immune-mediated inflammatory disorder with a relapsing and progressive course that may lead to cumulative bowel damage, disability, and impaired quality of life. Despite major therapeutic advances, most patients in routine clinical practice initiate advanced therapy with anti-tumour necrosis factor (anti-TNF) agents. A substantial proportion subsequently experience primary non-response or loss of response, resulting in refractory disease and an ongoing unmet clinical need [1–3].

Interleukin-23 (IL-23) plays a key role in the pathogenesis of CD by sustaining Th17-mediated intestinal inflammation. Selective inhibition of the IL-23 p19 subunit enables more targeted immune modulation than agents blocking the shared IL-12/23 p40 subunit. Risankizumab (RZB), a humanized monoclonal antibody targeting IL-23 p19, has demonstrated robust efficacy and a favourable safety profile in patients with moderate-to-severe CD, including those with prior biologic failure. In pivotal phase III trials (ADVANCE, MOTIVATE, and FORTIFY), RZB achieved clinical remission rates of approximately 40%–45% during induction, with sustained remission during maintenance, even in biologic-experienced populations [4–6].

While randomized controlled trials establish efficacy under controlled conditions, their generalizability to routine clinical practice is limited, particularly for patients with long-standing and highly refractory CD. Real-world studies include patients with more advanced disease, extensive prior biologic exposure, and multiple treatment failures, providing a complementary perspective. Across real-world cohorts, RZB has shown consistent effectiveness, with clinical remission rates of approximately 40%–50% after induction and steroid-free remission maintained in a substantial proportion of patients at 6 to 12 months [7–12].

However, available real-world evidence remains limited by relatively small sample sizes and short follow-up, particularly in highly refractory populations [8, 10]. In addition, data evaluating the impact of prior ustekinumab (UST) exposure on subsequent response to RZB are scarce. Prior UST exposure may reflect cumulative refractoriness rather than true mechanistic failure, highlighting the need for large multicentre studies to disentangle the effect of individual therapies from overall biologic burden.

The optimal positioning of RZB after UST exposure also remains unclear. Although the SEQUENCE trial demonstrated superior endoscopic outcomes with RZB compared with UST, real-world data on treatment sequencing are heterogeneous, especially in heavily pre-treated populations [13, 14]. Large multicentre studies are therefore needed to better characterize the impact of cumulative advanced therapy exposure and inform therapeutic sequencing in clinical practice.

The aims of the present study were therefore to assess the short-term real-world effectiveness and safety of RZB in patients with CD included in the ENEIDA registry, and to evaluate outcomes during follow-up, as well as the impact of prior UST exposure and cumulative advanced therapy use on treatment outcomes.

2 | Methods

2.1 | Study Design and Data Source

This was a multicentre, observational study conducted using data from the ENEIDA registry, a nationwide, prospectively maintained database promoted by the Spanish Working Group on Crohn's Disease and Ulcerative Colitis (GETECCU). ENEIDA includes patients with inflammatory bowel disease monitored in routine clinical practice across Spain [15]. The registry allows both prospective longitudinal follow-up and retrospective analyses of predefined cohorts. The present study was designed according to a prespecified protocol approved by the GETECCU scientific committee.

2.2 | Study Population

Adult patients (≥18 years) with an established diagnosis of CD who initiated treatment with RZB for active disease (Harvey–Bradshaw Index (HBI) > 4) in routine clinical practice were eligible for inclusion. Only patients registered in ENEIDA and RZB were administered according to the approved label, consisting of 600-mg intravenous induction at weeks 0, 4 and 8, followed by 360-mg subcutaneous maintenance therapy every 8 weeks from week 12 onward. Patients were excluded if RZB was prescribed for indications other than CD or if no post-baseline follow-up information was available. For short-term effectiveness analyses, patients who discontinued RZB before week 12 due to primary non-response, loss of response, or intolerance were classified as non-responders. Patients were considered to represent a predominantly refractory CD population, based on prior exposure to advanced therapies and previous biologic failure in routine clinical practice. This definition reflects a pragmatic real-world approach and does not imply that all patients fulfilled the same degree of refractoriness. Although the majority of patients had extensive prior biologic exposure, a minority were biologic-naïve or had limited prior exposure, consistent with routine clinical practice in which advanced therapies may be initiated at different stages of disease. Patients receiving combination therapy with more than one advanced therapy were excluded from the study.

2.3 | Baseline Variables and Prior Treatment Exposure

Baseline demographic and disease-related variables were extracted from the ENEIDA registry, including sex, age at RZB

initiation, smoking status, disease duration, and Montreal classification (age at diagnosis, disease location and disease behaviour). Additional baseline characteristics included the presence of perianal disease, extraintestinal manifestations, and history of CD-related surgery. Given the refractory nature of the study population, detailed information on prior exposure to advanced therapies was collected, including the total number of previous advanced agents and exposure to specific therapeutic classes such as anti-TNF agents, vedolizumab, upadacitinib and UST. Prior UST exposure was predefined as a key variable of interest based on its clinical relevance for treatment sequencing. Concomitant therapies at RZB initiation, including systemic corticosteroids and immunomodulators, were also recorded. Corticosteroid use and tapering were managed at the discretion of the treating physician, according to routine clinical practice. Disease activity was assessed using the HBI, as routinely recorded in the ENEIDA registry. Individual components of the HBI and PRO-2 data were not systematically collected.

2.4 | Treatment Exposure

RZB was administered according to the approved label and local clinical practice. Information on induction and maintenance regimens, treatment continuation, optimization strategies (including dose intensification or reinduction when applicable), and treatment discontinuation was collected throughout follow-up. Dates of RZB initiation and last available follow-up were collected for all patients.

2.5 | Outcomes and Definitions

The primary effectiveness outcome was steroid-free clinical remission, defined cross-sectionally as HBI ≤ 4 in the absence of systemic corticosteroid use at the time of assessment. No minimum corticosteroid-free interval was required before the assessment. This outcome was evaluated at two predefined time points: (1) short-term effectiveness, evaluated between weeks 8 and 12 after RZB initiation; and (2) at last available follow-up, defined as steroid-free clinical remission at the time of the last administered dose. Patients who discontinued treatment before week 12 due to lack of effectiveness or intolerance were considered non-responders for the short-term endpoint. Patients who had not yet reached the corresponding follow-up timepoint at the time of database lock were not included in the analysis for that timepoint. Biochemical markers, including faecal calprotectin and C-reactive protein, were assessed at baseline, at weeks 8–12, and at the last available follow-up. A combined clinical-biochemical endpoint was assessed and defined as steroid-free clinical remission together with faecal calprotectin $< 150\,\mu g/g$ at the same time point, among patients with available paired data. A sensitivity analysis was additionally performed for the primary effectiveness endpoints (steroid-free clinical remission at weeks 8–12 and at last follow-up) by excluding patients with confirmed low faecal calprotectin ($< 150\,\mu g/g$) at baseline, in order to assess whether patients without objective biochemical evidence of active inflammation at treatment initiation influenced the overall estimates. Patients with missing baseline faecal calprotectin were retained in the sensitivity cohort, as the absence of measurement in a predominantly ileal population does not preclude active disease, and clinical activity (HBI > 4) was confirmed in all included patients. Endoscopic assessment was recorded when available in routine clinical practice. Secondary outcomes included comparative analyses of steroid-free clinical remission according to prior advanced therapy exposure, specifically the number of previous biologic agents (≤ 2 vs. ≥ 3) and prior UST use. In addition, factors associated with steroid-free clinical remission at last available follow-up were explored. Exploratory outcomes included treatment optimization, defined as dose intensification and/or reinduction of RZB at any time during follow-up and captured at the time of last-dose evaluation.

2.6 | Safety

Safety outcomes included the occurrence of adverse events and serious adverse events during RZB therapy, as well as treatment discontinuations attributable to adverse events. Safety data were collected from ENEIDA and complementary study-specific data requests when available.

2.7 | Statistical Analysis

Categorical variables were described as frequencies and percentages and compared using the chi-square test, with Yates' correction when appropriate. Continuous variables were expressed as mean (standard deviation) or median (interquartile range [IQR]), depending on data distribution, and compared using Student's *t*-test or the Mann–Whitney *U*-test, as appropriate. All tests were two-sided, and $p < 0.05$ were considered statistically significant. Bivariate analyses were performed to explore associations between baseline demographic, clinical, and treatment-related variables and steroid-free clinical remission at short-term (weeks 8–12) and follow-up (last administered dose) evaluations. Multivariable logistic regression analysis was performed to identify factors independently associated with steroid-free clinical remission at the time of the last administered dose. Variables included in the multivariable model were selected based on clinical relevance and results of bivariate analyses, while avoiding collinearity. Particular focus was placed on cumulative biologic exposure and prior UST use. Exploratory multivariable logistic regression analysis was additionally performed to identify factors associated with treatment optimization, defined as dose intensification and/or reinduction of RZB during follow-up. Missing data were handled using an available-case analysis approach. Analyses at each predefined timepoint (weeks 8–12 and last available follow-up) were restricted to patients with available data at the corresponding evaluation, rather than the entire baseline cohort. No imputation methods were applied. For biochemical outcomes, analyses were performed in patients with paired available data. In addition, time-to-event analyses were performed to evaluate treatment persistence over time using Kaplan–Meier methodology, with treatment discontinuation defined as withdrawal due to lack of effectiveness or adverse events. Statistical analyses were conducted using IBM SPSS Statistics version 28 (IBM Corp., Armonk, NY, USA)

TABLE 1 | Baseline demographic and disease characteristics of the study population.

	N = 857 (%)
Demographics	
Age at risankizumab initiation, years, mean ± SD	50.3 ± 15.7
Age at Crohn's disease diagnosis, years, mean ± SD	36.2 ± 17.1
Male sex (%)	511 (59.6)
Montreal classification—disease location	
Ileal (L1 ± L4)	440 (51.3)
Colonic (L2 ± L4)	67 (7.8)
Ileocolonic (L3 ± L4)	324 (37.9)
Upper gastrointestinal only (L4)	26 (3.0)
Montreal classification—disease behaviour	
Inflammatory (B1)	363 (42.3)
Stricturing (B2)	308 (35.9)
Penetrating (B3)	186 (21.8)
Smoking status	
Never smoker	468 (54.6)
Current smoker	218 (25.4)
Former smoker	171 (20.0)
Disease characteristics	
Perianal disease	206 (24.0)
Extraintestinal manifestations	289 (33.7)
Surgical history	
Any prior Crohn's disease–related surgery	430 (50.1)
Concomitant therapy at risankizumab initiation	
Systemic corticosteroids	173 (20.1)
Immunomodulators	54 (6.3)
Prior biologic and or JAK exposure	
0 prior biologics	28 (3.2)
1 prior biologic	204 (23.8)
2 prior biologic	224 (26.1)
3 prior biologic	206 (24.1)
4 prior biologic	144 (16.8)
≥ 5 prior biologics	51 (6.0)
Prior ustekinumab exposure	594 (69.3)
Baseline disease activity	
Harvey–Bradshaw Index, median (IQR)	8.0 (4.0)
C-reactive protein, mg/dL, median (IQR)	1.21 (4.9)
Faecal calprotectin, μg/g, median (IQR)	586.8 (1535.0)

and R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

2.8 | Ethical Considerations

The ENEIDA registry was approved by the ethics committees of participating centres, and all patients provided informed consent. The study was conducted in accordance with the Declaration of Helsinki and applicable data protection regulations.

3 | Results

A total of 857 patients with refractory CD treated with RZB in 60 Spanish hospitals from the ENEIDA database were included in the study. Baseline demographic and disease characteristics are summarized in Table 1. The mean age at RZB initiation was 50.3 ± 15.7 years. The burden of prior advanced therapies was high, including a mean of 2.47 prior biologics, with nearly half of patients exposed to ≥ 3 biologics and a high prevalence of prior anti-TNF (89.6%) and UST (69.3%) exposure. Disease was predominantly ileal or ileocolonic, with a high proportion of complicated behaviour. Extraintestinal manifestations were present in 33.7% of patients, most commonly musculoskeletal (26.4%), followed by cutaneous (5.4%), ocular (0.9%) and other manifestations (2.7%), with 34% of patients presenting more than one type.

3.1 | Short-Term Clinical and Biochemical Outcomes

Short-term effectiveness was evaluated in the overall study population. After RZB induction between weeks 8–12, 483/857 patients (56.4%) achieved steroid-free clinical remission. These results were observed despite the high degree of prior exposure to advanced therapies. Patients who discontinued treatment before week 12 due to lack of effectiveness or intolerance were classified as non-responders (Figure 1). Median HBI decreased from 8.0 (IQR 4.0)

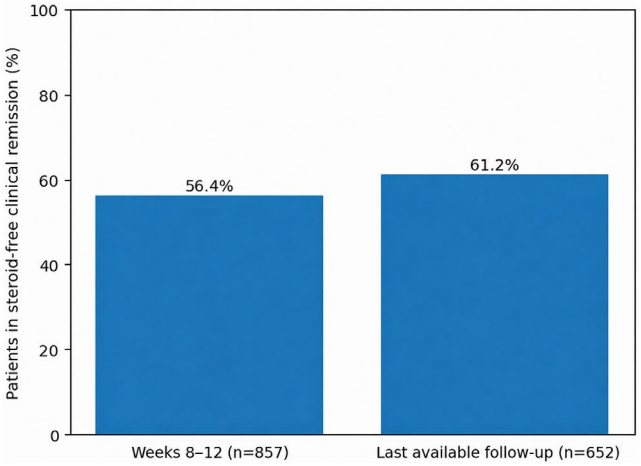

FIGURE 1 | Short and last-available follow-up steroid-free clinical remission following RZB treatment.

at baseline to 3.0 (IQR 4.0) at weeks 8–12. Median C-reactive protein also decreased from 1.21 mg/dL (IQR 4.9) at baseline to 0.98 mg/dL (IQR 2.6) at weeks 8–12. Median faecal calprotectin decreased from 586.8 μg/g (IQR 1535.0) at baseline to 290.0 μg/g (IQR 588.0) at weeks 8–12. Among patients with available paired clinical and faecal calprotectin data ($n = 595$), combined remission (steroid-free clinical remission plus faecal calprotectin < 150 μg/g) was achieved in 137 patients (23.0%) at weeks 8–12.

3.2 | Clinical, Biochemical and Endoscopic Outcomes at Last Available Follow-Up

Effectiveness was assessed among patients with available follow-up data ($n = 652$). The mean follow-up time at this evaluation was 7.4 months (standard deviation 5.73). At the time of the last administered dose, 399/652 patients (61.2%) were in steroid-free clinical remission, suggesting sustained clinical effectiveness among patients remaining on treatment (Figure 1). Clinical activity improved over time. Median HBI decreased from 8.0 (IQR 4.0) at baseline to 2.5 (IQR 4.0) at last available follow-up. Median C-reactive protein decreased from 1.21 mg/dL (IQR 4.9) to 0.92 mg/dL (IQR 2.34), and median faecal calprotectin from 586.8 μg/g (IQR 1535.0) to 281.0 μg/g (IQR 522.7). Among patients with available paired clinical and faecal calprotectin data ($n = 470$), combined remission (steroid-free clinical remission plus faecal calprotectin < 150 μg/g) was achieved in 122 patients (26.0%) at last available follow-up. In the pre-specified sensitivity analysis excluding patients with confirmed low baseline faecal calprotectin (< 150 μg/g), steroid-free clinical remission rates were 353/634 (55.7%) at weeks 8–12 and 327/544 (60.1%) at last available follow-up, consistent with the primary analysis. Combined remission in this sensitivity cohort was 78/483 (16.1%) at weeks 8–12 and 81/394 (20.6%) at last available follow-up.

Endoscopic data (SES-CD) at baseline and follow-up were available in 163 patients and showed a clear improvement over time, with median SES-CD decreasing from 9 at baseline to 2 at last follow-up.

Kaplan–Meier analysis of treatment persistence demonstrated a high probability of treatment continuation over time, with only a modest decline consistent with the low rate of treatment discontinuation observed in the cohort (Supplementary Figure 1).

3.3 | Impact of Previous Advanced Therapy Exposure on Clinical Remission

Clinical remission rates differed according to the number of advanced therapies received prior to RZB initiation. Patients with a lower biologic burden achieved higher rates of steroid-free clinical remission both at short-term and at last available follow-up. At short-term evaluation (weeks 8–12), patients with two or fewer prior biologics achieved significantly higher rates of steroid-free clinical remission compared with those previously exposed to three or more biologics (60.9% vs. 39.1%, $p < 0.001$). This pattern was maintained at follow-up, with remission rates of 60.1% in patients with two or fewer prior biologics and 39.9% in those with three or more prior biologic failures ($p < 0.001$) (Figure 2).

3.4 | Impact of Prior Ustekinumab Exposure on Clinical Remission

Prior exposure to UST was associated with lower rates of steroid-free clinical remission following RZB treatment. At short-term evaluation (weeks 8–12), remission was achieved in 63.5% of UST-naïve patients compared with 53.1% of those previously treated with UST ($p = 0.008$). This difference was more pronounced at follow-up evaluation, where 72.0% of UST-naïve patients were in clinical remission at the time of the last

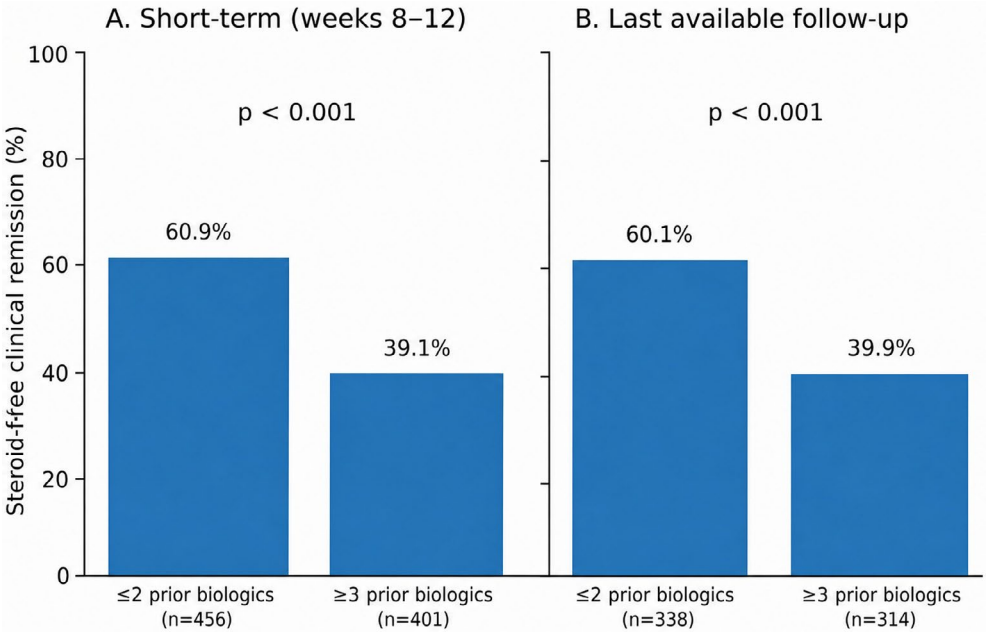

FIGURE 2 | Steroid-free clinical remission according to prior advanced therapies exposure.

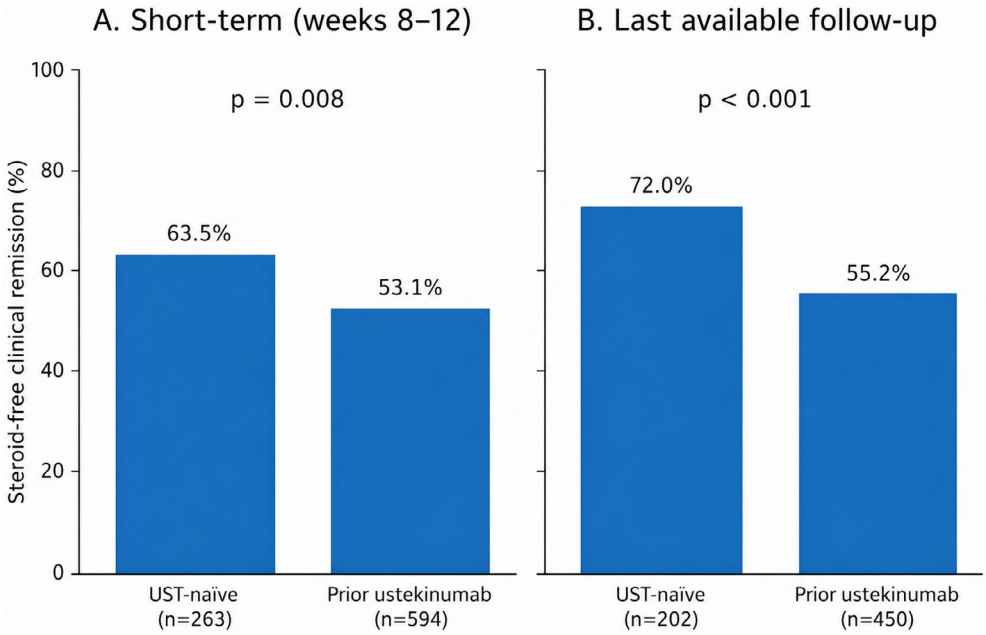

FIGURE 3 | Steroid-free clinical remission according to prior ustekinumab exposure at short-term and last available follow-up.

TABLE 2 | Multivariable analysis of factors associated with steroid-free clinical remission at last available follow-up.

Variable	Odds ratio	95% CI	*p*
Age (per year)	0.987	0.975–0.998	0.018
≥ 3 prior biologic therapies	0.517	0.332–0.798	0.003
Montreal behaviour (B2/B3 vs. B1)	0.864	0.577–1.294	0.486
Perianal disease	1.168	0.638–2.161	0.614
Prior perianal surgery	1.437	0.723–2.851	0.302
Prior ustekinumab exposure	0.795	0.487–1.297	0.354

Note: Multivariable logistic regression analysis evaluating factors associated with steroid-free clinical remission at the time of the last administered dose of risankizumab. Odds ratios < 1 indicate a lower probability of remission.

administered dose, compared with 55.2% of patients with prior UST exposure ($p < 0.001$) (Figure 3).

3.5 | Multivariable Analysis

In multivariable logistic regression analysis evaluating factors associated with steroid-free clinical remission at last available follow-up, cumulative biologic exposure was independently associated with treatment outcomes. Patients previously exposed to three or more biologic therapies had a significantly lower likelihood of achieving steroid-free clinical remission compared with those exposed to two or fewer biologics. Increasing age was also independently associated with a lower probability of steroid-free clinical remission. In contrast, prior UST exposure, disease behaviour, and perianal disease were not independently associated with clinical remission after adjustment (Table 2).

3.6 | Treatment Optimization

Treatment dose-escalation (intensification/reinduction). At last-dose evaluation, 11.3% of patients required RZB dose intensification and/or reinduction. In bivariate analyses, treatment optimization was more frequent among patients receiving initial concomitant systemic corticosteroids (40.0% vs. 18.2%; $p < 0.001$) and among those with ≥ 3 prior biologics (63.6% vs. 45.3%; $p = 0.002$). Prior UST exposure was also more frequent among patients requiring optimization (84.4% vs. 65.6%; $p < 0.001$). In multivariable analysis, concomitant corticosteroids remained independently associated with optimization (OR 2.737, 95% CI 1.607–4.615). Prior UST exposure was also associated with an increased probability of optimization in the categorical model (OR 2.140, 95% CI 1.015–4.717).

Among patients who underwent treatment optimization, steroid-free clinical remission at last available follow-up was achieved in 39% of cases, suggesting that a relevant proportion of patients may recapture response following optimization strategies.

3.7 | Safety

Overall, RZB demonstrated a favourable safety profile during follow-up. AEs were reported in 68/857 patients (7.9%), and treatment discontinuation due to AEs occurred in 12 patients (1.4% of the overall cohort; 17.6% of those with AEs) (Table 3).

The most frequently reported AEs were infections, followed by musculoskeletal symptoms (including arthralgia and myalgia), skin-related reactions, headache, and gastrointestinal symptoms. Infections were predominantly mild and included respiratory and urinary tract infections, while a minority were classified as opportunistic ($n = 5$), with no unexpected safety signals identified. AEs leading to treatment discontinuation were

TABLE 3 | Adverse events and treatment discontinuation.

	N = 857 (%)
Treatment discontinuation	
Total discontinuations	80 (9.3)
Due to treatment failure	68 (7.9)
Due to adverse events	12 (1.4)
Timing of discontinuation	
≤ week 12	19
> week 12	61
Adverse events	
Patients with ≥ 1 AE	68 (7.9)
Infections	18 (2.1)
Oportunistic	5
Respiratory	7
Urinary tract	4
Other	3
Skin-related reactions	11 (1.3)
Musculoskeletal (arthralgia/myalgia)	10 (1.2)
Headache/neurological	9 (1.0)
Gastrointestinal symptoms	7 (0.8)
Asthenia/flu-like	5 (0.6)
Others	8 (0.9)

infrequent and included opportunistic infections ($n = 5$), skin-related reactions ($n = 4$), and arthralgia ($n = 3$). A detailed classification of infections, including opportunistic, localized, and other types, is provided in Table 3.

Importantly, events clearly attributable to underlying CD activity (e.g., intestinal obstruction, surgery or disease flare) were not considered treatment-related AEs but were classified as treatment failure. Overall, these findings support a favourable safety profile of RZB in this large real-world cohort.

4 | Discussion

To our knowledge, RISANCROHN represents the largest real-world study evaluating RZB in CD reported to date. A total of 857 patients were included at baseline, reflecting routine clinical practice in a nationwide setting and substantially exceeding the sample size of previously published real-world cohorts, which have generally been limited to small or medium-sized multicentre series [7–9]. While effectiveness analyses were necessarily restricted to patients with available follow-up data, the size of the overall cohort enabled a robust assessment of both early and follow-up outcomes, as well as clinically relevant subgroup and multivariable analyses in a highly refractory population. Notably, the study population was characterized by long-standing disease, a high prevalence of complicated phenotypes—including penetrating and perianal fistulizing disease—and extensive prior exposure to advanced therapies, underscoring the advanced disease stage of patients treated with RZB in this real-world setting. Although a minority of patients were biologic-naïve or had limited prior exposure, the overall treatment history supports the characterization of the cohort as predominantly refractory. Importantly, this scale and level of treatment complexity clearly distinguish RISANCROHN from earlier real-world experiences with RZB and provide a complementary perspective to randomized controlled trials, where patient selection criteria and prior exposure to advanced therapies are inherently more restricted [4–6]. Moreover, these findings are aligned with emerging large contemporary real-world cohorts, including recent UK and Italian multicentre studies, which have reported consistent effectiveness of RZB in highly treatment-experienced populations [16, 17].

The effectiveness observed in RISANCROHN should be interpreted in the context of the pivotal phase 3 trials of RZB, while acknowledging the substantial differences in patient populations and study design. In the ADVANCE and MOTIVATE induction studies, RZB achieved clinical remission rates of approximately 40%–45% at week 12, with sustained efficacy during maintenance in the FORTIFY trial [4–6]. Post hoc analyses of these trials further demonstrated that a substantial proportion of patients were able to achieve and maintain corticosteroid-free clinical remission during maintenance therapy [18–20]. In our real-world cohort, 56.4% of patients achieved steroid-free clinical remission after induction, and 61.2% were in steroid-free remission at last available follow-up. Although these figures appear numerically comparable or even higher than those reported in clinical trials, such comparisons should be interpreted with caution. In pivotal trials, maintenance outcomes were assessed in rerandomized populations enriched for induction responders, whereas RISANCROHN reflects routine clinical practice, including patients with extensive prior exposure to advanced therapies and a high burden of refractoriness. Taken together, these findings suggest that the steroid-sparing benefits of selective IL-23 p19 inhibition observed in randomized controlled trials translate into real-world settings, even in more complex and treatment-refractory populations, particularly during the early maintenance phase of treatment.

Across real-world studies, early effectiveness of RZB shows variability, largely driven by differences in population complexity, baseline corticosteroid use, and outcome definitions. In this context, the early steroid-free remission observed in ENEIDA lies within the upper range of published estimates. European multicentre cohorts enriched for multirefractory disease have reported more modest early outcomes, with steroid-free clinical remission around one third of patients at week 12 when assessed using PRO-based definitions [8]. In contrast, larger international cohorts with a broader case mix have described higher early remission rates, particularly when less restrictive clinical indices are used or when analyses are limited to patients remaining on treatment [9, 11].

Notably, recent large contemporary real-world cohorts have reported early remission rates broadly consistent with our findings, despite including highly treatment-experienced populations and using heterogeneous outcome definitions [16, 17]. Real-world data from tertiary-care cohorts using HBI-based definitions have reported early steroid-free clinical remission rates approaching 60% [21].

Follow-up data in RISANCROHN indicate that a substantial proportion of patients maintain steroid-free clinical remission over time, supporting the persistence of effectiveness of RZB in routine clinical practice. These findings are consistent with real-world cohorts reporting maintenance steroid-free remission rates generally ranging between 45% and over 60% at 1 year, depending on population characteristics and study design [8, 9, 11, 21]. In particular, cohorts enriched for refractory disease tend to report more modest outcomes, highlighting the impact of cumulative treatment burden on long-term effectiveness [21].

In RISANCROHN, prior UST exposure was associated with a more complex treatment course rather than a lack of effectiveness, as reflected by a significantly higher probability of RZB treatment optimization during follow-up [22]. This finding is consistent with real-world data from other cohorts enriched for UST-experienced patients. Alzaabi et al. reported that prior UST exposure was independently associated with a markedly increased likelihood of dose intensification, as well as lower odds of achieving clinical remission during maintenance [11]. Similarly, in the RESOLVE cohort, prior UST exposure was associated with lower early clinical remission and reduced endoscopic remission at 1 year, supporting the concept of UST exposure as a surrogate of advanced refractoriness rather than primary non-response to RZB [17].

A key finding of RISANCROHN is the independent association between cumulative biologic exposure and treatment outcomes. Patients previously exposed to three or more biologic therapies had a significantly lower likelihood of achieving steroid-free clinical remission compared with those exposed to two or fewer agents, highlighting cumulative treatment burden as a major determinant of refractoriness. In contrast, prior exposure to individual mechanisms of action, including UST, did not independently predict remission once overall biologic burden was considered. The high prevalence of prior anti-TNF exposure in our cohort (89.6%) further supports the interpretation that this population represents a highly refractory disease phenotype. In this context, response to RZB appears to be driven more by cumulative biologic burden than by failure of a specific mechanism of action. Together, these findings suggest that treatment history may be more relevant than mechanism of action in determining response to RZB in advanced CD, and support the concept that earlier use of selective IL-23 inhibition may maximize clinical benefit. Disease location was not included in the multivariable model because the number of patients with isolated colonic disease was limited in all ENEIDA studies, which reduced the robustness of adjusted comparisons. In addition, the predominance of ileal and ileocolonic disease in the cohort should be considered when interpreting treatment outcomes. Although increasing age was associated with a lower probability of remission, the magnitude of this effect was small and should be interpreted with caution.

The main strength of RISANCROHN is its scale and representativeness. To our knowledge, this is the largest real-world cohort of patients with CD treated with RZB reported to date, allowing robust estimation of early and follow-up outcomes and meaningful multivariable analyses, particularly regarding cumulative biologic exposure. The nationwide ENEIDA registry reflects routine clinical practice across diverse centres, enhancing the external validity of the findings. However, several limitations inherent to real-world observational studies should be acknowledged. The non-randomized design precludes causal inference, and residual confounding cannot be excluded. Outcome assessment relied mainly on clinical indices, including the HBI, which may be subject to inter-observer variability and does not fully capture objective inflammatory activity, while endoscopic data were available only in a subset of patients and did not allow systematic assessment across the entire cohort, although available data demonstrated a clear improvement in objective inflammatory activity.

In addition, follow-up was not standardized across centres, corticosteroid tapering was not standardized, and steroid-free status was defined cross-sectionally, without accounting for possible intermittent corticosteroid use between visits or the duration of corticosteroid discontinuation. Missing data may have influenced outcome estimates. A proportion of patients ($n = 114$, 13.3%) had a baseline faecal calprotectin $< 150\,\mu g/g$; although FCP is known to have limited sensitivity in predominantly ileal disease, a sensitivity analysis excluding these patients yielded remission rates fully consistent with the primary analysis, supporting the robustness of the effectiveness estimates. In addition, the duration of follow-up was relatively short. Although outcomes at last available follow-up provide insight beyond early assessment, the mean follow-up time does not reach longer-term clinically meaningful endpoints such as 12 months, and therefore long-term effectiveness and durability of response cannot be fully assessed. Detailed information on reasons for discontinuation of prior therapies and on treatment sequencing, including the last advanced therapy before RZB initiation and the interval between treatments, was not systematically available in the registry. However, the large sample size and multicentre design provide a robust representation of routine clinical practice in a highly treatment-experienced population.

In this large nationwide real-world cohort, RZB demonstrated clinically meaningful effectiveness in patients with CD treated in routine practice. Steroid-free clinical remission was achieved in a substantial proportion of patients across a heterogeneous and treatment-experienced population, with supportive evidence of objective inflammatory improvement. Cumulative biologic exposure emerged as a key determinant of treatment outcomes, with reduced remission rates observed in patients exposed to three or more prior biologic therapies. These findings support the use of RZB as an effective therapeutic option across advanced lines of therapy and suggest that earlier positioning within the treatment sequence may maximize clinical benefit.

Author Contributions

Maia M. Boscá-Watts: investigation. **Cristina Martínez-Cuevas:** investigation. **Laura Nieto-García:** data curation, investigation. **Pilar Varela Trastoy:** investigation. **Sol Porto-Silva:** data curation, investigation. **Rocío Ferreiro-Iglesias:** investigation, writing – review and editing, supervision, data curation, formal analysis, visualization, methodology, validation. **Marta Calvo:** investigation. **Mariam Aguas:** investigation. **Marta Poncela:** investigation. **Daniel Ceballos:** investigation. **Yamile Zabana:** investigation, writing – review and editing, data curation, supervision. **Federico Argüelles-Arias:** investigation. **Manuel Barreiro-de Acosta:** conceptualization, investigation, writing – original draft, methodology, validation, visualization, writing – review and editing, data curation, supervision, resources, formal analysis. **Lucía Zabalza:** investigation. **Patricia Suárez:** investigation. **Vanesa Royo:** investigation. **Blau Camps:** investigation. **María Dolores Martín-Arranz:** investigation. **María Luisa de Castro Parga:** investigation. **Ruth de Francisco:** investigation. **Santiago García-Lopez:** investigation. **Cristina Martínez Pascual:** investigation. **Inmaculada Alonso-Abreu:** investigation. **Iria Baston-Rey:** investigation. **Ángel Ponferrada Díaz:** investigation. **Isabel Nicolás:** investigation. **Paola Fradejas:** investigation. **Elena Ricart:** investigation. **Fernando Bermejo:** investigation. **Montserrat Rivero:** investigation. **Pilar Robledo:** investigation. **Marta Teller:** investigation. **Javier P. Gisbert:** investigation. **Marta Piqueras:** investigation. **Carla J. Gargallo-Puyuelo:** investigation. **Ana M. Trapero:** investigation. **María Teresa Diz-Lois Palomares:** investigation. **Beatriz Sicilia:** investigation. **María Algara:** investigation. **Francisco Rodríguez-Moranta:** investigation. **Alejandro Hernandez-Camba:** investigation. **Eduard Brunet-Mas:** investigation. **Ainara Elorza:** investigation. **Eva Sesé:** investigation. **Juan A. Ferrer:** investigation. **Lucía Madero:** investigation. **Carlos Martínez Flores:** investigation. **Miriam Manosa:** investigation. **Nuria Maroto:** investigation. **Sandra Izquierdo:** investigation. **Eva Iglesias:** investigation. **Martín Irabien:** investigation. **Luis Bujanda:** investigation. **David Busquets:** investigation. **Daniel Carpio:** investigation. **Rufo Lorente:** investigation. **Javier Santos:** investigation. **Mari Fe García-Sepulcre:** investigation. **Francisco Mesonero:** investigation. **Carlos González-Muñoza:** investigation. **Daniel Martín:** investigation. **Margarita Menacho:** investigation. **Jesús Castro Poceiro:** investigation. **Ramón Pajares:** investigation. **Eugeni Domènech:** validation, supervision.

Affiliations

[1]Department of Gastroenterology, Complexo Hospitalario Universitario de Santiago and Fundación Instituto de Investigación Sanitaria de Santiago de Compostela (FIDIS), Santiago de Compostela, Spain | [2]Department of Gastroenterology, Hospital Universitari MútuaTerrassa, Terrassa, Centro de Investigación Biomédica en Red en Enfermedades Hepáticas y Digestivas (CIBERehd), Terrassa, Spain | [3]Department of Gastroenterology, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Biomédica Gregorio Marañón (IiSGM), Madrid, Spain | [4]Department of Gastroenterology, Hospital Universitari i Politècnic La Fe, Instituto de Investigación Sanitaria La Fe, Valencia, Spain | [5]Department of Gastroenterology, Hospital Universitario Río Hortega, Valladolid, Spain | [6]Universidad de Sevilla. Facultad de Medicina. Department of Gastroenterology, Hospital Universitario Virgen Macarena, Sevilla, Spain | [7]Department of Gastroenterology, Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain | [8]Department of Gastroenterology, Hospital Clínico Universitario Lozano Blesa, IIS Aragón and CIBERehd, Zaragoza, Spain | [9]Department of Gastroenterology, Hospital Universitario de Navarra, Pamplona, Spain | [10]Department of Gastroenterology, Hospital de Cabueñes, Gijón, Spain | [11]Department of Gastroenterology, Hospital Clínico Universitario de Valencia, Universitat de València, Valencia, Spain | [12]Department of Gastroenterology, Hospital Universitario de Gran Canaria Dr. Negrín. Departamento de Ciencias Médicas y Quirúrgicas. Universidad de Las Palmas, Las Palmas, Spain | [13]Department of Gastroenterology, Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain | [14]Department of Gastroenterology, Hospital Universitario de Bellvitge, IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain | [15]Department of Gastroenterology, Hospital Álvaro Cunqueiro, Grupo de Investigación en Patología Digestiva, Instituto de Investigación Sanitaria Galicia Sur (IIS), Vigo, Spain | [16]Department of Gastroenterology, Complejo Asistencial Universitario de León, León, Spain | [17]Department of Gastroenterology, Hospital del Mar, IMIM, Barcelona, Spain | [18]Department of Gastroenterology, Hospital Son Espases, Palma de Mallorca, Spain | [19]Department of Gastroenterology, Hospital Universitario Central de Asturias, Oviedo, Spain | [20]Department of Gastroenterology, Hospital Universitario Miguel Servet, Zaragoza, Spain | [21]Department of Gastroenterology, Hospital Universitario La Paz, Madrid, Spain | [22]Department of Gastroenterology, Hospital Universitario de Fuenlabrada, Madrid, Spain | [23]Department of Gastroenterology, Hospital Universitario de Canarias, Santa Cruz de Tenerife, Spain | [24]Department of Gastroenterology, Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa (IIS-Princesa), Universidad Autónoma de Madrid (UAM), Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Madrid, Spain | [25]Department of Gastroenterology, Hospital Universitario Marqués de Valdecilla, IDIVAL, Santander, Spain | [26]Department of Gastroenterology, Hospital Universitario de Burgos, Burgos, Spain | [27]Department of Gastroenterology, Hospital General Universitario Reina Sofía, Murcia, Spain | [28]Department of Gastroenterology, Althaia Xarxa Assistencial Universitària de Manresa, Manresa, Spain | [29]Department of Gastroenterology, Hospital Universitario Infanta Leonor, Madrid, Spain | [30]Department of Gastroenterology, Hospital Clínic i Provincial, IDIBAPS, Barcelona, Spain | [31]Department of Gastroenterology, Hospital Universitario 12 de Octubre, Madrid, Spain | [32]Department of Gastroenterology, Complejo Asistencial de Zamora, Zamora, Spain | [33]Department of Gastroenterology, Hospital Universitario de Cáceres, Cáceres, Spain | [34]Department of Gastroenterology, Hospital General Universitario de Alicante, Alicante, Spain | [35]Department of Gastroenterology, Hospital de Galdakao-Usansolo, Vizcaya, Spain | [36]Department of Gastroenterology, Hospital Universitari Consorci Sanitari de Terrassa (CST), Barcelona, Spain | [37]Department of Gastroenterology, Hospital General Universitario de Elche, Alicante, Spain | [38]Department of Gastroenterology, Hospital Universitario Arnau de Vilanova, Lleida, Spain | [39]Department of Gastroenterology, Hospital Universitario Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Spain. Instituto de Investigación Sanitaria de Canarias (IISC), Santa Cruz de Tenerife, Spain | [40]Department of Gastroenterology, Hospital Clínico Universitario Río Valladolid, Valladolid, Spain | [41]Department of Gastroenterology, Hospital de Jaén, Jaén, Spain | [42]Department of Gastroenterology, Hospital Reina Sofía, Córdoba, Spain | [43]Department of Gastroenterology, Hospital Universitario a Coruña, Coruña, Spain | [44]Department of Gastroenterology, Parc Taulí Hospital Universitari. Institut d'Investigació i Innovació Parc Taulí (I3PT-CERCA). Sabadell, Catalunya, Departament de Medicina, Universitat Autònoma de Barcelona y Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), and Universitat Autònoma de Barcelona, Barcelona, Spain | [45]Department of Gastroenterology, Hospital de Sant Joan Despí Moisès Broggi, Barcelona, Spain | [46]Department of Gastroenterology, Hospital Dr. Josep Trueta, Girona, Spain | [47]Department of Gastroenterology, Hospital Universitari Germans Trias i Pujol, Badalona, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), and Universitat Autònoma de Barcelona, Barcelona, Spain | [48]Department of Gastroenterology, Hospital Universitario Infanta Sofía, Madrid, Spain | [49]Department of Gastroenterology, Hospital Universitario Fundación Alcorcón, Madrid, Spain | [50]Department of Gastroenterology, Hospital Universitario de Pontevedra, Pontevedra, Spain | [51]Department of Gastroenterology, Hospital Universitario Ramón y Cajal, Madrid, Spain | [52]Department of Gastroenterology, Hospital Universitario Donostia, San Sebastián, Spain | [53]Department

of Gastroenterology, Hospital General Universitario de Ciudad Real, Ciudad Real, Spain | [54]Department of Gastroenterology, Complejo Asistencial Universitario de Palencia, Palencia, Spain | [55]Department of Gastroenterology, Hospital General La Mancha Centro, Ciudad Real, Spain | [56]Department of Gastroenterology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain | [57]Department of Gastroenterology, Hospital Universitario Infanta Cristina, Parla, Madrid, Spain | [58]Department of Gastroenterology, Hospital Joan XXIII, Tarragona, Spain | [59]Department of Gastroenterology, Hospital de Manises, Valencia, Spain | [60]Department of Gastroenterology, Hospital Urduliz-Alfredo Espinosa, Vizcaya, Spain

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Conflicts of Interest

M.B.-d.A. has been a speaker, consultant, and advisory member for or has received research funding from MSD, AbbVie, Janssen, Kern Pharma, Celltrion, Takeda, Alphasigma, Lilly, Pfizer, Sandoz, Biocon, Abivax, Fresenius, Faes Farma, Ferring, Tillots, Chiesi, Adacyte, Diasorin, Oncostellae, and SunRock. Y.Z. has served as a speaker, or has received research or education funding or advisory fees from: AbbVie, Adacyte Therapeutics, Alfa-Sigma, Amgen, Boehringer Ingelheim, Dr. Falk Pharma, FAES Pharma, Fresenius Kabi, Ferring, Galapagos, Janssen-J&J, Kern Pharma, Lilly, MSD, Pfizer, Sanofi, Sandoz, Takeda, Tillots Pharma. M.A.P. has been speaker, consultant and advisory member for or has received research funding from Abbott, Abbvie, Adacyte, Alfasigma, Chiesi, Faes, Ferring, Kern Pharma, Janssen, Lilly, Norgine, Pfizer. J.P.G. has served as speaker, consultant, and advisory member for or has received research funding from MSD, Abbvie, Pfizer, Kern Pharma, Biogen, Mylan, Takeda, Janssen, Roche, Sandoz, Celgene/Bristol Myers, Gilead/Galapagos/Alfasigma, Lilly, Sanofi, STADA, Teva, Ferring, Faes Farma, Shire Pharmaceuticals, Dr. Falk Pharma, Tillotts Pharma, Chiesi, Casen Fleet, Gebro Pharma, Otsuka Pharmaceutical, Norgine, Italfarmaco, and Vifor Pharma. M.P.C. has served as a speaker or has received research or education funding from Takeda, Abbvie, FAES Pharma, Tillots Phasma, Galapagos, Lilly and Janssen. E.B.-M. has served as a speaker and consultant for Janssen, Chiesi, Kern, Takeda, Lilly, and Alfasigma. D.B.C. has served as a speaker or has received research or education funding from Lilly, Takeda, Abbvie, Tillots Phasma, Pfizer, Chiesi and Janssen. M.C.M. has served as a speaker, a consultant and advisory member for or has received research funding from AbbVie, Takeda, Johnson & Johnson, Pfizer, Lilly, MSD, Chiesi, Dr. Falk Pharma, Shire Pharmaceuticals, FAES, FERRING, Tillotts Pharma, Galapagos and Alfasigma. A.H.C. has served as a speaker and advisory member for or has received research funding from AbbVie, Adacyte, Kern Pharma, Takeda, Johnson & Johnson, Pfizer, Lilly, Chiesi, Dr. Falk Pharma, FAES, FERRING, Tillotts Pharma, Galapagos, and Alfasigma. C.M.P. has served as a speaker or has received research or education funding from Abbvie, Adacyte, Alfasigma, Chiesi, Faes, Ferring, Kern Pharma, Janssen, Lilly, Pfizer. M.T.M. has served as a speaker or has received research or education funding from Abbvie, Alfasigma, faesfarma, falk, Ferring, Johnson&Johson, Lilly, Norgine, Schwabe farma Ibérica, Takeda and Tillots Pharma. F. Mesonero has served as a speaker for and received consulting fees from MSD, AbbVie, Takeda, Janssen, Pfizer, Ferring Pharmaceuticals, Kern Pharma, Dr. Falk Pharma, Galapagos, Chiesi Farmaceutici, Tillots Pharma, Lilly, and Faes Farma. M.M. has served as a speaker for and received consulting fees from AbbVie, Janssen, Pfizer, Ferring Pharmaceuticals, Kern Pharma, Dr. Falk Pharma, Alfasigma, Tillots Pharma, Lilly, and Faes Farma.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Supplementary Figure 1.** Kaplan–Meier curve of treatment persistence in patients treated with Risankizumab.