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Multicenter Real-World Outcomes of Risankizumab in Crohn's Disease: The RESOLVE IG-IBD Study

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INTRODUCTION: **To assess the effectiveness and safety of Risankizumab (RZB) in a large, nationwide real-world cohort of patients with Crohn's disease (CD).**

METHODS: **We conducted a multicenter, retrospective observational cohort of adults initiating RZB with assessments at weeks 12, 26, and 52. Coprimary end points were (i) week-12 steroid-free clinical remission (SFCR) (Harvey-Bradshaw Index <5 in the absence of systemic corticosteroids or budesonide) and (ii) week-52 endoscopic remission (Simple Endoscopic Score-CD 0–2 or Rutgeerts i0–i1 postoperatively). The main**

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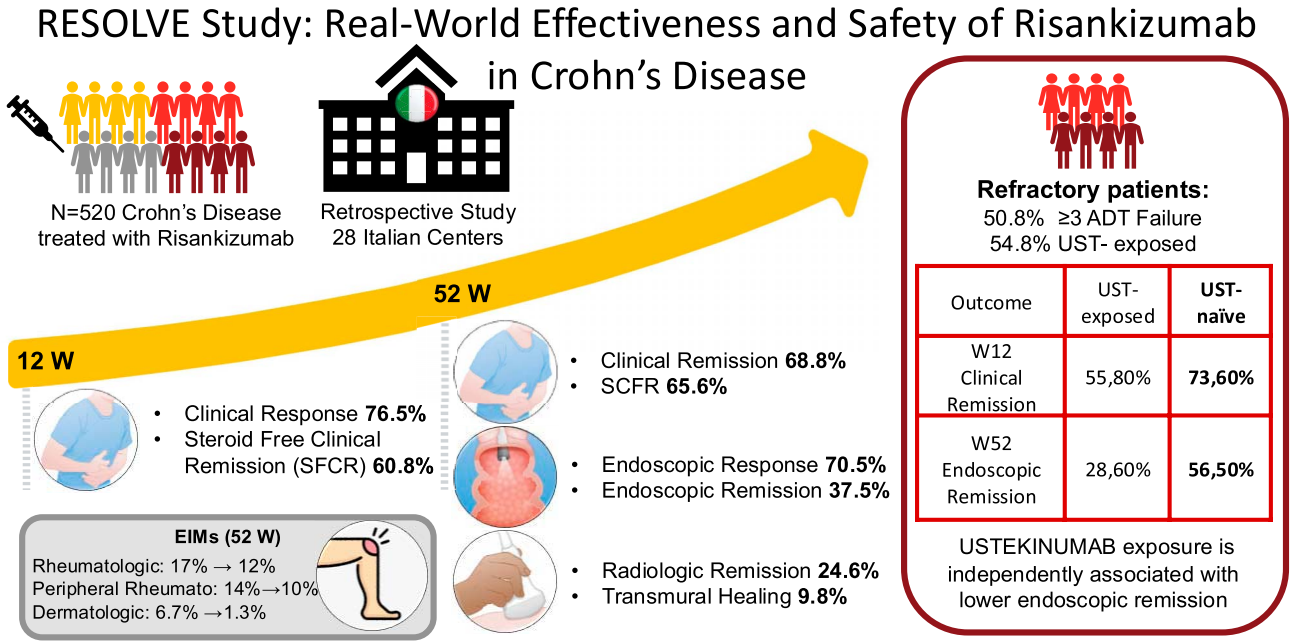

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effectiveness analysis was as-observed; a preplanned sensitivity analysis included patients expected to reach week-52 before database lock and applied nonresponder imputation.

RESULTS: **We included 520 patients, 45.0% failed ≥3 and 54.8% were ustekinumab (UST)-exposed. At week 12, clinical response was 76.5% and 60.8% achieved SFCR. By week 52, SFCR was 65.6%; endoscopic remission occurred in 37.5%, whereas radiologic remission and transmural healing were 24.6% and 9.8%, respectively. UST-naïve patients showed significantly superior early clinical outcomes (week-12 SFCR: 69.8% vs 53.3%) and a higher rate of endoscopic remission at week 52 (56.5% vs 28.6%) compared with UST-exposed patients. Notably, week-52 effectiveness was comparable between patients with 2 and those with ≥3 previous failures. Extraintestinal manifestations decreased over time, whereas perianal disease improved modestly. In the sensitivity cohort (N = 213), SFCR was 47% at week-52. RZB was well-tolerated with no new safety signals identified.**

DISCUSSION: **In a large, refractory, real-world CD population, RZB induced rapid and sustained favorable clinical, endoscopic, and radiologic outcomes. Importantly, one-year effectiveness was similar in patients with 2, and ≥3 previous failures, supporting RZB as a valuable option for a refractory population.**

KEYWORDS: anti IL-23; real-life; Crohn's disease; effectiveness; Risankizumab

ABBREVIATIONS: ADTs, advanced therapies; AEs, adverse events; APS, abdominal pain score; BWT, Bowel wall thickness; CD, Crohn's disease; CI/CIs, confidence interval/confidence intervals; CRP, C-reactive protein; CT, computed tomography; EIMs, extraintestinal manifestations; ECCO, European Crohn's and Colitis Organisation; EMA, European Medicines Agency; GCP, good clinical practice; GETAID, Groupe d'Étude Thérapeutique des Affections Inflammatoires du Tube Digestif; HBI, Harvey–Bradshaw index; IBD, inflammatory bowel disease; IG-IBD, Italian Group for the Study of Inflammatory Bowel Disease; IgG1, immunoglobulin G1; IL, interleukin; IL-12/23, interleukin-12/23; IL-17, interleukin-17; IL-22, interleukin-22; IL-23, interleukin-23; IL-23R, interleukin-23 receptor; IQR, interquartile range; IV, intravenous; JAK, Janus kinase; MR, magnetic resonance; OR/ORs, odds ratio/odds ratios; PGA, physician's global assessment; PRO/PROs, patient-reported outcome/patient-reported outcomes; REBOOT-IBD, REal world Biologics and small mOlecules OuTcomes in IBD; REDCap, research electronic data capture; RZB, risankizumab; SC, subcutaneous; SD, standard deviation; SES-CD, simple endoscopic score for Crohn's disease; SFCR, steroid-free clinical remission; Th17, T helper 17; TNF / TNFα, tumor necrosis factor/ tumor necrosis factor alpha; UST, ustekinumab

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/D895

INTRODUCTION

Crohn's disease (CD) is a chronic, multifactorial relapsing-remitting inflammatory disorder of the gastrointestinal tract, characterized by transmural inflammation, progressive tissue damage, and substantial impairment in quality of life (1). Its prevalence is rising globally with attendant healthcare burden (2). During the disease course, up to 50% develop extra-intestinal manifestations (EIMs), most commonly rheumatologic (20%–30%), dermatologic (10%–15%), ocular (2%–6%), and hepatobiliary (3,4), whereas 20% develop perianal disease within 10 years, frequently manifesting as complex fistulizing lesions with or without abscesses that deeply affect well-being (5,6).

Therapeutic strategies have evolved from corticosteroids and immunomodulators to advanced therapies (ADTs), including anti-tumor necrosis factor α, anti-integrins, anti-IL-12/23, Janus kinase-inhibitors, with proven efficacy for induction and maintenance (7,8). Nevertheless, many patients exhibit primary non-response, secondary loss of response, or adverse events (AEs) necessitating optimization or switching (9–11). Efficacy diminishes with successive lines, with bionaïve patients outperforming bioexposed cohorts (12–14), and corticosteroid dependence remains common despite available treatments (15).

Selective IL-23 inhibition targets a central pathway sustaining Th17-mediated intestinal inflammation. IL-23 (p19/p40) promotes differentiation and survival of pathogenic Th17 cells and downstream IL-17/IL-22 production (16–18). Elevated IL-23 levels have been consistently observed in patients with inflammatory bowel diseases, particularly in CD compared with ulcerative colitis (19). Moreover, genome-wide association studies have identified IL-23R polymorphisms associated with an increased CD risk (19). Risankizumab (RZB), a humanized IgG1 monoclonal antibody against IL-23 p19, is approved for moderate-to-severe CD. In 3 phase 3 trials (ADVANCE, MOTIVATE, and FORTIFY) RZB achieved clinical remission and endoscopic response with a favorable safety profile, exhibiting superior efficacy in bionaïve vs bioexposed patients (20,21). The relative efficacy of RZB in patients previously treated with ustekinumab (UST)—an IL-12/23 inhibitor targeting the p40 subunit—remains a key clinical question. Mechanistic and clinical data suggest selective IL-23 blockade may be more impactful than dual IL-12/23 inhibition (22); the SEQUENCE head-to-head trial showed RZB superiority over UST across clinical and endoscopic end points (23). However, pivotal RZB trials included few UST-exposed patients (≤20%), limiting definitive conclusions in this subgroup (20,21).

Because randomized trials enroll highly selected populations, real-world studies are needed to define RZB effectiveness and safety across heterogeneous CD, including previous biologic failures, UST exposure, and complex phenotypes (perianal, stricturing/penetrating behavior, EIMs). Existing retrospective series in multirefractory cohorts are limited (24–27), but most of these analyses primarily focused on early end points (week-12) and did not evaluate radiological outcomes, nor its impact on EIMs or perianal disease.

We therefore report the largest Italian, multicenter real-world study to date, evaluating 52-week effectiveness and safety of RZB with comprehensive clinical, endoscopic, radiologic, biochemical, and patient-reported outcomes (PROs), and dedicated analyses of EIMs and perianal disease.

METHODS

Study design and population

This retrospective, observational, multicenter cohort—promoted by the Italian Group for the Study of Inflammatory Bowel Disease (IBD)—enrolled patients from 28 Italian tertiary IBD referral centers. The study complied with the Declaration of Helsinki and good clinical practice; the protocol received central approval from the Ethics Committee Lazio Area 3 (No. 7036). Consecutive adults (18 years and older) with histologically confirmed CD per European Crohn's and Colitis Organisation criteria (28) who initiated RZB between September 2023 and March 2025 and had ≥12 weeks of follow-up were eligible. Exclusions were previous exposure to RZB within interventional trials, indeterminate colitis, ulcerative colitis, and ileal pouch-anal anastomosis. All participants gave written informed consent. Data lock was prespecified for June 30, 2025. RZB was administered per European Medicines Agency labeling: IV 600 mg at weeks 0, 4, and 8, then subcutaneous 360 mg every 8 weeks starting at week 12.

Data collection

Chart abstraction from electronic medical records used a unique study identifier and a secure Web-based Research Electronic Data Capture electronic Case Report Form with a standardized data dictionary, compliant with Italian data-protection regulations. Variables included demographics (age, sex, smoking, comorbidities), disease features (Montreal classification (29), duration, perianal disease), previous CD-related surgeries, previous immunosuppressants/biologics, baseline concomitant therapies, EIMs, and the indication for starting RZB. Baseline activity captured the Harvey-Bradshaw Index (HBI) (30), PROs, including average daily stool frequency (SF) or stoma output in patients with ileostomy (average daily output reported as either volume per 24 hours when available or, when not documented, as the average daily number of bag emptying events per day) average daily abdominal pain score (APS), Bristol Stool Scale, and the physician's global assessment (PGA) (31). EIMs were classified as active/remission by physician judgment using symptoms and, when available, physical examination findings. Endoscopic activity used the Simple Endoscopic Score (SES)-CD (32) and, postoperatively, the Rutgeerts score. Cross-sectional/intestinal ultrasound (computed tomography or magnetic resonance enterography, or intestinal ultrasound) recorded the number and cumulative length of diseased segments, maximal bowel wall thickness (BWT), contrast enhancement/Doppler hyperemia (yes/no), luminal stenosis (yes/no), mesenteric lymphadenopathy (yes/no), and intra-abdominal fistulas/abscesses (yes/no). Serologic markers included C-reactive protein (CRP), hemoglobin, and fecal calprotectin. Scores/measurements were derived by site investigators from reports and available images. Clinical, endoscopic, radiologic, laboratory, and safety data were recorded at weeks 12, 26, and 52.

Outcomes

Coprimary outcomes were: (i) week-12 (±4 weeks) steroid-free clinical remission (SFCR), defined as HBI <5 without systemic corticosteroids or budesonide; for ileostomy, remission relied on PROs (APS ≤1 with stoma output improved or not worse than baseline) together with the PGA, acknowledging that a universally validated remission threshold for stoma output is lacking; and (ii) week-52 (±8 weeks) endoscopic remission, defined as

SES-CD 0–2 or, in postoperative patients with confined anastomotic/neoterminal ileal inflammation, Rutgeerts i0–i1. Secondary outcomes included weeks-26/52 SFCR; weeks-12/26/52 clinical remission; weeks-12/26/52 biochemical-SFCR (SFCR with CRP <5 mg/L); week-12 clinical response (≥3-point HBI decrease or, for ileostomy, ≥50% reduction in stoma output or ≥35% reduction in APS, or both, with neither worsening); week-12 response in those with baseline HBI >4; weeks-12/26/52 stool-frequency remission (≤2.8/d and not worse than baseline) and abdominal-pain remission (≤1 and not worse than baseline); week-26 (±8 weeks) endoscopic remission; longitudinal change in CRP, hemoglobin, and fecal calprotectin; weeks-26/52 endoscopic response (≥50% reduction in SES-CD) weeks-26/52 radiologic remission (BWT ≤4 mm without increased enhancement/hyperemia and no complications on cross-sectional imaging); weeks-26/52 transmural healing (BWT ≤3 mm with the same ancillary requirements); quantitative change in BWT and cumulative diseased-segment length; proportion with active EIMs, and proportion with active perianal disease (at least 1 actively draining perianal fistula on clinical examination [spontaneous drainage, or drainage after gentle finger compression of the tract/external opening], and/or presence of perianal sepsis [perianal abscess or sepsis requiring antibiotics and/or surgical drainage] at baseline, with or without a seton *in situ* (33) at weeks 12/26/52. Safety outcomes (infectious and noninfectious AEs) were collected at each timepoint.

Statistical analysis

Continuous variables were summarized as mean (SD) or median (interquartile range) and categorical variables as n (%). Between-group comparisons (e.g., UST-exposed vs naïve; failure of ≥3 vs 2 ADTs) were performed using χ^2 or the Fisher exact tests for categorical data and the Student *t* test or Mann-Whitney U test for continuous data. Paired dichotomous changes were assessed with the McNemar test, and longitudinal continuous changes with paired *t*-tests or Wilcoxon signed-rank tests. Two-sided $P < 0.05$ was significant. Multivariable logistic regression with Firth penalization estimated adjusted odds ratios (ORs) and 95% CIs for predictors of clinical and endoscopic remission. Primary effectiveness analyses were conducted as-observed: at each visit window denominators included only patients with available assessments; discontinuations/switches or missing data before a window were not imputed. Paired tests included only patients with both baseline and follow-up data. Safety analyses included all patients who received at least 1 dose of RZB. A prespecified sensitivity analysis restricted to patients with evidence of active disease at baseline was performed and is reported in the Supplementary Materials (http://links.lww.com/AJG/D895). A second prespecified sensitivity analysis included all patients whose index date allowed a week-52 assessment before database lock (N = 213); identical definitions/windows were used, applying nonresponder imputation (patients with discontinuation, surgery, loss to follow-up, death, or missing outcomes counted as nonresponders). Composite end points required all components; if any component was missing, the composite was considered not achieved. When multiple assessments fell within a window, the value closest to the nominal visit was used. Analyses were performed using Stata version 18 (StataCorp, College Station, TX).

RESULTS

Patient characteristics

Of 619 patients with CD initiating RZB, 520 completed 12-week follow-up and were analyzed (Table 1). Mean age at start was 47.5 ± 17.2 years; median disease duration 13 years [interquartile range 7–21]. Disease was mainly ileocolonic (56.0%), with stricturing 55.4% and penetrating 24.4% behavior; 29.0% had perianal disease, and 60.4% had previous CD surgery. Previous exposure was extensive (71.7% failed ≥2 ADTs; 50.8% ≥ 3; 54.8% were UST–exposed). Baseline activity reflected an overall active cohort (HBI 5.9 ± 4.3; SES-CD 9.2 ± 7.0; CRP 9.1 ± 19.4 mg/L).Totally, 11.9% received budesonide and 13.9% systemic steroids at baseline.

Clinical and biochemical outcomes

At week 12, SFCR was 60.8% and clinical response 76.5% (Table 2). Symptom improvements were rapid and sustained: 87.9% had minimal abdominal pain and 50.6% achieved normalized SF by week-12, with similar proportions at weeks 26 and 52 (Figure 1d–f). At week 26, clinical remission was 70.7% and SFCR 67.8%; 65.6% presented SFCR at week 52. Week-52 remission did not differ after failure of ≥3 vs 2 ADTs (63.7% vs 69.0%, $P = 0.607$). UST-naïve patients had higher week-12 clinical remission (73.6% vs 55.8%, $P < 0.001$) and SFCR (69.8% vs 53.3%, $P < 0.001$), with convergence by weeks 26–52 (Table 2).

Composite biochemical + SFCR increased from 36.7% (week-12) to 45.2% (week-26), and 49.4% (week-52). Fecal calprotectin declined from 870 to 380 μg/g at week 12 and remained lower thereafter; CRP fell by week 12 and stabilized; hemoglobin rose modestly (Figure 1a–c). In the sensitivity cohort (N = 213), corresponding SFCR were 57% at weeks 12 and 26, and 47% at week 52; week-52 clinical remission was 50% (Figure 2).

Endoscopic and radiologic outcomes

Endoscopic remission was 36.6% at week 26 and 37.5% at week 52 among patients with available endoscopic data (Table 2). Rates favored UST-naïve vs UST-exposed at week 52 (56.5% vs 28.6%, $P = 0.022$) and after failure of 2 vs ≥ 3 ADTs (week-26 64.3% vs 25.5%, $P = 0.007$; week-52 72.7% vs 25.6%, $P = 0.003$). Radiology mirrored these patterns: among patients with available imaging, radiologic remission was 25.7% (week-26) and 24.6% (week-52); transmural healing 13.9% and 9.8%, respectively. Quantitatively, bowel-wall thickness decreased from 7.2 to 5.6 mm ($P < 0.001$) and cumulative diseased length from 249 to 75 mm ($P = 0.018$) by week 52; mesenteric lymphadenopathy improved by week 26, whereas luminal strictures were unchanged (Figure 3a–d). Week-52 radiologic remission and transmural healing were higher in UST-naïve vs UST-exposed (43.5% vs 13.2%, $P = 0.008$; 26.1% vs 0%, $P = 0.001$; Table 2).

Results of the prespecified sensitivity analysis in patients with active disease at baseline were consistent with the primary analyses; detailed findings are reported in Supplementary Table 1 (http://links.lww.com/AJG/D895).

EIMs and perianal disease

EIM activity declined over time, with significant reductions in dermatologic (from 6.7% to 1.3% at week 52, $P = 0.039$) and peripheral rheumatologic manifestations (from 17.1% to 11.7%, $P = 0.0389$); whereas axial remained relatively stable. Ocular EIMs were less frequent, with minimal change (Table 3). Active

Table 1. Baseline demographics and clinical characteristics of RZB-treated patients with Crohn's disease

Patient characteristics	
Patients	N = 520
Female, n (%)	231 (44.4)
Age (yr), average ± SD	47.5 ± 17.2
Smokers, n (%)	
Active	104 (20.4)
Ex	117 (23.0)
Duration of CD (yr), mean ± SD	15.2 ± 10.8
CD-location (Montreal L)[a], n (%)	
Ileal (L1)	165 (31.7)
Colonic (L2)	55 (10.6)
Ileocolonic (L3)	291 (56.0)
Upper GI (L4)	72 (13.8)
Perianal disease, n (%)	149 (29.0)
CD-behavior (Montreal B)[b], n (%)	
Inflammatory (B1)	197 (37.9)
Stricturing (B2)	288 (55.4)
Penetrating (B3)	127 (24.4)
Previous biologics, n (%)	
None (naïve)	17 (3.3)
Infliximab	302 (58.0)
Adalimumab	362 (69.6)
Vedolizumab	171 (32.9)
Ustekinumab	285 (54.8)
JAK inhibitors	33 (6.4)
Number of previous advanced therapies, n (%)	
1	147 (28.3)
2	109 (21.0)
3	95 (18.3)
≥4	169 (32.5)
Previous immunomodulators, n (%)	268 (52.0)
Previous surgery, n (%)	313 (60.4)
Stoma wearers, n (%)	37 (7.2)
Mean baseline HBI ± SD	5.9 ± 4.3
Mean baseline CRP, mg/L ± SD	9.1 ± 19.4
Mean baseline SES-CD	9.2 ± 7.0
Extraintestinal manifestations, n (%)	
Rheumatological	109 (21.0)
Dermatological	79 (15.2)
Corticosteroids at baseline, n (%)	
Budesonide	61 (11.9)
Systemic steroids	71 (13.9)
Reason for initiating RZB, n (%)	
Clinical disease activity	305 (58.7)
Endoscopic/Radiologic disease activity	337 (64.8)
Post-operative recurrence[c]	25 (4.8)
Treatment of POR[d]	79 (15.2)
Intolerance/side effects with previous treatment	60 (11.5)

CD, Crohn's disease; CRP, C-reactive protein; GI, gastrointestinal; HBI, Harvey-Bradshaw Index; JAK, Janus kinase; n, number; POR, postoperative recurrence; RZB, risankizumab; SES-CD, Simple Endoscopic Score for Crohn's Disease.
[a]Based on the Montreal classification, B1 represents nonstricturing, nonpenetrating disease, B2 is stricturing, and B3 is penetrating disease.
[b]As for the location of disease, based on the Montreal classification, L1 represents isolated ileal disease, L2 isolated colonic disease, L3 ileocolonic disease, and L4 upper GI disease.
[c]Postoperative recurrence indicates initiation of RZB for recurrence prevention after surgery.
[d]Treatment of postoperative recurrence indicates initiation of RZB for endoscopically confirmed recurrence.

perianal disease decreased modestly (from 8.9% to 5.2% by week 52); among 15 with draining fistulae at baseline, 40% ceased drainage by week 12 (13% complete closure) and 50% by week 26 (30% complete closure); limited week-52 data showed 1/2 complete closure (Table 4).

Predictors of clinical and endoscopic remission

At week 12, lower clinical remission was associated with previous UST (OR 0.45, 95% CI 0.31–0.66, $P < 0.001$) and vedolizumab exposure (OR 0.55, 0.38–0.80, $P = 0.002$), longer disease duration (OR 0.97, 0.95–0.99, $P < 0.001$), previous surgery (OR 0.64, 0.44–0.94, $P = 0.021$), and isolated colonic (L2) vs ileal (L1) disease (OR 0.51, 0.27–0.95, $P = 0.034$); on multivariable analysis, UST exposure remained independently negative (OR 0.61, 0.40–0.93, $P = 0.021$). For week 52 endoscopic remission, older age (OR 0.95, 0.91–0.99, $P = 0.023$), and UST exposure (OR 0.25, 0.07–0.92, $P = 0.037$) independently predicted lower odds; sex, smoking, CRP, and behavior were not associated (Table 5).

Safety

RZB was overall well tolerated: 6.9% experienced AEs (infections 2.1%, injection/infusion reactions 1.2%, headache 1.0%, rash 0.8%, arthralgia 0.6%; single shingles, and basal cell carcinoma 0.2% each). Discontinuations occurred in 40 patients; 6 stopped for AEs (including infusion-related reactions [n = 2], severe arthralgia [n = 1], fever [n = 1], and lichenoid drug eruption [n = 1]). CD-related complications were 5.4% overall, with 0.6% of CD-related surgery. No unexpected safety signals were detected (Table 6).

DISCUSSION

This multicenter, observational, real-world study provides a comprehensive assessment of both short- and long-term clinical, endoscopic, and radiologic outcomes of RZB in the largest, nationwide, real-world CD cohort to date, with over 96% of

Table 2. Clinical, biochemical, endoscopic, and radiologic outcomes after RZB induction at weeks 12, 26, and 52 in the overall Crohn's disease cohort, in patients previously exposed to ustekinumab, ustekinumab-naïve patients, and patients with prior failure to 2 or ≥3 ADTs

	Total	UST-exposed	UST-naïve	*P* value	Failure ≥3 ADT	Failure to 2 ADT	*P* value
12 wk							
Clinical response	398/520 (76.5%)	204/285 (71.6%)	194/235 (82.6%)	**0.003**	194/264 (73.5%)	86/109 (78.9%)	0.272
Clinical remission	332/520 (63.9%)	159/285 (55.8%)	173/235 (73.6%)	**<0.001**	153/264 (57.9%)	74/109 (67.9%)	0.074
SFCR	316/520 (60.8%)	152/285 (53.3%)	164/235 (69.8%)	**<0.001**	147/264 (55.7%)	71/109 (65.1%)	0.092
Clinical response in HBI > 4 at baseline	194/305 (64.6%)	105/179 (58.7%)	89/126 (70.6%)	**0.032**	100/163 (61.3%)	45/67 (67.2%)	0.407
Biochemical + SFCR	191/520 (36.7%)	87/285 (30.5%)	104/235 (44.3%)	**0.001**	88/264 (33.3%)	37/109 (33.9%)	0.909
APS ≤ 1[a]	457/520 (87.9%)	249/285 (87.4%)	208/235 (88.5%)	0.691	230/264 (87.1%)	99/109 (90.8%)	0.313
SF ≤ 2.8[b]	263/520 (50.6%)	121/285 (42.5%)	142/235 (60.4%)	**<0.001**	121/264 (45.8%)	53/109 (48.6%)	0.623
26 wk							
Clinical remission	244/345 (70.7%)	130/193 (67.4%)	114/152 (75.0%)	0.121	122/175 (69.7%)	50/72 (69.4%)	0.967
APS ≤ 1	309/345 (89.6%)	170/193 (88.1%)	139/152 (91.4%)	0.310	157/175 (89.7%)	61/72 (84.7%)	0.268
SF ≤ 2.8	193/345 (55.9%)	99/193 (51.3%)	94/152 (61.8%)	**0.050**	92/175 (52.6%)	43/72 (59.7%)	0.305
SFCR	234/345 (67.8%)	126/193 (65.3%)	108/152 (71.1%)	0.255	120/175 (68.6%)	49/72 (68.1%)	0.937
Biochemical + SFCR	156/345 (45.2%)	79/193 (40.9%)	77/152 (50.7%)	0.072	78/175 (44.6%)	35/72 (48.6%)	0.562
Endoscopic response	31/67 (46.3%)	22/45 (48.9%)	9/22 (40.9%)	0.538	17/38 (44.7%)	7/13 (53.8%)	0.570
Endoscopic remission	30/82 (36.6%)	17/54 (31.5%)	13/28 (46.4%)	0.183	12/47 (25.5%)	9/14 (64.3%)	**0.007**
Radiologic remission (BT ≤ 4 mm)[c]	26/101 (25.7%)	15/59 (25.4%)	11/42 (26.2%)	0.931	13/49 (26.5%)	4/19 (21.1%)	0.640
Transmural healing (BT ≤ 3 mm)[d]	14/101 (13.9%)	7/59 (11.9%)	7/42 (16.7%)	0.491	7/49 (14.3%)	2/19 (10.5%)	0.681
52 wk							
Clinical remission	106/154 (68.8%)	65/98 (66.3%)	41/56 (73.2%)	0.375	61/91 (67.0%)	21/29 (72.4%)	0.588
APS ≤ 1	137/154 (89.0%)	83/98 (84.7%)	54/56 (96.4%)	**0.025**	77/91 (84.6%)	27/29 (93.1%)	0.242
SF ≤ 2.8	84/154 (54.6%)	46/98 (47.0%)	38/56 (67.9%)	**0.012**	40/91 (45.1%)	19/29 (65.5%)	**0.043**
SFCR	101/154 (65.6%)	62/98 (63.3%)	39/56 (69.6%)	0.423	58/91 (63.7%)	20/29 (69.0%)	0.607
Biochemical + SFCR	76/154 (49.4%)	45/98 (45.9%)	31/56 (55.4%)	0.260	40/91 (44.0%)	16/29 (55.2%)	0.292
Endoscopic response	43/61 (70.5%)	28/40 (70.0%)	15/21 (71.4%)	0.907	24/37 (64.9%)	9/10 (90.0%)	0.123
Endoscopic remission	27/72 (37.5%)	14/49 (28.6%)	13/23 (56.5%)	**0.022**	11/43 (25.6%)	8/11 (72.7%)	**0.003**
Radiologic remission (BT ≤ 4 mm)	15/61 (24.6%)	5/38 (13.2%)	10/23 (43.5%)	**0.008**	6/34 (17.6%)	2/12 (16.7%)	0.939
Transmural healing (BT ≤ 3 mm)	6/61 (9.8%)	0/38 (0.0%)	6/23 (26.1%)	**0.001**	2/34 (5.9%)	0/12 (0.0%)	0.390

ADT, advanced therapy; APS, abdominal pain score; BT, bowel wall thickness; HBI, Harvey-Bradshaw Index; RZB, risankizumab; SF, stool frequency; SFCR, steroid-free clinical remission; UST, ustekinumab.
[a]APS ≤1: Average daily abdominal pain score ≤1 and not worse than baseline.
[b]Stool frequency ≤2.8: Average daily stool frequency ≤2.8 and not worse than baseline.
[c]Radiologic remission: BT ≤ 4 mm, no contrast enhancement/Doppler hyperemia, and no disease complications on imaging.
[d]Transmural healing: BT ≤ 3 mm with the same ancillary criteria as above.
Bold *P* values are considered statistically significant.

patients previously exposed to ADTs, and >30% failure to ≥3 ADTs. Despite this case-mix, induction results were robust: by week 12, clinical remission was 64%, SFCR exceeded 60%, and clinical response was observed in >75% of patients. These findings are comparable to, and in some respects exceeds that reported in ADVANCE/MOTIVATE trials (clinical remission ≈40%–45%) (20,21), align with the Groupe d'Étude Thérapeutique des Affections Inflammatoires du Tube Digestif (GETAID) series (45% remission at week 12 in a ≥3-failure cohort of 174 patients with CD) (24) and the US multicenter REal world Biologics and small mOlecules OuTcomes in IBD (REBOOT-IBD) consortium study (49.7% remission) (26), while are slightly inferior to that of a single-center experience showing 70% remission by HBI at week 12 (27).

Beyond induction, persistence of effectiveness was a key observation: weeks-26 and 52 SFCR remained 68% and 66%, respectively, among patients with in-window data. Long-term real-world evidence for RZB is limited, but generally concordant: GETAID reported 48% remission at week-52 (24), whereas REBOOT-IBD described 38% and 65% cumulative remission at 6 and 12 months, respectively, using HBI and PGA when HBI was unavailable (26). A Belgian cohort—enriched for extreme refractoriness (98% UST-exposed, 86% with ≥4 failures, 20% ostomy) and using PRO-based thresholds (SF ≤2.8/d and APS ≤1)—reported 18.2% week-24 and

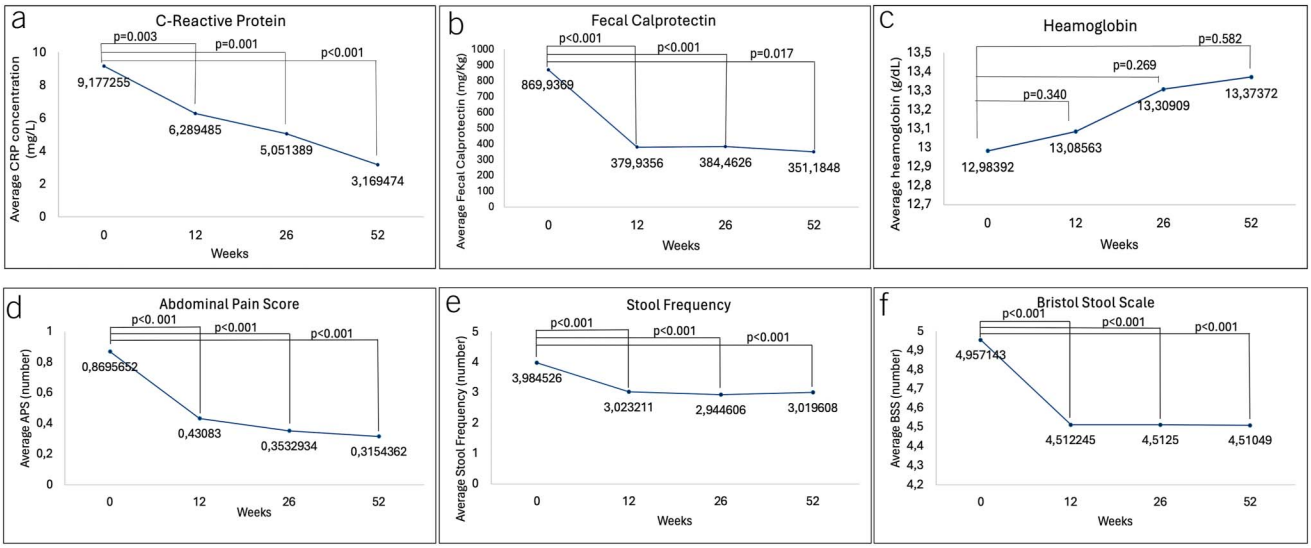

Figure 1. Longitudinal evolution of biochemical and patient-reported outcomes over 52 weeks of risankizumab treatment, assessed at baseline, week 12, week 26, and week 52. (**a**) Average C-reactive protein concentrations. (**b**) Average fecal calprotectin levels. (**c**) Average hemoglobin levels. (**d**) Abdominal pain score. (**e**) Stool frequency. (**f**) Bristol stool scale score.

27.3% week-52 remission (25), likely reflecting differences in population and definitions. Durability is further supported by the FORTIFY open-label extension, where 77.6% of RZB-treated patients maintained clinical remission at 3 years (34).

Although symptom control remains relevant, therapeutic goals in CD have shifted toward objective markers of intestinal healing. Achieving deep remission (35), predicts sustained clinical benefit, improved quality of life, and reduces risk of disease-related complications (36). In our cohort, endoscopic remission was 37% at both week 26 and week 52—closely mirroring FORTIFY (39% at week 52 with 360 mg maintenance) (21). Endoscopic response (≥50% SES-CD reduction) ranged from 46% to 71% from week 26 to 52, mirroring the Belgian study's 50% endoscopic response within 52 weeks (37). Higher cumulative rates of endoscopic remission reported by REBOOT-IBD (54% and 50% at 6 and 12 months) (26) may be attributable to differences in the endoscopic scoring systems used (e.g., Simplified Endoscopic Mucosal Assessment for Crohn's Disease or documentation of presence/absence of ulcers), thereby contributing to inter-study variability.

Crucially, for the first time, we systematically assessed cross-sectional imaging, addressing a major evidence gap (24,37) and aligning with treat-to-target frameworks that emphasize transmural healing in CD (35,38). By week 52, radiologic remission—BWT ≤4 mm without hyperemia/contrast enhancement and no complications—was achieved in ~25%, and transmural healing (BWT ≤3 mm with same ancillary criteria) in ~10%. Quantitatively, we observed a significant reduction in mean BWT and in cumulative diseased-segment length through week 52, alongside improvements in mesenteric lymphadenopathy; luminal strictures were unchanged, consistent with limited reversibility of established fibrotic remodeling. Although these radiologic targets were more challenging to reach than endoscopic remission, they are clinically relevant given associations with reduced disease progression, hospitalizations, and surgery (35,38,39). To our knowledge, only 1 previous study has reported radiologic outcomes with RZB, describing a 36% radiologic response at 12 months defined qualitatively by local radiologists (improvement/resolution of baseline activity), underscoring the need for standardized, quantitative criteria (26).

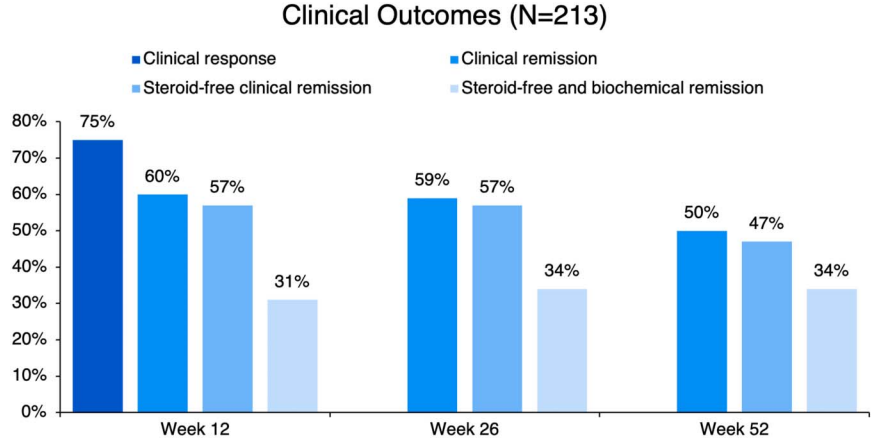

Figure 2. Clinical outcomes in the sensitivity cohort (N = 213).

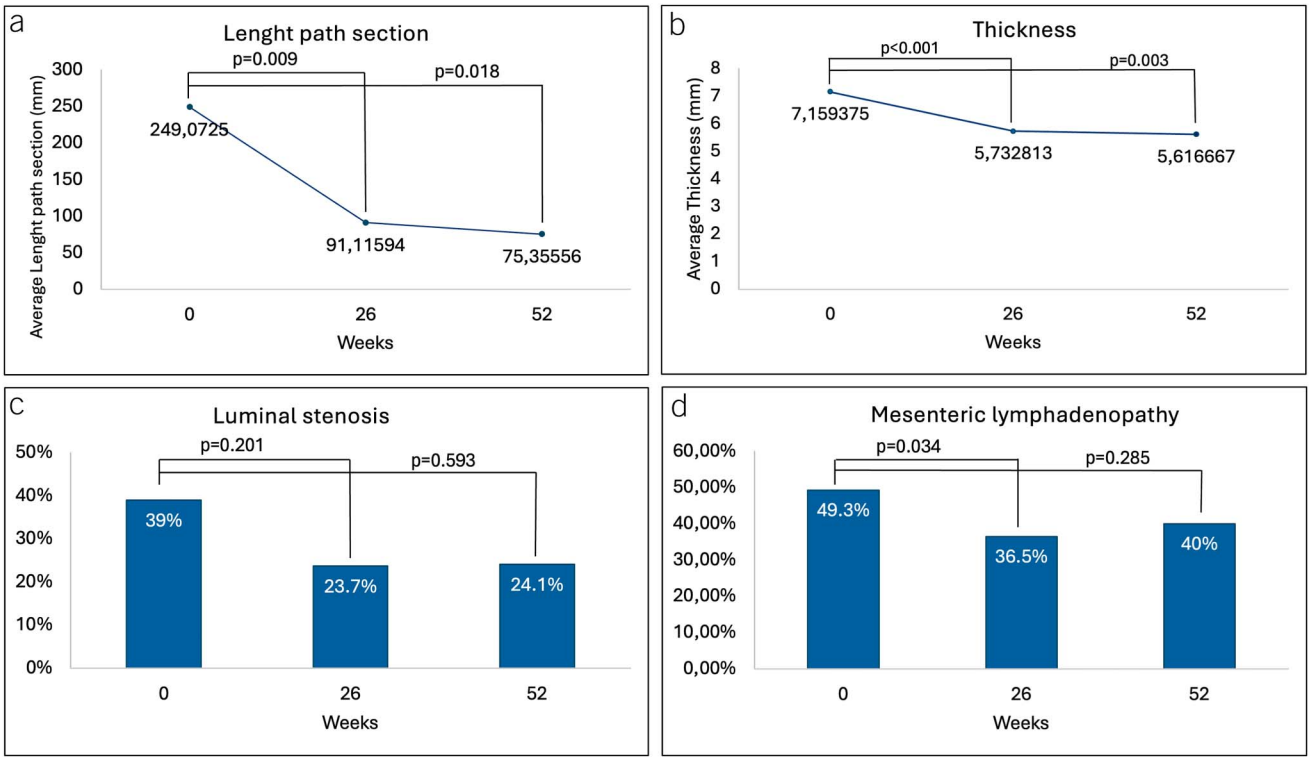

Figure 3. Radiologic outcomes over 52 weeks of risankizumab treatment in patients with Crohn's disease. (**a**) Cumulative length of affected intestinal segments. (**b**) Bowel wall thickness. (**c**) Proportion of patients with luminal stenosis. (**d**) Proportion of patients with mesenteric lymphadenopathies.

A significant complication of IBD is represented by EIMs, affecting up to 50% of patients with CD over the disease course and significantly impairing quality of life (1,40). In our cohort, over 35% of patients had at least 1 EIM at baseline, with rheumatologic manifestations being the most common. Encouragingly, within 52-weeks EIMs improved progressively, with dermatologic and peripheral rheumatologic manifestations exhibiting the largest declines, consistent with the central role of IL-23 in peripheral spondyloarthropathy (41–43) and psoriasis pathobiology (4,42). These data suggest dual intestinal-extraintestinal benefits (44) and motivate prospective studies to confirm durability and identify predictors of EIM response.

Perianal fistulizing CD remains a major therapeutic challenge in CD, with limited evidence supporting the efficacy of currently available ADTs (45). Although our study was not powered for fistula outcomes, approximately half of evaluable patients reported reduced drainage/pain and nearly one-third achieved complete closure by week-26, concordant with the GETAID physician-judged response/remission rates of 33%/33% (24). However, the absence of standardized perianal assessments warrants cautious interpretation and highlights a priority for future real-world protocols.

With respect to sequencing, differential outcomes by previous UST exposure are clinically relevant. UST-naïve patients achieved significantly higher week-12 response (82.6% vs 71.6%, $P = 0.003$), clinical remission (73.6% vs 55.8%, $P < 0.001$), and SFCR (69.8% vs 53.3%, $P < 0.001$); these clinical differences narrowed by week-52. Similar findings were reported by Zinger et al (27), who observed significantly higher SFCR rates in UST-naïve patients (74% vs 54%, $P = 0.03$) at week-12, with only numerically higher rates at weeks 26 and 52. Conversely, endoscopic and radiologic healing diverged over time: endoscopic remission was numerically higher at week-26 (46.4% vs 31.5%, $P = 0.183$) and significantly higher by week-52 (56.5% vs 28.6%, $P = 0.022$), whereas radiologic remission and transmural healing at week-52

Table 3. Activity of EIMs during RZB therapy in patients with Crohn's disease

EIMs activity	Baseline	12 wk	*P* value	26 wk	*P* value	52 wk	*P* value
Rheumatologic EIMs	89/520 (17.1%)	64/520 (12.3%)	**0.001**	39/345 (11.3%)	**0.001**	18/154 (11.7%)	**0.039**
Axial rheumatologic EIMs	23/520 (4.4%)	17/520 (3.3%)	0.134	4/345 (1.2%)	**0.001**	3/154 (2.0%)	0.180
Peripherals rheumatologic EIMs	75/520 (14.4%)	52/520 (10.0%)	**0.001**	36/345 (10.4%)	**0.034**	16/154 (10.4%)	0.083
Dermatologic EIMs	35/520 (6.7%)	13/520 (2.5%)	**<0.001**	3/345 (0.9%)	**<0.001**	2/154 (1.3%)	**0.039**
Ocular EIMs	6/520 (1.2%)	4/520 (0.8%)	0.500	1/345 (0.3%)	0.063	0/154 (0.0%)	**0.031**

EIMs, extraintestinal manifestations; RZB, risankizumab.
Bold *P* values are considered statistically significant.

Table 4. Evolution of perianal disease activity during risankizumab therapy

Perianal disease	Baseline	12 wk	*P* value	26 wk	*P* value	52 wk	*P* value
Active perianal disease (total)	46/520 (8.9%)	43/520 (8.3%)	0.467	23/345 (6.7%)	0.180	8/154 (5.2%)	0.727
Active draining fistula	15/520 (2.9%)	16/520 (3.1%)	0.782	6/345 (1.7%)	0.453	3/154 (2.0%)	1.000
Open, nondraining fistula	31/520 (6.0%)	27/520 (5.2%)	0.371	17/345 (5.0%)	0.581	5/154 (3.3%)	0.625

favored UST-naïve patients (43.5% vs 13.2%, $P = 0.008$ and 26.1% vs 0%, $P = 0.001$, respectively). These findings align with the REBOOT-IBD consortium, which reported significantly higher endoscopic remission rates at 6 and 12 months in UST-naïve patients (75.6% vs 33.3%, $P < 0.001$ and 68.1% vs 33.9%, $P < 0.001$, respectively) (26). In addition, previous UST exposure independently predicted lower week-12 clinical and week-52 endoscopic remission on multivariable analysis. Although multidrug refractoriness may confound these associations, previous vedolizumab or anti-tumor necrosis factor exposure did not independently predict outcomes, suggesting a specific signal related to previous IL-12/23 blockade rather than cumulative exposure per se.

Positioning RZB across the treatment pathway is further informed by the comparison of 2 vs ≥ 3 previous failures. Clinical, radiologic, and most PRO outcomes were similar at all time points, whereas endoscopic remission was significantly higher after 2 failures than after ≥3 at weeks 26 and 52. These observations align with phase 3 post hoc analyses showing attenuated but preserved RZB efficacy with increasing previous exposure (46). Collectively, these findings suggest earlier use of RZB, while also validating later-line use in highly refractory disease, potentially postponing or avoiding surgery (47,48).

The safety profile was favorable: AEs occurred in 6.9%, discontinuations for AEs in 1.2%, and no new safety signals emerged—consistent with previous real-world reports and the FORTIFY long-term extension (24,26,34). These findings are reassuring given the comorbidity burden and polypharmacy typical of patients with complex CD.

This study has several strengths, including its large sample size; nationwide, multicenter design; and comprehensive evaluation across clinical, endoscopic, radiologic, biochemical, PRO, EIMs,

Table 5. Predictors of clinical and endoscopic remission after risankizumab treatment in Crohn's disease on univariable and multivariable logistic regression analyses

	Clinical remission at 12 wk, n = 520				Endoscopic remission at 52 wk, n = 72			
	Univariable OR (95% CI)	*P* value	Multivariable OR (95% CI)	*P* value	Univariable OR (95% CI)	*P* value	Multivariable OR (95% CI)	*P* value
Age	0.99 (0.98, 1.00)	0.277			0.96 (0.93, 0.99)	**0.019**	0.95 (0.91, 0.99)	**0.023**
Male sex	1.24 (0.86, 1.79)	0.251	1.31 (0.89, 1.94)	0.167	0.40 (0.15, 1.10)	0.075	0.29 (0.08, 1.08)	0.064
Nonsmoker	1.11 (0.70, 1.77)	0.658			0.60 (0.18, 2.05)	0.415		
Perianal disease	0.88 (0.59, 1.30)	0.508			0.21 (0.05, 0.79)	**0.021**	0.22 (0.04, 1.11)	0.066
CD behavior (Montreal B)								
B1	1.20 (0.83, 1.75)	0.326			1.25 (0.67, 3.32)	0.660		
B2	0.91 (0.63, 1.30)	0.597			0.44 (0.16, 1.18)	0.103		
B3	0.95 (0.63, 1.44)	0.818			0.68 (0.16, 2.88)	0.599		
CD location (Montreal L)								
L1	—	—	—	—	—	—		
L2	0.51 (0.27, 0.95)	**0.034**	0.52 (0.26, 1.04)	0.064	5.67 (0.94, 34.03)	0.058	5.70 (0.63, 51.60)	0.121
L3	0.69 (0.46, 1.05)	0.082	0.77 (0.49, 1.19)	0.235	0.91 (0.31, 2.62)	0.856	0.88 (0.22, 3.47)	0.856
L4 (yes/no)	1.07 (0.64, 1.81)	0.785			2.92 (0.74, 11.53)	0.124		
CRP	0.99 (0.98, 1.00)	0.148			0.97 (0.91, 1.03)	0.261		
Disease duration	0.97 (0.95, 0.99)	<**0.001**	0.98 (0.96, 1.00)	0.055	0.96 (0.92, 1.01)	0.135		
Previous surgery	0.64 (0.44, 0.94)	**0.021**	0.78 (0.50, 1.23)	0.282	0.51 (0.19, 1.37)	0.182		
Previous immunosuppressant	0.74 (0.52, 1.07)	0.109			0.40 (0.15, 1.07)	0.067		
Previous UST	0.45 (0.31, 0.66)	<**0.001**	0.61 (0.40, 0.93)	**0.021**	0.31 (0.11, 0.86)	**0.025**	0.25 (0.07, 0.92)	**0.037**
Previous VEDO	0.55 (0.38, 0.80)	**0.002**	0.78 (0.50, 1.20)	0.258	0.44 (0.16, 1.21)	0.112		
Previous anti-TNF	0.57 (0.31, 1.08)	0.084			5.62 (0.66, 47.71)	0.114		

CD, Crohn's disease; CI, confidence interval; CRP, C-reactive protein; OR, odd ratio; TNF, tumor necrosis factor; UST, ustekinumab; VEDO, vedolizumab.
Bold *P* values are considered statistically significant.

Table 6. Adverse events reported after RZB initiation in patients with CD

	RZB-treated patients (n = 520)
Adverse event, n (%)	36 (6.9%)
Skin rash	4 (0.8%)
Arthralgia	3 (0.6%)
Infusion/injection site reaction	6 (1.2%)
Infection	11 (2.1%)
Shingles	1 (0.2%)
Malignancy	1 (0.2%)
Headaches	5 (1.0%)
Others	5 (1.0%)
RZB discontinuation, n	40
12 wk	10
26 wk	14
52 wk	16
CD-complications, n (%)	28 (5.4%)
New intra-abdominal fistula or abscess	6 (1.2%)
New bowel stricture	14 (2.7%)
New perianal fistula or abscess	4 (0.8%)
Severe acute colitis	1 (0.2%)
CD-related surgery	3 (0.6%)

CD, Crohn's disease; n, number; RZB, risankizumab.

and perianal domains, with prespecified subgroup analyses by UST exposure and previous-failure strata, which offer novel insights to inform sequencing strategies in CD. However, several limitations must be acknowledged, including the retrospective design, potential referral bias from secondary/tertiary centers, nonstandardized assessments for perianal disease and EIMs, variable timing/availability of endoscopy and imaging necessitating ±2-month windows, and fewer paired baseline–follow-up assessments, limiting response calculations. Moreover, the incomplete availability of objective assessments, particularly endoscopy and cross-sectional imaging, resulted in denominators for objective outcomes that were substantially smaller than the overall cohort size. This reflects real-world clinical practice, where endoscopic and radiologic reassessments are typically performed based on clinical indication rather than at fixed protocol-driven timepoints. Therefore, patients undergoing follow-up endoscopy or imaging are likely to represent a selected subgroup, potentially enriched for either persistent disease activity (prompting reassessment) or favorable early clinical response (allowing planned treat-to-target evaluation). This selection process may introduce both underestimation or overestimation of true endoscopic and radiologic effectiveness. To mitigate this risk, denominators were explicitly reported for all outcomes, and a prespecified sensitivity analyses was performed. Nonetheless, these results should be interpreted with caution, and confirmed in prospective studies with standardized, endoscopic and radiologic assessments.

In conclusion, RZB demonstrated effective and durable induction and maintenance across several phenotypes, with meaningful benefits on endoscopic and radiologic targets, and improvements in EIMs and perianal disease. Although previous UST exposure was associated with lower rates of early clinical response and reduced likelihood of endoscopic and radiologic healing, a substantial proportion of these patients still achieved clinically meaningful benefits over time, supporting the continued role of p19 inhibition even after IL-12/23 failure. In parallel, our analyses by number of previous advanced therapy failures provide additional guidance for treatment positioning: whereas clinical outcomes were broadly comparable between patients with 2 vs 3 or more previous failures, endoscopic remission rates were higher in those treated earlier in the disease sequence. Taken together, these data support a nuanced, individualized approach to sequencing. In UST-naïve patients and in those with fewer previous failures, earlier positioning of RZB may maximize the probability of achieving objective healing targets, whereas in more heavily pretreated or UST-exposed patients, RZB remains a reasonable and effective option, although with more modest expectations for deep endoscopic or transmural remission and the need for closer objective monitoring. Therefore, our results argue for tailored decision-making that balances previous treatment history, disease phenotype, and therapeutic goals.

Prospective studies should refine patient selection, standardize EIMs and perianal end points, and inform evidence-based sequencing strategies to maximize long-term outcomes.

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CONFLICTS OF INTEREST

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

Ethics approval statement: This study received central approval from the Ethics Committee *Lazio Area 3* (Protocol No. 7036), followed by approval from the institutional review boards or ethics committees of all participating centers. The study was conducted in accordance with the principles of the Declaration of Helsinki and relevant local regulations.

Patient consent statement: Written informed consent was obtained from all patients before inclusion in this retrospective study. Participants provided consent for the collection, analysis, and anonymized publication of their clinical and laboratory data under the supervision of the *Lazio Area 3* Ethics Committee.

Clinical trial registration: This was a retrospective observational study.

Study Highlights

WHAT IS KNOWN

- ✓ Risankizumab (RZB) (IL-23 p19 inhibitor) exhibited efficacy in phase 3 clinical trials for the treatment of moderate-to-severe Crohn's Disease (CD). However, real-world data in heterogeneous CD populations, including patients with stricturing/penetrating behavior, extraintestinal manifestations/perianal disease, and multiple previous failure to advanced therapies, such as ustekinumab (UST), are limited.
- ✓ Treat-to-target strategies in CD now prioritizes objective intestinal healing (endoscopic and transmural), yet radiologic outcomes after RZB therapy are underreported.

WHAT IS NEW HERE

- ✓ Largest nationwide real-world CD cohort on RZB (n = 520; 45% ≥ 3 previous biologics, 55% UST-exposed): steroid-free clinical remission 60.8% at week 12, sustained to 65.6% at week 52.
- ✓ First systematic inclusion of radiologic outcomes: week-52 endoscopic remission 37.5%, radiologic remission 24.6%, transmural healing 9.8%, with significant reductions in bowel-wall thickness and diseased-segment length.
- ✓ Sequencing signal: UST-naïve patients achieved higher week-52 endoscopic remission (56.5% vs 28.6%), and previous UST independently predicted lower clinical (week-12) and endoscopic (week-52) remission.
- ✓ Extraintestinal/perianal outcomes: progressive improvement in extraintestinal manifestations (largest gains in dermatologic and peripheral rheumatologic domains) and modest perianal benefit, including cessation of drainage and occasional fistula closure by week 26.

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