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Original Article

Corticosteroid-sparing effects of risankizumab efficacy and safety in patients with moderately to severely active ulcerative colitis

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Abstract

Background and aims: This post hoc analysis evaluated the corticosteroid-sparing effects of risankizumab (RZB) therapy in patients with moderate-to-severe ulcerative colitis in the phase 3 induction and maintenance studies, INSPIRE and COMMAND.

Methods: Patients were randomized (2:1) to 12 weeks of intravenous RZB or placebo (PBO) induction therapy; responders to intravenous RZB were randomized (1:1:1) to receive subcutaneous RZB 180 mg, 360 mg, or PBO (RZB withdrawal) maintenance therapy. Baseline corticosteroid doses were maintained during induction, with a mandatory taper beginning at maintenance week 0. Efficacy outcomes were evaluated by baseline corticosteroid use at induction week 12, while corticosteroid-free clinical and endoscopic outcomes were assessed at maintenance week 52 among the overall population and among patients on corticosteroids at baseline. Safety was also assessed.

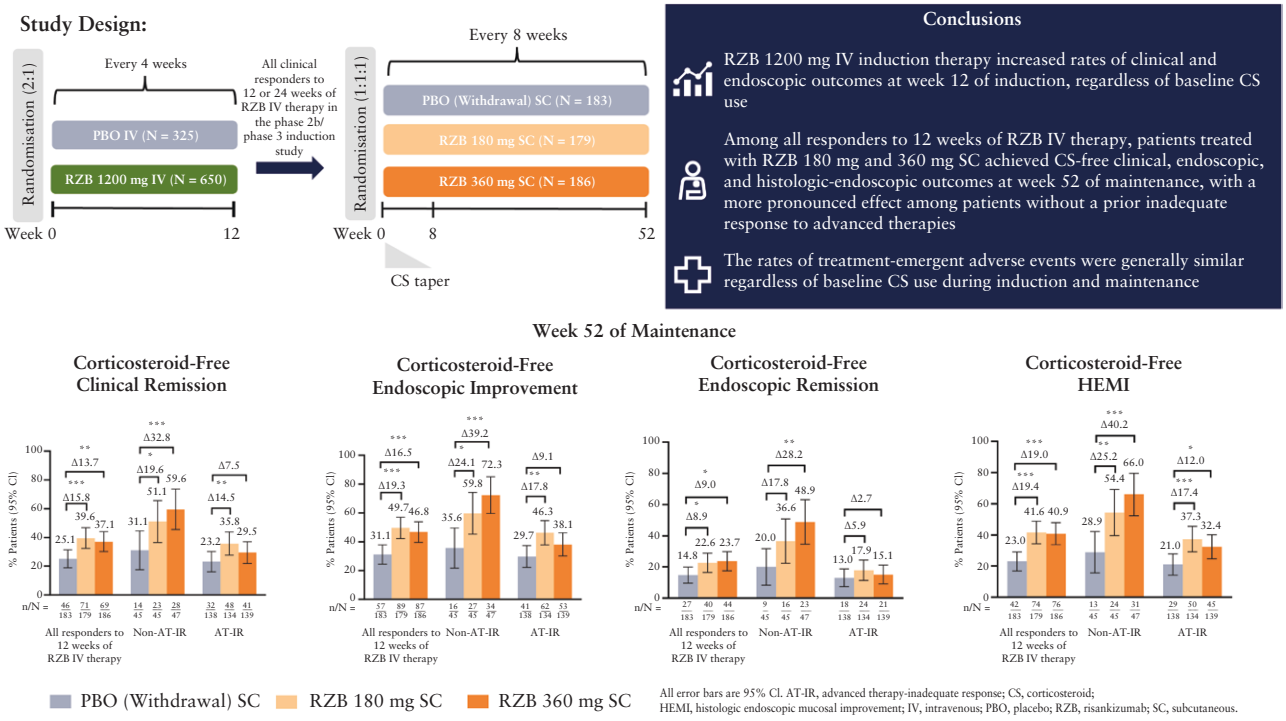
Results: At baseline, 35.7% (348/975) of patients were taking corticosteroids. At induction week 12, greater rates were observed for clinical, endoscopic, and patient-reported outcomes in RZB 1200 mg-treated patients compared with PBO, regardless of baseline corticosteroid use. RZB 180 mg and 360 mg treatment resulted in higher corticosteroid discontinuation rates (RZB 180 mg 64.9% [48/74]; RZB 360 mg 54.2% [32/59]; PBO [withdrawal] 36.8% [25/68], $P \leq .01$) and corticosteroid-free clinical, endoscopic, and patient-reported outcomes at week 52, compared with PBO (withdrawal). The rates of treatment-emergent adverse events were similar regardless of baseline corticosteroid use during induction and maintenance.

Conclusions: The efficacy of RZB induction therapy was independent of corticosteroid use, with high rates of corticosteroid-free outcomes observed in the overall population and among patients with baseline corticosteroid use, reaffirming the potential of RZB to serve as a corticosteroid-sparing therapy for patients with ulcerative colitis.

Clinicaltrial.gov numbers: NCT03398148 and NCT03398135

Key words: corticosteroids; IL-23 inhibitor; risankizumab; ulcerative colitis.

Graphical abstract



1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease affecting the rectum and colon, characterized by frequent diarrhea, rectal bleeding, and bowel urgency. Uncontrolled symptoms are associated with a reduction in quality of life, resulting in profound socioeconomic and psychological burden for patients.[1,2] Real-world data indicate that patients with UC often have suboptimal disease control, which may lead to depression, fatigue, and reduced work productivity.[3,4]

Due to their rapid onset of action, systemic corticosteroids (CSs) are an effective short-term treatment for patients with moderately to severely active UC.[5] However, CS is not recommended as long-term maintenance therapy due to CS refractiveness, dependency, and unwanted adverse events (AEs).[6] These AEs may affect multiple organ systems, including behavioral and neurological disturbances (mood changes, sleep disruption), endocrine changes (weight gain, risk of developing diabetes mellitus, osteoporosis), and hematologic disturbances, including an increased risk of infections.[7–10] CS dependency is a chronic issue in UC treatment, particularly in patients with more severe disease.[11] Current treatment guidelines recommend a CS-sparing therapeutic approach aiming to achieve and sustain CS-free clinical remission[12,13]

Interleukin-23 (IL-23) is a proinflammatory cytokine that has been implicated in the pathogenesis of UC.[14] Risankizumab (RZB) is a humanized immunoglobulin G1 monoclonal antibody that selectively binds to the IL-23p19 subunit, attenuating the IL-23–mediated inflammatory cytokine cascade. RZB is approved for the treatment of UC, Crohn's disease, plaque psoriasis, and psoriatic arthritis by the United States Food and Drug Administration and European Medicines Agency; and for palmoplantar pustulosis by the Japanese Pharmaceuticals and Medical Devices Agency.[15–17]

Using data from the pivotal phase 3 studies of RZB in UC, INSPIRE, and COMMAND, we investigated the effect of baseline CS use on the achievement of clinical, endoscopic, and endoscopic-histologic outcomes with RZB induction therapy in patients with moderately to severely active UC. Further, we evaluated the ability of RZB maintenance therapy to achieve CS-free outcomes in patients who responded to 12 weeks of RZB intravenous (IV) induction therapy. Safety outcomes were assessed by baseline CS use through week 12 of induction and week 52 of maintenance.

2. Materials and methods

2.1. Study design and patients

INSPIRE (NCT03398148) and COMMAND (NCT03398135) were randomized, multicenter, double-blind placebo (PBO)-controlled phase 3 studies. A detailed description of the study designs has been previously reported.[18] The phase 3 induction trial was preceded by a dose-ranging, phase 2b induction substudy, followed by an open-label induction treatment arm (Figure S1). Eligible patients were 18-80 years of age with moderately to severely active UC, defined as an Adapted Mayo score of ≥5 points and an endoscopic subscore of ≥2, per blinded, central review. All patients were required to demonstrate an intolerance or inadequate response (IR) to either 1 or more prior advanced therapies (eg, infliximab, adalimumab, golimumab, vedolizumab, tofacitinib, filgotinib, upadacitinib, and/or ozanimod) (advanced therapy-IR, AT-IR) or conventional treatments ([non-AT-IR]; eg, aminosalicylates, CS, and/or immunomodulators). Key exclusion criteria included prior exposure to p40 inhibitors or p19 inhibitors. For maintenance, eligible patients were clinical responders to RZB induction therapy.

Patients in the phase 3 induction trial were randomized 2:1 to receive IV RZB 1200 mg or PBO at weeks 0, 4, and 8, stratified by baseline UC-related CS use (yes vs no), baseline Adapted Mayo score (≤5-7 vs > 7), and a history of AT-IR (0,

1, >1). Patients who failed to achieve a clinical response after 12 weeks of RZB induction therapy received an additional 12 weeks of induction therapy. Patients who achieved clinical response per Adapted Mayo score (decrease from baseline ≥2 points and ≥30% from baseline, plus a decrease in rectal bleeding score [RBS] ≥ 1 or an absolute RBS ≤ 1) after 12 or 24 weeks of RZB IV induction therapy in the phase 2b or phase 3 induction study were randomized in the maintenance trial (1:1:1) to receive subcutaneous (SC) RZB 180 mg, 360 mg, or PBO (RZB withdrawal [WD]), every 8 weeks. Randomization for maintenance was stratified by AT-IR status (yes, no), last IV RZB induction dose, and clinical remission per Adapted Mayo score (per local read) from the last induction visit. Patients who achieved a clinical response to 12 or 24 weeks of RZB IV induction therapy were included in the safety outcome analysis for maintenance; however, only randomized patients who achieved a clinical response after 12 weeks of RZB IV treatment were included in the maintenance efficacy analysis.

2.2. Concomitant CS use and taper

Patients taking CS at baseline (week 0) of induction were required to maintain their baseline dose for the duration of induction. For the induction study, patients taking oral CS at maximum doses of budesonide 9 mg/day, beclomethasone dipropionate 5 mg/day, or prednisone 20 mg/day or the equivalent were eligible if they had been on the current CS treatment course for ≥14 days and were taking a stable dose for ≥7 days prior to baseline. Decreasing a CS dose was prohibited during the induction study, except in the event of moderate-to-severe treatment-related toxicities. Patients who entered the 12-week extended induction treatment period were permitted to taper CS at the discretion of the investigator. At week 0 of maintenance, patients taking CS began to taper their dose, with completion of the CS taper by week 8 (Figure S1). Per the protocol schedule, prednisone or equivalent doses >10 mg/day were tapered by 5 mg/day per week, prednisone or equivalent doses ≤ 10 mg/day were tapered by 2.5 mg/day/week, and budesonide ≤ 9 mg/day doses were tapered by 3 mg/week. Patients taking oral budesonide-multi matrix system formulation or oral beclomethasone discontinued medication without a taper. Patients taking CS at week 0 of maintenance who have a loss of satisfactory clinical response per the investigator's judgment after the CS taper has been initiated may have their CS dose increased up to the dose used at the baseline of induction, per the investigator's discretion.

2.3. Independent ethics committees and institutional review boards

The Independent Ethics Committee or Institutional Review Board at each study site approved the study protocol, informed consent forms, and recruitment materials before patient enrollment. The studies were conducted in accordance with the International Conference for Harmonisation guidelines, applicable regulations, and the Declaration of Helsinki. All patients provided written informed consent before screening.

2.4. Efficacy outcomes

This post hoc analysis of clinical, endoscopic, histologic-endoscopic, and patient-reported outcomes was performed at week 12 of the phase 3 induction study (INSPIRE) and week 52 of the phase 3 maintenance study (COMMAND). Endpoints assessed at week 12 of induction by CS use (yes/no) included clinical remission per Adapted Mayo score (stool frequency subscore ≤ 1, and not greater than baseline, RBS = 0, and endoscopic subscore ≤ 1 without evidence of friability), endoscopic improvement (endoscopic subscore ≤ 1 without evidence of friability), endoscopic remission (endoscopic subscore = 0), histologic-endoscopic mucosal improvement (HEMI; endoscopic subscore of 0 or 1 without evidence of friability and Geboes score ≤ 3.1), and patient-reported outcomes, including fatigue (Functional Assessment of Chronic Illness Therapy-Fatigue [FACIT-F]), bowel urgency, abdominal pain, nocturnal bowel movements, tenesmus, fecal incontinence, and sleep disruption due to UC.

Functional Assessment of Chronic Illness Therapy-Fatigue is a 13-item assessment of fatigue associated with disease and the subsequent impact on daily activities and function, with data expressed as a mean change in FACIT-F score from baseline.[19] Bowel urgency, abdominal pain, nocturnal bowel movements, and tenesmus were evaluated using a scoring system, where a higher score signified more severe pain. Bowel urgency, abdominal pain, and nocturnal bowel movements were quantified as the percent of patients who achieved the absence of each symptom. Fecal incontinence scoring quantified the number of weekly episodes of accidental bowel leakage (eg, accidental soiling of underwear) prior to each study visit. Scores were determined by calculating the mean of the number of fecal incontinence episodes over the most recent week (ie, 7 days) prior to a study visit and then multiplying by 7, with a reduction from baseline indicating improvement. Fatigue (FACIT-F), fecal incontinence, and sleep disruption were expressed as mean change in total score from baseline, with a greater change from baseline indicative of an improvement in each symptom.

Week 52 CS-free outcomes were defined as no CS use for at least 90 days immediately prior to week 52 plus 1 of the following endpoints: clinical remission per Adapted Mayo score, endoscopic improvement, endoscopic remission, HEMI, and for categorical patient-reported outcomes (no bowel urgency, no nocturnal bowel movements, no abdominal pain, no tenesmus). Systemic corticosteroid-free analysis was not possible for continuous endpoints assessed as a mean change from baseline (FACIT-F, fecal incontinence, and sleep disruption). Among patients who were taking CS at baseline of induction, the proportion of patients who discontinued CS use (complete cessation of UC-related CS at the time of evaluation) over time during maintenance from week 0 to week 52 was evaluated.

2.5. Subgroup analysis

Among all clinically responding patients to 12 weeks of RZB IV who were also taking CS at baseline (week 0 of induction), comparisons were also made for CS-free clinical and endoscopic outcomes at week 52 of maintenance. In addition, among all clinical responders to 12 weeks of RZB IV, CS-free clinical and endoscopic outcomes were evaluated in AT-IR and non-AT-IR patients at week 52. The nonresponder-multiple imputation (NRI-MI) approach was used for the analysis of missing data. For comparisons between RZB and PBO, nominal *P* values were calculated for statistical comparisons. Type I error was not controlled for.

2.6. Safety outcomes

Safety outcomes were analyzed through week 12 of induction and week 52 of maintenance in patients who received at least 1 dose of the study drug. At week 52, analysis was also restricted to clinically responding patients to 12 or 24 weeks of RZB IV induction therapy. Safety was stratified by UC-related CS use (yes vs no) at baseline (week 0 of induction). Overall treatment-emergent adverse events (TEAEs) and TEAEs of special interest were assessed based on prespecified outcomes, in accordance with previously published RZB studies.[20,21] Nonresponding patients were included in the safety analysis. AEs were coded using the Medical Dictionary for Regulatory Activities, version 25.1.

2.7. Statistical analysis

The efficacy analyses for induction and maintenance included all randomized patients who received at least 1 dose of the study drug during the induction or were randomized to maintenance and responded to 12 weeks of RZB IV of induction therapy, respectively (Figure S1). Baseline demographics and clinical characteristics were summarized using descriptive statistics for each treatment group. Categorical endpoints were analyzed using Cochran-Mantel-Haenszel (CMH) tests for common risk difference, while continuous endpoints (eg, FACIT-F) were analyzed using analysis of covariance, with each adjusted for stratification factors between treatment groups. Missing data due to logistic restrictions (eg, COVID-19 or geopolitical restrictions) were imputed using NRI-MI for categorical variables or multiple imputation incorporating return-to-baseline for continuous variables. For comparisons between RZB and PBO, nominal *P* values were calculated for statistical comparisons. Any patients with missing baseline stratification factors used in the stratified statistical analysis models had their strata assigned per the Interactive Response Technology at the time of randomization.

Safety data were summarized descriptively, with no missing data imputed. All statistical analyses were completed using Statistical Analysis Software (version 9.4 or newer; SAS Institute).

3. Results

3.1. Patient demographics and disease characteristics

3.1.1. Induction

Of the patients randomized to induction, 36.3% (236/650) of RZB 1200 mg and 34.5% (112/325) of PBO-treated patients were taking CS at baseline (week 0), respectively (Table 1). Baseline demographics and disease characteristics were similar among treatment groups regardless of baseline CS use, with the exceptions of race, with greater percentages of White (RZB 1200 mg 82.6%, PBO 77.7%) and lower percentages of Asian (RZB 1200 mg 14.9%, PBO 19.6%) for those with CS use at baseline compared with no CS use. There was a slightly greater percentage of patients with a Mayo endoscopy subscore of 3 for those with CS use (RZB 1200 mg 73.3%, PBO 75.9%) compared with those without CS use (RZB 1200 mg 65.0%, PBO 68.5%). There were also slightly higher percentages of AT-IR patients among those taking CS at baseline (RZB 1200 mg 58.1%, PBO 61.6%), compared with those without baseline use (RZB 1200 mg 47.3%, PBO 47.4%) (Table 1). In addition, among patients taking CS, a higher proportion had previously failed 2 AT (RZB 1200 mg 23.3%; PBO 25.9%) or more (RZB 1200 mg 13.6%, PBO 13.4%) compared with those without baseline use (2 AT: RZB 1200 mg 13.8%; PBO 12.2%; > 2 AT: RZB 1200 mg 8.7%; PBO 9.4%). The median (interquartile range [IQR]) daily CS dose at baseline was 20.0 (10.0-20.0) and 20.0 (10.0-20.0) mg/day for patients treated with RZB 1200 mg or PBO, respectively. CS dosing at baseline ranged from 0 to 50 mg/day, with most patients taking >5 to ≤ 20 mg dose (RZB 1200 mg [74.4%]; PBO [78.6%], Table S1).

3.1.2. Maintenance

Of the patients who responded to 12 weeks of RZB IV induction therapy and were allocated to RZB 180 mg, RZB 360 mg, or PBO (WD), 41.3% (74/179), 31.7% (59/186), and 37.2% (68/183) of patients were taking CS at baseline, respectively (Table S2). Among RZB 180 mg- or 360 mg-treated patients, those who were taking CS were more likely to have an endoscopic subscore of 3 at baseline of induction compared with those without CS use (Table S2). The median (IQR) daily CS dose at baseline was 20.0 (8.8-20.0), 20.0 (10.0-20.0), and 15.0 (8.8-20.0), mg/day for patients treated with RZB 180 mg, RZB 360 mg, or PBO (WD), respectively (Table S2). CS doses ranged from 0 to 50 mg/day, with most patients taking >5 to ≤ 20 mg dose (RZB 180 mg [82.2%]; RZB 360 mg [72.9%]; PBO [WD] [66.2%], Table S3).

3.2. Efficacy

3.2.1. Induction therapy

Patients treated with RZB 1200 mg achieved higher rates of clinical remission (16.9% with baseline CS use, 22.2% without baseline CS use) at week 12 of induction compared with PBO (7.4% with baseline CS use, 5.6% without baseline CS use; differences: 9.3%, 16.5%), regardless of CS use at baseline, $P \le .01$ for both comparisons (Figure 1A). Patients treated with RZB 1200 mg exhibited higher rates of clinical response, endoscopic improvement, endoscopic remission, and HEMI in comparison to PBO-treated patients, with consistency maintained regardless of baseline CS use (Figure 1B-E).

An improvement in fatigue (FACIT-F) was observed in patients treated with RZB 1200 mg (mean change from baseline: 7.6 with baseline CS use, 8.1 without baseline CS use) compared with PBO-treated patients, regardless of CS use at baseline (4.3 with baseline CS use, 2.9 without baseline CS use; differences: 3.3%, 5.3%; $P \le .01$, $P \le .001$, respectively, Figure S2A). In patients with or without baseline CS use, those treated with RZB 1200 mg also experienced an increase in the absence of nocturnal bowel movements (RZB 1200 mg: 60.6%, 71.1% vs PBO: 49.1%, 39.9%) compared with patients treated with PBO ($P \le .05$, Figure S2E). Among patients without baseline CS use, RZB 1200 mg had higher rates for the achievement of no bowel urgency (49.1% vs 26.3%; difference: 22.7%), no abdominal pain (38.0% vs 25.8%; difference: 12.1%), and no tenesmus (51.8% vs 28.2%; difference: 23.5%), compared with PBO-treated patients, $P \le .01$ for all comparisons (Figure S1B-D). Among patients without CS use at baseline, treatment with RZB 1200 mg also improved fecal incontinence (mean change from baseline: −3.9 vs −2.0; difference: −1.9) and sleep disruption (mean change from baseline: −2.5 vs −1.2; difference: −1.3) compared with PBO, $P \le .001$ for both comparisons

Table 1. Baseline demographics and disease characteristics by corticosteroid use at week 0 of induction.

Characteristic, *n* (%) unless otherwise noted	No corticosteroid use at baseline		With corticosteroid use at baseline	
	PBO IV *N* = 213	RZB 1200 mg IV *N* = 414	PBO IV *N* = 112	RZB 1200 mg IV *N* = 236
Sex				
Female	84 (39.4)	170 (41.1)	40 (35.7)	95 (40.3)
Male	129 (60.6)	244 (58.9)	72 (64.3)	141 (59.7)
Age, years, mean (SD)	43.8 (14.3)	41.9 (13.6)	40.8 (14.1)	41.6 (13.3)
Body mass index,[a] kg/m^2, mean (SD)	*N* = 213 24.7 (5.1)	*N* = 413 24.6 (5.4)	*N* = 112 25.3 (5.2)	*N* = 234 24.8 (5.1)
Race				
American Indian or Alaska Native	0	0	0	1 (0.4)
Asian	74 (34.7)	136 (32.9)	22 (19.6)	35 (14.9)
Black or African American	5 (2.3)	8 (1.9)	2 (1.8)	4 (1.7)
Native Hawaiian or Other Pacific Islander	0	0	0	0
White	131 (61.5)	265 (64.2)	87 (77.7)	194 (82.6)
Multiple	3 (1.4)	4 (1.0)	1 (0.9)	1 (0.4)
Ethnicity				
Hispanic or Latino	13 (6.1)	21 (5.1)	7 (6.3)	23 (9.8)
Not Hispanic or Latino	200 (93.9)	392 (94.9)	105 (93.8)	212 (90.2)
Disease duration, years, mean (SD)	8.4 (7.2)	7.5 (6.6)	7.4 (6.6)	8.1 (7.4)
Disease extent				
Left-sided	99 (46.5)	195 (47.1)	51 (45.5)	118 (50.0)
Extensive/pancolitis	113 (53.1)	218 (52.7)	61 (54.5)	116 (49.2)
Limited to rectum	1 (0.5)	1 (0.2)	0	2 (0.8)
Adapted Mayo score	*N* = 213	*N* = 413		
Mean (SD)	7.0 (1.3)	7.0 (1.2)	7.1 (1.2)	7.2 (1.2)
≤7	125 (58.7)	246 (59.6)	65 (58.0)	130 (55.1)
>7	88 (41.3)	167 (40.4)	47 (42.0)	106 (44.9)
Mayo endoscopy subscore, mean (SD)	2.7 (0.5)	2.6 (0.5)	2.8 (0.4)	2.7 (0.4)
2	67 (31.5)	145 (35.0)	27 (24.1)	63 (26.7)
3	146 (68.5)	269 (65.0)	85 (75.9)	173 (73.3)
FCP, mg/kg, median (min, max)	*N* = 200 1593 (30-25 376)	*N* = 382 1496 (30-28 800)	*N* = 102 1635 (30-28 800)	*N* = 220 1658 (30-28 800)
hs-CRP, mg/L, median (min, max)	*N* = 209 4.1 (0.2-113.0)	*N* = 406 3.3 (0.2-199.0)	*N* = 109 3.2 (0.2- 83.8)	*N* = 232 3.6 (0.2-130.0)
Medications at baseline				
Immunosuppressant use	36 (16.9)	67 (16.2)	17 (15.2)	41 (17.4)
Aminosalicylates use	163 (76.5)	312 (75.4)	75 (67.0)	163 (69.1)
Corticosteroid dose, mg/day, median (IQR)	--	--	*N* = 112 20.0 (10.0-20.0)	*N* = 234 20.0 (10.0-20.0)
Advanced therapy-IR	101 (47.4)	196 (47.3)	69 (61.6)	137 (58.1)
Number of prior failed advanced therapies				
0	112 (52.6)	218 (52.7)	43 (38.4)	99 (41.9)
1	55 (25.8)	103 (24.9)	25 (22.3)	50 (21.2)
2	26 (12.2)	57 (13.8)	29 (25.9)	55 (23.3)
> 2	20 (9.4)	36 (8.7)	15 (13.4)	32 (13.6)

Data were calculated on nonmissing values. 1 mg budenoside = 5 mg prednisone.
Abbreviations: FCP, fecal calprotectin; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; IR, inadequate response; IV, intravenous; PBO, placebo; RZB, risankizumab; TNF, tumor necrosis factor.

(Figure S1F and G). No differences were observed in the absence of bowel urgency, absence of abdominal pain, absence of tenesmus, absence of fecal incontinence, or sleep disruption due to UC symptoms among patients with CS use at baseline (Figure S1B-D, F and G).

3.2.2. Maintenance therapy

Following completion of the mandatory CS taper at maintenance week 8, discontinuation of CS use among patients who were on CS at baseline of induction and were treated with RZB 180 mg or 360 mg plateaued at week 24, while

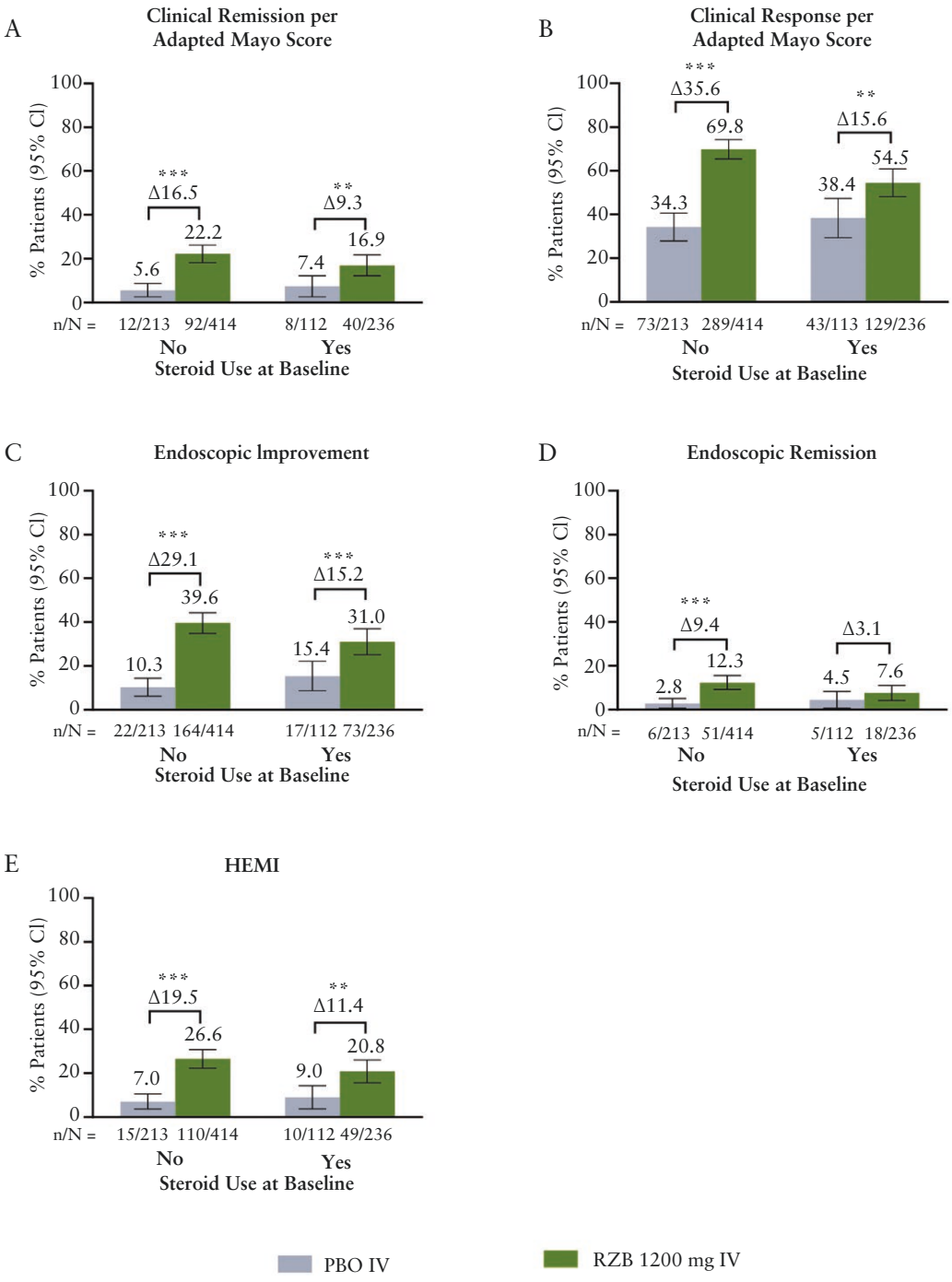


Figure 1. Clinical and endoscopic endpoints by corticosteroid use at week 12 of induction. Shown are the percent of patients who achieved clinical remission (A), clinical response (B), endoscopic improvement (C), endoscopic remission (D), and HEMI (E) by baseline corticosteroid use at week 12 of induction. Response rates 95% CI were the synthetic result based on the Student's t-distribution from PROC MIANALYZE. Between-group differences and 95% CI were calculated using the CMH test Mantel-Haenszel common rate difference with NRI-MI for categorical endpoints. *P* values were calculated according to the CMH test adjusted for strata. The calculations were based on NRI-MI to handle missing data due to logistic restrictions caused by COVID-19 or geopolitical restrictions. Nominal $^{**}P \leq .01$ vs PBO IV; nominal $^{***}P \leq .01$ vs PBO IV. CI, confidence interval; CMH, Cochran-Mantel-Haenszel; COVID-19, coronavirus disease 2019; HEMI, histologic-endoscopic mucosal improvement; IV, intravenous; NRI-MI, nonresponder-multiple imputation; PBO, placebo; RZB, risankizumab.

the discontinuation rate among the PBO (WD) group continued to decrease through week 52 (Figure 2). By week 52, discontinuation rates for patients treated with RZB 180 mg ($N = 74$, 64.9%) and 360 mg ($N = 59$, 54.2%) were higher, compared with patients in the PBO (WD) group ($N = 68$, 36.8%); $P \leq .001$ and $P \leq .05$, respectively (Figure 2). Among the patients not on CS at baseline, only a small percentage required CS use per PI discretion (4.8% RZB 180 mg, 4.7% RZB 360 mg, 4.3% PBO [WD] SC).

Among all clinical responders to 12 weeks of RZB IV therapy, both the RZB 180 mg ($N = 179$) and 360 mg ($N = 186$) treatment groups demonstrated superior rates for CS-free clinical remission (39.6%, 37.1%) compared with the PBO (WD) group ($N = 183$, 25.1%, difference: 15.8%,

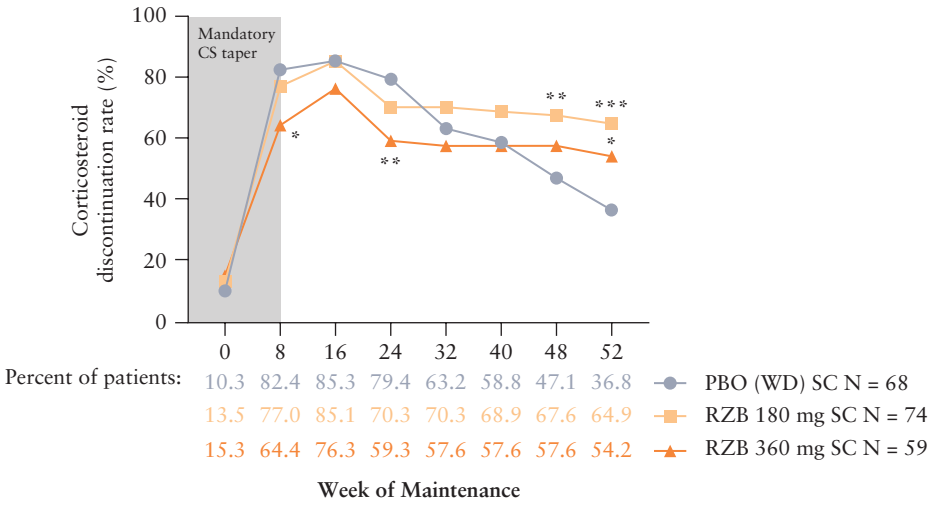


Figure 2. Discontinuation of corticosteroid use in patients taking corticosteroids at baseline of the induction study through week 52 of maintenance. The mandatory CS taper was initiated at maintenance week 0 and completed by week 8. Shown are the percentage of patients who had discontinued CS use (complete cessation of UC-related CS at time of evaluation) at each time point during maintenance among patients with CS use at baseline, regardless of whether they needed any additional CS per investigator's discretion after the taper was completed. Response rates 95% CI were based on the normal approximation to the binomial distribution. *P* values were calculated according to the CMH test adjusted for strata. Nominal *$P \leq .05$ vs PBO (WD) SC; nominal ** $P \leq .0.01$ vs PBO (WD) SC; nominal ***$P \leq .001$ vs PBO (WD) SC. CMH, Cochran-Mantel-Haenszel; CI, confidence interval; CS, corticosteroid; IV, intravenous; PBO, placebo; RZB, risankizumab; SC, subcutaneous; UC, ulcerative colitis; WD, withdrawal.

13.7%) at week 52 of maintenance; $P \leq .01$ for both comparisons (Figure 3A). Among the RZB-treated patients in clinical remission at week 52, 98.6% were CS-free for at least 90 days before the study visit at week 52 of maintenance (RZB 180 mg: 70/71; RZB 360 mg: 69/70; PBO [WD]: 46/46). Higher rates of CS-free endoscopic improvement, endoscopic remission, and HEMI were also observed among patients treated with RZB 180 mg (49.7%, 22.6%, 41.6%) or 360 mg (46.8%, 23.7%, 40.9%) at week 52 of maintenance compared with patients who received PBO (WD) treatment (31.1%, 14.8%, 23.0%, Figure 3B-D).

When analyzed by advanced therapy status, non-AT-IR patients treated with RZB 180 mg ($N = 45$, 51.1%) or 360 mg ($N = 47$, 59.6%) achieved higher rates for CS-free clinical remission compared with the PBO (WD) group ($N = 45$, 31.1%; difference: 19.6%, 32.8%, $P \leq .05$ or $P \leq .001$, respectively, Figure 3) at week 52 of maintenance. Similar results were observed for other CS-free endpoints at week 52, including endoscopic improvement, endoscopic remission, and HEMI, with RZB 180 mg or 360 mg treatment resulting in higher rates compared with PBO (WD) therapy. RZB 180 mg treatment also resulted in numerically higher rates for CS-free endoscopic improvement, endoscopic remission, and HEMI among non-AT-IR patients (59.8%, 36.6%, 54.4%) compared with RZB 180 mg-treated AT-IR patients (46.3%, 17.9%, 37.3%) (Figure 3). Similarly, among RZB 360 mg-treated patients, higher rates for CS-free endoscopic improvement, endoscopic remission, and HEMI were observed among non-AT-IR patients (72.3%, 48.9%, 66.0%) compared with RZB 360 mg-treated AT-IR patients (38.1%, 15.1%, 32.4%) (Figure 3). Among non-AT-IR patients, those treated with RZB 360 mg demonstrated numerically higher efficacy rates compared to RZB 180 mg-treated patients, as a dose-response relationship was also observed. However, these results should be interpreted with caution due to the limited number of patients in some subgroups.

Among patients taking CS at baseline of induction, patients treated with RZB 180 mg (35.0%) or 360 mg (33.9%) achieved greater rates of CS-free endoscopic improvement at week 52 compared with PBO (WD) treatment (17.6%, difference: 16.1%, 18.1%); $P \leq .05$ for both comparisons (Figure S3B). Treatment with either RZB 180 mg (29.0%) or 360 mg (28.8%) also achieved higher rates for HEMI among patients taking CS at baseline compared with PBO (WD) treatment (11.8%; 15.1%, 18.4%); $P \leq .05$ for both comparisons (Figure S3D). Numerical differences were observed for CS-free clinical or endoscopic remission in patients treated with RZB 180 mg or 360 mg compared with PBO (WD) treatment, respectively (Figure S3A and C). Among all 12-week responders to RZB IV therapy, patients treated with RZB 180 mg or 360 mg were more likely to achieve CS-free patient-reported outcomes including the absence of bowel urgency, nocturnal bowel movements, abdominal pain, and tenesmus, compared who received PBO (WD) treatment (Figure S4).

3.3. Safety

In patients treated with or without baseline CS, rates for overall TEAEs were similar among treatment groups through week 12 of induction (Table 2). Patients who received RZB 1200 mg (1.7%, 2.7%) had lower incidences of serious AEs compared with PBO-treated patients (9.8%, 10.4%), among those with or without baseline CS use at baseline, respectively. Similarly, patients who received RZB 1200 mg (2.5%, 2.4%) had lower incidences of severe AEs compared with PBO-treated patients (9.8%, 10.4%), among those with or without baseline CS use at baseline, respectively. A treatment-emergent death occurred in the RZB 1200 mg group with baseline CS use, caused by respiratory failure due to COVID-19 pneumonia. During induction, rates of TEAEs of special interest were generally similar among patients taking or not taking CS at baseline while treated with RZB 1200 mg (Table 2).

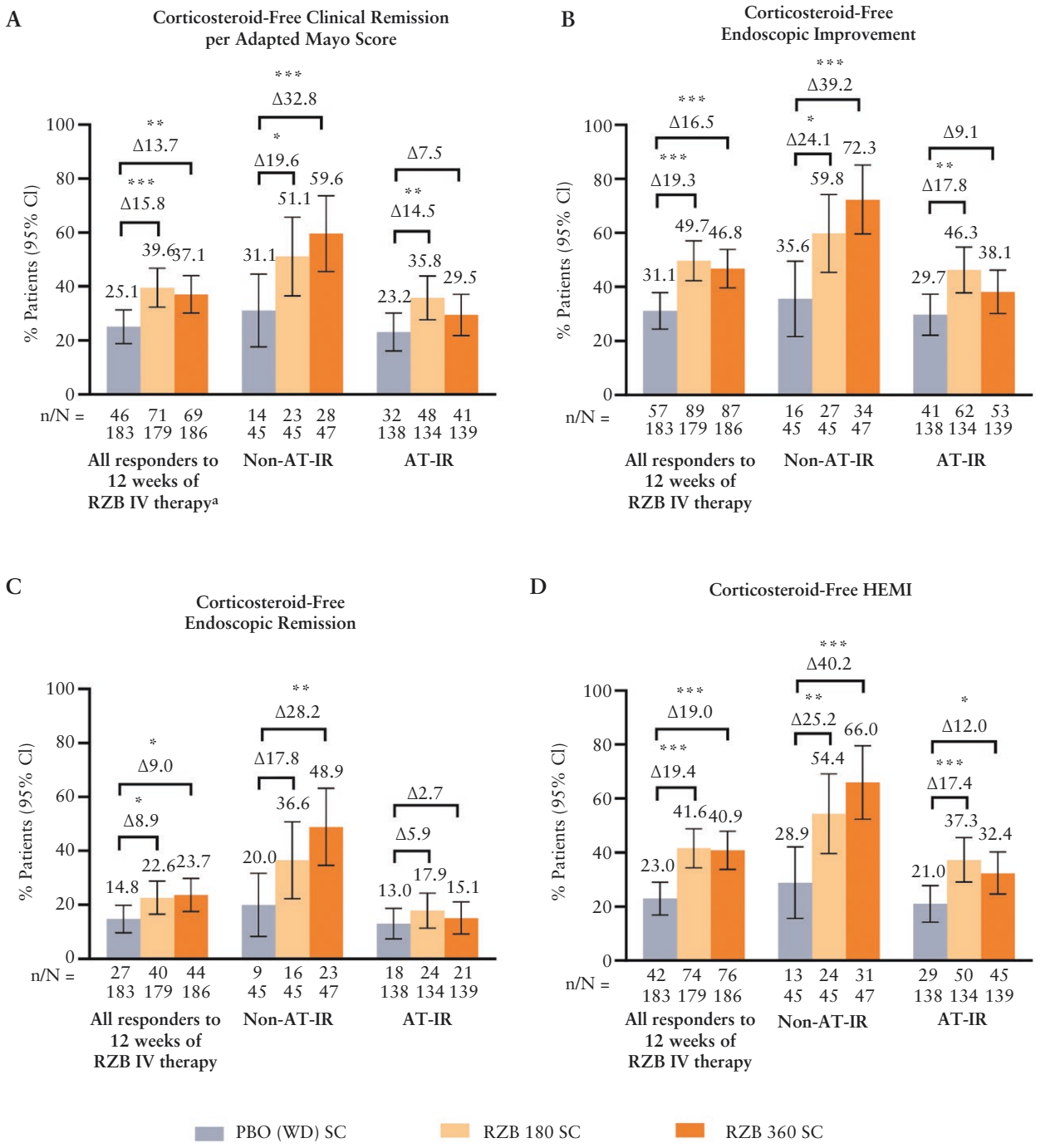


Figure 3. Corticosteroid-free clinical and endoscopic outcomes in the overall population and by advanced therapy status at week 52 of maintenance. Shown are the percent of patients who achieved corticosteroid-free clinical remission (A), corticosteroid-free endoscopic improvement (B), corticosteroid-free endoscopic remission (C), and corticosteroid-free HEMI (D) at week 52 of maintenance among all patients who were randomized to maintenance and who clinically responded to 12 weeks of IV RZB therapy. Among these patients were 2 subgroups, non-AT-IR and AT-IR patients. CS-free clinical and endoscopic outcomes were evaluated at week 52 among patients who abstained from CS use for 90 days before assessment. Above each endpoint are response rates, along with adjusted treatment differences vs PBO (WD) SC. Response rates 95% CI were the synthetic result based on the Student's t-distribution from PROC MIANALYZE. Between-group differences and 95% CI were calculated using the CMH test common rate difference with NRI-MI for categorical endpoints. *P* values were calculated according to the CMH test adjusted for strata. The calculations were based on NRI-MI to handle missing data due to logistic restrictions caused by COVID-19 or geopolitical restrictions. Nominal $*P \leq .05$ vs PBO (WD) SC; nominal $**P \leq .01$ vs PBO (WD) SC; nominal $***P \leq .001$ vs PBO (WD) SC. AT-IR, advanced therapy-inadequate response; CMH, Cochran-Mantel-Haenszel; CI, confidence interval; HEMI, histologic-endoscopic mucosal improvement; IV, intravenous; Non-AT-IR, non-advanced therapy-inadequate response; NRI-MI, nonresponder-multiple imputation; PBO, placebo; RZB, risankizumab; SC, subcutaneous; WD, withdrawal.

Through week 52 of maintenance, the incidence of overall, serious AEs (RZB 180 mg 5.0%, 5.3%; RZB 360 mg 8.1%, 3.8%; PBO [WD] 7.7%, 8.5%) and severe AEs (RZB 180 mg 1.3%, 1.8%; RZB 360 mg 4.8%, 2.3%; PBO [WD] 7.7%, 3.4%) were generally similar among all treatment groups in patients with or without induction baseline CS use,

Table 2. Treatment-emergent adverse events by corticosteroid use through week 12 of induction.

TEAE, *n* (%)	No corticosteroid use at baseline		With corticosteroid use at baseline	
	PBO IV *N* = 212[a]	RZB 1200 mg IV *N* = 415	PBO IV *N* = 112	RZB 1200 mg IV *N* = 236
Overview of TEAE				
Any TEAE	103 (48.6)	162 (39.0)	58 (51.8)	112 (47.5)
AE related to study drug[b]	17 (8.0)	40 (9.6)	9 (8.0)	21 (8.9)
Severe AE	22 (10.4)	10 (2.4)	11 (9.8)	6 (2.5)
Serious AE	22 (10.4)	11 (2.7)	11 (9.8)	4 (1.7)
AE leading to discontinuation of study drug	8 (3.8)	2 (0.5)	4 (3.6)	2 (0.8)
Any COVID-19 related TEAE	15 (7.1)	14 (3.4)	4 (3.6)	21 (8.9)
All deaths	0	0	0	1 (0.4)[c]
TEAE of Special Interest				
Serious infections	3 (1.4)	2 (0.5)	1 (0.9)	2 (0.8)
Active tuberculosis	0	0	0	0
Opportunistic infections excluding tuberculosis and herpes zoster	0	0	0	0
Herpes zoster	0	1 (0.2)	0	1 (0.4)
All malignancies	2 (0.9)	0	0	0
Malignancies excluding NMSC	2 (0.9)	0	0	0
NMSC	0	0	0	0
Hepatic events	7 (3.3)	7 (1.7)	7 (6.3)	3 (1.3)
Adjudicated MACE	0	0	0	0
Hypersensitivity[d]	4 (1.9)	12 (2.9)	2 (1.8)	12 (5.1)
Serious hypersensitivity	0	0	0	0
Injection site reactions	3 (1.4)	3 (0.7)	1 (0.9)	1 (0.4)
Adjudicated anaphylactic reactions	0	0	0	0

Data were calculated using nonmissing values. The safety population consisted of all patients who received at least 1 dose of the study drug during the 12-week double-blind induction study.
[a]Patients are reported here according to the treatment they received, as 1 patient was randomized to RZB 1200 mg and treated with PBO.
[b]As assessed by the study investigator.
[c]One treatment-emergent death occurred due to respiratory failure caused by COVID-19 pneumonia.
[d]Events identified with hypersensitivity SMQ, a broader medical concept, which included injection and infusion site-related terms, overlapping with the term in injection site reaction CMQ. Hypersensitivity includes both nonserious and serious hypersensitivity reaction events.
Abbreviations: CMQ; customized medical dictionary of regulatory activity queries; COVID-19, coronavirus disease 2019; IV, intravenous; MACE, major adverse cardiovascular event; NMSC, nonmelanoma skin cancer; PBO, placebo; RZB, risankizumab; SMQ, standardized medical dictionary of regulatory activity queries; TEAE, treatment-emergent adverse events.

respectively (Table 3). The majority of TEAEs of special interest were generally similar among all treatment groups at week 52 of maintenance regardless of baseline CS use.

3. Discussion

Corticosteroid is useful in moderation for patients with moderately to severely active UC due to their rapid onset of action. However, a large proportion of patients are either CS refractory or CS dependent.[11] Corticosteroids are often associated with an increase in the number of relapses and disease progression.[10] Given the strong association between CS dependency and poor safety outcomes, it is critical for patients to reach the long-term goal of CS-free clinical remission.[22] This post hoc study evaluated the effect of baseline CS use on the achievement of efficacy outcomes at week 12 of induction in patients with moderately to severely active UC. CS-free analysis was evaluated at week 52 of maintenance among all maintenance patients who responded to 12 weeks of RZB IV therapy, by AT-IR status, and among patients only on CS at baseline. Safety was assessed through week 12 of induction and week 52 of maintenance. As similar results were observed for clinical, endoscopic, and histologic-endoscopic outcomes at week 12 regardless of baseline CS use, this reiterates the potential of RZB to serve in conjunction with CS or, importantly, in their absence, as an effective CS-sparing therapy during maintenance. While greater differences from PBO were observed among RZB-treated patients without baseline CS use compared with those with baseline use for patient-reported outcomes, this difference may have been due to a variety of reasons, such as differences in baseline demographics and disease characteristics. We also are not able to determine whether CS use may have resulted in different clinical outcomes due to other unmeasured biological effects of the CS.

With a mandatory CS taper beginning at maintenance week 0, higher rates of CS discontinuation were observed in patients treated with either RZB maintenance dose (180 mg or 360 mg) compared with the PBO (WD) group at week 52.[23] The high rates of CS discontinuation in the PBO (WD) group

Table 3. Treatment-emergent adverse events by corticosteroid use at baseline through week 52 of maintenance.

TEAE, *n* (%)	No corticosteroid use at baseline			With corticosteroid use at baseline		
	PBO (WD) SC *N* = 118	RZB 180 mg SC *N* = 113	RZB 360 mg SC *N* = 133	PBO (WD) SC *N* = 78	RZB 180 mg SC *N* = 80	RZB 360 mg SC *N* = 62
Overview of TEAE						
Any TEAE	92 (78.0)	82 (72.6)	89 (66.9)	58 (74.4)	58 (72.5)	49 (79.0)
AE related to study drug[a]	21 (17.8)	15 (13.3)	24 (18.0)	20 (25.6)	21 (26.3)	10 (16.1)
Severe AE	4 (3.4)	2 (1.8)	3 (2.3)	6 (7.7)	1 (1.3)	3 (4.8)
Serious AE	10 (8.5)	6 (5.3)	5 (3.8)	6 (7.7)	4 (5.0)	5 (8.1)
AE leading to discontinuation of study drug	3 (2.5)	1 (0.9)	3 (2.3)	0	2 (2.5)	2 (3.2)
Any COVID-19 related TEAE	17 (14.4)	9 (8.0)	18 (13.5)	10 (12.8)	11 (13.8)	8 (12.9)
All deaths	0	0	1 (0.8)[b]	0	0	0
TEAE of Special Interest						
Serious infections	3 (2.5)	1 (0.9)	0	1 (1.3)	1 (1.3)	1 (1.6)
Active tuberculosis	0	0	0	0	0	0
Opportunistic infections excluding tuberculosis and herpes zoster	0	0	1 (0.8)	0	0	0
Herpes zoster	2 (1.7)	0	1 (0.8)	1 (1.3)	2 (2.5)	0
All malignancies	1 (0.8)	0	2 (1.5)	0	0	0
Malignancies excluding NMSC	0	0	2 (1.5)	0	0	0
NMSC	1 (0.8)	0	0	0	0	0
Hepatic events	0	3 (2.7)	8 (6.0)	1 (1.3)	0	5 (8.1)
Adjudicated MACE	0	0	0	0	0	0
Hypersensitivity[c]	7 (5.9)	6 (5.3)	6 (4.5)	3 (3.8)	14 (17.5)	4 (6.5)
Serious hypersensitivity	0	0	0	0	0	0
Injection site reactions	2 (1.7)	4 (3.5)	4 (3.0)	0	3 (3.8)	1 (1.6)
Adjudicated anaphylactic reactions	0	0	0	0	0	0

Baseline refers to week 0 of induction. The safety population consisted of clinical responding patients after 12 or 24 weeks of RZB IV induction therapy who received at least 1 dose of the study drug. Data were calculated on nonmissing values. Patients who re-initiated corticosteroids after the baseline of induction were analyzed by their corticosteroid status at baseline.
[a]As assessed by the study investigator.
[b]One death was reported in a patient treated with RZB 360 mg who had a diagnosis of colon adenocarcinoma. The death of the patient was due to colon adenocarcinoma and was found to have no reasonable possibility of being related to the study drug.
[c]Events identified with hypersensitivity SMQ, a broader medical concept, which included injection and infusion site-related terms, overlapping with the term in injection site reaction CMQ. Hypersensitivity includes both nonserious and serious hypersensitivity reaction events.
Abbreviations: CMQ; customized medical dictionary of regulatory activity queries; COVID-19, coronavirus disease 2019; IV, intravenous; MACE, major adverse cardiovascular event; NMSC, nonmelanoma skin cancer; PBO, placebo; RZB, risankizumab; SC, subcutaneous.

early during maintenance may be explained by remnants of the prolonged half-life and durability of RZB. However, patients in the PBO (WD) group increased CS use over time, with RZB-treated patients showing higher rates of CS discontinuation at week 52. Among all patients who clinically responded to 12 weeks of RZB IV therapy, treatment with either RZB maintenance dose achieved CS-free clinical and endoscopic outcomes after 52 weeks of maintenance treatment, including clinical remission, endoscopic improvement, endoscopic remission, and HEMI.

Patients with baseline CS use were a more refractory population, as those who received CS at baseline and were treated with RZB 180 mg or 360 mg were more likely to have a baseline endoscopic subscore of 3 compared with those without CS use. In addition, more than 80.0% of patients in the maintenance study with baseline CS use had previously failed at least 1 AT; at least 54.1% failed 2 or more AT (Table S2). However, despite these differences, patients on CS at baseline who received RZB 180 mg or 360 mg achieved higher rates for CS-free endoscopic improvement or HEMI compared with PBO-treated patients at week 52. Among all patients who were responders to 12 weeks of IV RZB and were randomized to maintenance, higher efficacy rates were observed for all CS-free clinical and endoscopic outcomes for non-AT-IR patients compared with AT-IR patients. Previous studies have suggested that response rates for non-AT-IR patients are typically higher than those of AT-IR patients.[24–26] A dose-response relationship was also observed for RZB 180 mg and 360 mg CS-free clinical and endoscopic outcomes among non-AT-IR patients. Other studies have suggested that a shorter disease duration and a lack of prior exposure to anti-tumor necrosis factor (TNF) therapies favor the achievement of CS-free clinical remission.[27,28] The data from this study align with treatment guidelines that propose CS-free clinical remission as a treatment goal for patients with UC.[5,27]

Reducing safety risks associated with the long-term use of CS without influencing efficacy outcomes is an important treatment goal for patients with moderately to severely active UC. When analyzed by baseline CS use, minimal disparities were noted in safety outcomes, particularly in overall TEAE, serious, and TEAE of special interest, during both induction and maintenance studies. The RZB safety profile was similar

between patients with or without baseline CS use during induction and maintenance, suggesting that it could be used as a CS-sparing therapy. No new safety risks were observed during induction or maintenance, and the RZB safety profile was consistent with previously published findings in UC and other therapeutic areas.[18,20,21] These findings indicate that tapering CS during RZB maintenance therapy does not significantly impede the attainment of clinical and endoscopic outcomes and holds the potential to mitigate the safety risks associated with CS exposure.

Limitations of this analysis include that fewer patients who enrolled in induction were taking CS at baseline, resulting in a limited number of patients in CS subgroups, particularly during maintenance, and further analysis is required to determine the effect of CS on the long-term efficacy outcomes of RZB treatment in patients with UC. Conversely, the study design included stratification by UC-related CS use at the baseline of induction, as opposed to CS used for indications unrelated to UC. This prevents the possibility of including patients using CS for non-UC-related indications in the analysis.

In summary, the efficacy of RZB induction therapy was independent of baseline CS use, while RZB maintenance therapy was associated with high rates of CS-free clinical, endoscopic, and histologic outcomes at 52 weeks. These data support RZB as a treatment option that can be effective without CS use, and patients with CS use are able to achieve steroid-free improvements in clinical and endoscopic outcomes.

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Author contributions

Walter Reinisch, Edward V. Loftus, Jr, Stefan Schreiber, David T. Rubin, Edouard Louis, and Remo Panaccione were involved in patient recruitment and data collection. Patrick M. Hecht, Elena Marced Barrachina, Jasmina Kalabic, Ramona Vladea, Dolly Sharma, and W. Rached Duan were responsible for the study design. First draft was written by Patrick M. Hecht. Yafei Zhang was responsible for statistical analysis. All authors were involved in manuscript development, reviewing and editing, and data interpretation.

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Conflicts of interest

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Data availability

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (eg, protocols, clinical study reports, or analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by any qualified

researchers who engage in rigorous, independent, scientific research, and will be provided following review and approval of a research proposal, Statistical Analysis Plan (SAP), and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the United States and Europe and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://vivli.org/ourmember/abbvie/ then select "Home".

Supplementary material

Supplementary material is available at *ECCO-JCC* online.

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