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Efficacy and safety of risankizumab by baseline corticosteroid use and achievement of corticosteroid-free clinical and endoscopic outcomes in patients with moderately to severely active Crohn's disease

Stefan Schreiber[1] | Raymond K. Cross[2] | Remo Panaccione[3] | Geert D'Haens[4] | Peter Bossuyt[5] | Iris Dotan[6,7] | Jean-Frederic Colombel[8] | Edouard Louis[9] | Marla C. Dubinsky[8] | Kristina Kligys[10] | Ezequiel Neimark[10] | Alexandra Song[10] | Javier Zambrano[10] | Jasmina Kalabic[11] | Erica Cheng[10] | Yafei Zhang[10] | Marc Ferrante[12]

[1]Department Internal Medicine I, University Hospital Schleswig-Holstein, Kiel University, Kiel, Germany

[2]Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland, USA

[3]Inflammatory Bowel Disease Unit, University of Calgary, Calgary, Alberta, Canada

[4]Department of Gastroenterology and Hepatology, Amsterdam University Medical Center, Amsterdam, The Netherlands

[5]Department of Gastroenterology, Imelda General Hospital, Bonheiden, Belgium

[6]Division of Gastroenterology, Rabin Medical Center, Petah Tikva, Israel

[7]Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

[8]Icahn School of Medicine at Mt Sinai, New York, New York, USA

[9]University Hospital CHU of Liège, Liège, Belgium

[10]AbbVie Inc., North Chicago, Illinois, USA

[11]AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany

[12]Department of Gastroenterology and Hepatology, University Hospitals Leuven, KU Leuven, Leuven, Belgium

Correspondence
Stefan Schreiber, Department Internal Medicine I, University Hospital Schleswig Holstein, Kiel University, Kiel Arnold-Heller Str. 3, Kiel 24105, Germany.
Email: s.schreiber@ikmb.uni-kiel.de

Summary

Background: Risankizumab is efficacious and well tolerated in adults with moderately to severely active Crohn's disease (CD).

Aim: To evaluate the corticosteroid-sparing effect of risankizumab in CD.

Methods: During the 12-week induction period, patients maintained stable baseline corticosteroid doses, up to 20 mg/day prednisone or equivalent. At week 0 of maintenance, a mandatory corticosteroid taper was started. This post hoc analysis evaluated corticosteroid-free clinical and endoscopic outcomes at week 52 of maintenance; safety was also assessed.

Results: Of 889 patients randomised to induction with risankizumab 600 mg or placebo, 285 (32.1%) were taking baseline concomitant corticosteroids. Week 12 clinical remission and endoscopic response rates were greater for risankizumab 600 mg versus placebo, regardless of concomitant corticosteroid use. At week 52, 66.7%, 50.0% and 41.2% of patients taking risankizumab 180 mg, risankizumab 360 mg and (withdrawal) placebo, respectively, discontinued corticosteroids. Week 52 corticosteroid-free clinical remission per stool frequency/abdominal pain score (risankizumab 180 mg [42.7%] or 360 mg [49.8%]; [withdrawal] placebo [39.0%]), corticosteroid-free clinical remission per Crohn's Disease Activity Index (risankizumab 180 mg [51.0%] or 360 mg [49.5%]; [withdrawal] placebo [40.2%]), and corticosteroid-free endoscopic response (risankizumab 180 mg [44.6%] or 360 mg [44.7%]; [withdrawal] placebo [20.7%]) rates were greater for risankizumab than placebo. Adverse event rates were generally similar, regardless of baseline corticosteroid use.

Conclusions: Efficacy of risankizumab 600 mg induction therapy was independent of concomitant corticosteroid use. Risankizumab 180 and 360 mg maintenance therapy yielded high rates of corticosteroid-free clinical and endoscopic outcomes at week 52.

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1 | INTRODUCTION

Crohn's disease (CD) is a progressive, chronic inflammatory bowel disorder that when left uncontrolled can cause irreversible bowel damage and permanent reductions in quality of life.[1] Corticosteroids are generally effective at inducing remission in patients with CD but cannot sustain maintenance.[2] Results from the Determinants, Incidence and Consequence of Corticosteroid Excess study evaluating corticosteroid excess among 2618 patients with inflammatory bowel disease across seven countries showed that 20.3% of patients had excess corticosteroid use.[3] Chronic overuse of corticosteroids can also lead to high risks for significant short-term (e.g. mood disorders, insomnia, weight gain) and long-term (e.g. cataracts, osteoporosis, fractures) adverse effects.[4–6] In comparison with oral immunomodulators or targeted therapies/biologic therapies, long courses of corticosteroids have been associated with an increased risk of morbidity and mortality relative to oral immunosuppressants or targeted/biologic therapies,[7] and studies have also demonstrated an association between corticosteroid-related adverse effects and high economic burden to patients and the healthcare system, respectively.[8,9] Data collected from surveys showed that patients were far more likely than physicians to express concern about corticosteroid use, with approximately 25% of patients reporting they had chosen not to take their prescribed corticosteroid at some point, most often due to adverse effects.[10] Treatment guidelines recommend a corticosteroid-sparing strategy for patients who are corticosteroid dependent.[11–14]

The efficacy and safety of risankizumab, a fully humanised immunoglobulin G1 monoclonal antibody inhibitor of interleukin 23 approved for the treatment of moderately to severely active CD in adults,[15] was demonstrated in two phase 3 induction studies (ADVANCE and MOTIVATE) and a phase 3 maintenance study (FORTIFY).[16,17] Using data from the pivotal phase 3 clinical trials of risankizumab in CD, we evaluated the effect of concomitant corticosteroid use on the achievement of clinical and endoscopic outcomes with risankizumab induction therapy. We also evaluated the ability of risankizumab maintenance therapy to achieve corticosteroid-free clinical and endoscopic outcomes while maintaining corticosteroid-free response in patients with active CD.

2 | METHODS

2.1 | Study design and patients

Two phase 3, multicentre, double-blinded, randomised, placebo-controlled induction studies, ADVANCE (NCT03105128) and MOTIVATE (NCT03104413), were performed at 297 sites in 39 countries (ADVANCE) and 214 sites in 40 countries (MOTIVATE). A detailed description of the study designs has been previously reported.[17] Briefly, patients aged 16–80 years with a confirmed diagnosis of CD for ≥3 months prior to baseline, moderately to severely active disease, and intolerance or inadequate response to biologic and/or conventional therapy (ADVANCE study) or biologic therapy only (MOTIVATE study) were enrolled. Patients were randomised (2:2:1 in the ADVANCE study, 1:1:1 in the MOTIVATE study) to receive intravenous (IV) risankizumab (600 or 1200 mg) or placebo over 12 weeks. For both induction studies, patients taking oral corticosteroids at maximum doses of budesonide 9 mg/day, beclomethasone dipropionate 5 mg/day, or prednisone 20 mg/day or equivalent were eligible if they had been on the current corticosteroid treatment course for ≥14 days and were taking a stable dose for ≥7 days prior to baseline. Patients were required to continue taking corticosteroids at the baseline dose through the entire 12-week induction period; dose reductions were only permitted in the event of moderate-to-severe treatment-related toxicities.

Patients achieving clinical response (defined as ≥30% decrease from baseline in average daily stool frequency [SF] or ≥30% decrease from baseline in average daily abdominal pain score [APS], or both, and neither worse than baseline) after 12 weeks of IV risankizumab induction treatment were eligible to enrol in the FORTIFY (NCT03105102) maintenance study, a phase 3, multicentre, double-blinded, randomised, placebo-controlled withdrawal study conducted at 273 sites in 44 countries.[16] Patients were re-randomised (1:1:1) to receive subcutaneous (SC) risankizumab (180 or 360 mg) or (withdrawal) placebo every 8 weeks for 52 weeks. In the FORTIFY study, mandatory protocol-specified tapering of concomitant corticosteroid therapy started at week 0. Prednisone or equivalent doses >10 mg/day were tapered by 5 mg/day/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/day/week; corticosteroid taper had to be completed by week 8. After initiation of corticosteroid taper at week 0, patients who had a loss of clinical response per investigator judgement, or for whom the investigator felt steroid taper was not advisable could have had their corticosteroid doses increased during the maintenance study up to the dose used at baseline of the induction study at the investigator's discretion; the number of escalations and/or restarts of the corticosteroid was not limited.

All clinical trials were conducted in accordance with the operations manual, protocol, International Council for Harmonisation guidelines, and applicable guidelines and regulations governing ethical principles and study conduct originating in the Declaration of Helsinki. An independent ethics committee/institutional review board ensured the ethical, scientific and medical appropriateness of the study before it was conducted and approved all relevant documentation. All clinical trials were prospectively registered at Clinicaltrials.gov (NCT03105128, NCT03104413, NCT03105102). Written informed consent was obtained from all patients before enrolment.

2.2 | Assessments

Post hoc efficacy analyses at week 12 of the induction period included clinical remission per SF/APS (average daily SF ≤2.8 and daily APS ≤1 and both not worse than baseline of the induction study), clinical remission per Crohn's Disease Activity Index (CDAI; CDAI <150) and endoscopic response (>50% decrease from baseline in Simple Endoscopic Score for Crohn's Disease [SES-CD] or ≥2-point reduction from baseline for

patients with isolated ileal disease and baseline SES-CD of 4); induction efficacy was assessed by concomitant corticosteroid use (yes/no). In the FORTIFY study, the proportion of patients who discontinued corticosteroid use among patients taking corticosteroids at induction baseline was assessed at each study visit. A prespecified ranked secondary endpoint, assessed only in patients taking corticosteroids at baseline of induction, was the proportion of patients who discontinued corticosteroid use for 90 days and achieved clinical remission at week 52; patients must have discontinued corticosteroid use for at least 90 days immediately prior to week 52. Post hoc analyses at week 52 included corticosteroid-free clinical and endoscopic outcomes, assessed in all randomised patients with an eligible baseline SES-CD ≥6 (or ≥4 for isolated ileal disease), regardless of their baseline corticosteroid usage. Week 52 corticosteroid-free outcomes were defined as no corticosteroid use for at least 90 days immediately prior to week 52 plus one of the following endpoints: clinical remission per SF/APS, clinical remission per CDAI, endoscopic response, endoscopic remission (SES-CD ≤4 and ≥2-point reduction vs. baseline of the induction study and no subscore >1 in any individual variable) and deep remission (a composite of CDAI clinical remission and endoscopic remission). Achievement of week 52 corticosteroid-free outcomes was also assessed using a definition of 'no corticosteroids at week 52'. Safety by induction baseline corticosteroid use was evaluated during the induction and maintenance studies. Safety assessments included treatment-emergent adverse events (TEAEs), standard laboratory tests, physical examination results and vital signs. TEAEs were tabulated using (MedDRA) version 24.0 system organ class and preferred terms.

2.3 | Statistical analysis

The post hoc induction efficacy analysis included randomised patients who received at least one dose of IV risankizumab 600 mg or placebo and had an eligible SES-CD of ≥6 (or ≥4 for isolated ileal disease) at baseline; the risankizumab 1200 mg induction dose was not reported in this induction efficacy analysis as this dose did not demonstrate a treatment benefit over the 600 mg dose in the primary analyses[17] and is not an approved induction dose.[15,18] For maintenance analyses, patients enrolled in the FORTIFY study must have received IV risankizumab (600 or 1200 mg) for only one period of 12 weeks in the induction studies, had an eligible SES-CD of ≥6 (or ≥4 for isolated ileal disease) at baseline, and received at least one dose of study drug in the maintenance study. Patients who had new corticosteroid initiation or a corticosteroid dose increase above the induction baseline dose were considered nonresponders. Categorical endpoints were analysed using the Cochran–Mantel–Haenszel test, stratified by study centre. Missing data were imputed using nonresponder imputation incorporating multiple imputation to handle missing data due to COVID-19. Pooled safety data from the ADVANCE and MOTIVATE induction studies were analysed in all patients who received at least one dose of IV risankizumab 600 mg or placebo during the 12-week induction period and had eligible SES-CD scores at baseline of induction. Safety in the FORTIFY study was analysed in all patients who received IV risankizumab (600 or 1200 mg) for only one period of 12 weeks in the ADVANCE or MOTIVATE studies, received at least one dose of study drug in the FORTIFY study, and had eligible SES-CD (≥6, or ≥4 for isolated ileal disease) at baseline of induction.

3 | RESULTS

3.1 | Patients

In the induction studies, 889 patients were randomised to either risankizumab 600 mg or placebo; 285 (32.1%) of these patients were taking concomitant corticosteroids at baseline. The median (interquartile range [IQR]) daily prednisone or equivalent dose at baseline was 20.0 (12.5–20.0) mg/day and 20.0 (15.0–20.0) mg/day in the risankizumab 600 mg and placebo groups, respectively. Baseline demographics and disease characteristics were generally similar among patients, regardless of corticosteroid use, with the exception that 48.8%–48.9% of patients without corticosteroid use were biologic-naïve versus 34.1%–39.8% of patients taking corticosteroids at baseline (Table 1). Patients with no corticosteroid use at baseline of induction had less severe endoscopic disease activity as evidenced by lower mean (SD) SES-CD scores (RZB, 13.6 [7.1]; PBO, 13.7 [7.3]) versus patients taking corticosteroids at baseline (RZB, 16.6 [8.4]; PBO, 16.0 [7.6]). Of the patients taking concomitant corticosteroids at baseline of induction, 31.3%–31.7% of patients in each treatment group had been taking corticosteroids for at least 3 months prior to baseline.

3.2 | Efficacy

3.2.1 | Impact of concomitant corticosteroid use on outcomes during induction

At week 12, patients treated with induction risankizumab 600 mg achieved higher rates of clinical remission (per SF/APS or CDAI) and endoscopic response compared with placebo, regardless of concomitant corticosteroid use (Figure 1). No meaningful differences in symptomatic remission or endoscopic improvement at week 12 were observed between patients receiving concomitant corticosteroids versus those who did not.

3.2.2 | Achievement of corticosteroid-free outcomes during maintenance

Of the 462 patients who responded to 12 weeks of risankizumab induction treatment (600 or 1200 mg) and who were randomised in the maintenance study, 144 (31.2%) had taken concomitant corticosteroids at stable doses, as required by the study protocol, throughout induction. The median (IQR) prednisone or equivalent dose among induction responders who were taking corticosteroids at induction baseline and were randomised

TABLE 1 Demographics and characteristics at induction baseline by corticosteroid use.

Parameter	Corticosteroid use		No corticosteroid use	
	PBO ($n=118$)	RZB 600 mg ($n=167$)	PBO ($n=244$)	RZB 600 mg ($n=360$)
Female, *n* (%)	53 (44.9)	74 (44.3)	122 (50.0)	172 (47.8)
Age, years, mean (SD)	38.2 (13.4)	37.5 (13.1)	38.3 (13.5)	39.7 (13.6)
Weight, kg, mean (SD)	68.6 (16.8)	68.7 (17.3)	73.1 (19.3)	72.0 (19.2)
Corticosteroid use, *n* (%)	118 (100)	167 (100)	0	0
Budesonide	29 (24.6)	36 (21.6)	–	–
Deflazacort	0	1 (0.6)	–	–
Dexamethasone	1 (0.9)	0	–	–
Meprednisone	2 (1.7)	1 (0.6)	–	–
Methylprednisolone	10 (8.5)	20 (12.0)	–	–
Prednisolone	29 (24.6)	45 (26.9)	–	–
Prednisone	48 (40.7)	64 (38.3)	–	–
Unspecified	1 (0.9)	0	–	–
Daily prednisone equivalent dose, median (IQR)	20.0 (15.0–20.0)	20.0 (12.5–20.0)	–	–
Immunomodulator use, *n* (%)	24 (20.3)	30 (18.0)	58 (23.8)	94 (26.1)
Prior biologic failure, *n* (%)				
0	47 (39.8)	57 (34.1)	119 (48.8)	176 (48.9)
1	50 (42.4)	72 (43.1)	90 (36.9)	127 (35.3)
≥1	21 (17.8)	38 (22.8)	35 (14.3)	57 (15.8)
CD duration, mean (SD)	10.1 (8.3)	9.4 (8.2)	10.6 (9.1)	9.8 (8.6)
Disease location, *n* (%)				
Ileal only	12 (10.2)	21 (12.6)	33 (13.5)	64 (17.8)
Colonic only	56 (47.5)	72 (43.1)	87 (35.7)	118 (32.8)
Ileal-colonic	50 (42.4)	74 (44.3)	124 (50.8)	178 (49.4)
FCP, mg/kg, mean (SD)	2930 (5043)	2232 (2720)	2386 (4306)	1861 (3034)
hsCRP, mg/L, mean (SD)	18.3 (22.7)	20.4 (29.7)	18.5 (24.3)	17.7 (25.1)
CDAI, mean (SD)	322.4 (71.3)	315.3 (62.0)	318.0 (61.7)	309.1 (63.1)
SES-CD, mean (SD)	16.0 (7.6)	16.6 (8.4)	13.7 (7.3)	13.6 (7.1)
Average daily SF, mean (SD)	7.0 (3.0)	6.3 (2.8)	5.9 (2.7)	5.8 (2.9)
Average daily APS, mean (SD)	1.8 (0.6)	1.8 (0.6)	1.9 (0.6)	1.9 (0.5)

Note: All drugs were administered intravenously during induction. Baseline characteristics were pooled from the ADVANCE and MOTIVATE induction studies.

Abbreviations: APS, abdominal pain score; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; FCP, faecal calprotectin; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; PBO, placebo; RZB, risankizumab; SES-CD, Simple Endoscopic Score for Crohn's Disease; SF, stool frequency.

in the maintenance study was 15.0 (10.0–20.0) mg/day at week 0 of maintenance. Following the mandatory taper at week 0 of maintenance, beginning at week 32 and continuing to week 52, more patients discontinued corticosteroid use while receiving risankizumab relative to patients receiving (withdrawal) placebo (Figure 2). Among patients taking corticosteroids at induction baseline, 41.2%, 66.7% and 50.0% of patients in the withdrawal (placebo; $n=51$), risankizumab 180 mg ($n=51$), risankizumab 360 mg ($n=42$) groups, respectively, discontinued corticosteroid use by week 52. Further, the mean daily corticosteroid dose among patients taking corticosteroids at induction baseline across all treatment groups gradually decreased over time. The mean (SD) prednisone or equivalent dose across all treatment groups ($n=144$) at week 8 of maintenance was 5.0 (9.4) mg/day (median [IQR], 0 [0–8.0] mg/day); the mean (SD) was 5.3 (9.3), 5.7 (10.6) and 4.1 (8.6) for risankizumab 180 mg, risankizumab 360 mg and (withdrawal) placebo, respectively. At week 52 of maintenance, the mean (SD) prednisone or equivalent dose across all treatment groups ($n=144$) had decreased to 2.5 (7.1) mg/day (median [IQR], 0 [0–0] mg/day); the mean (SD) was 3.1 (8.0), 2.6

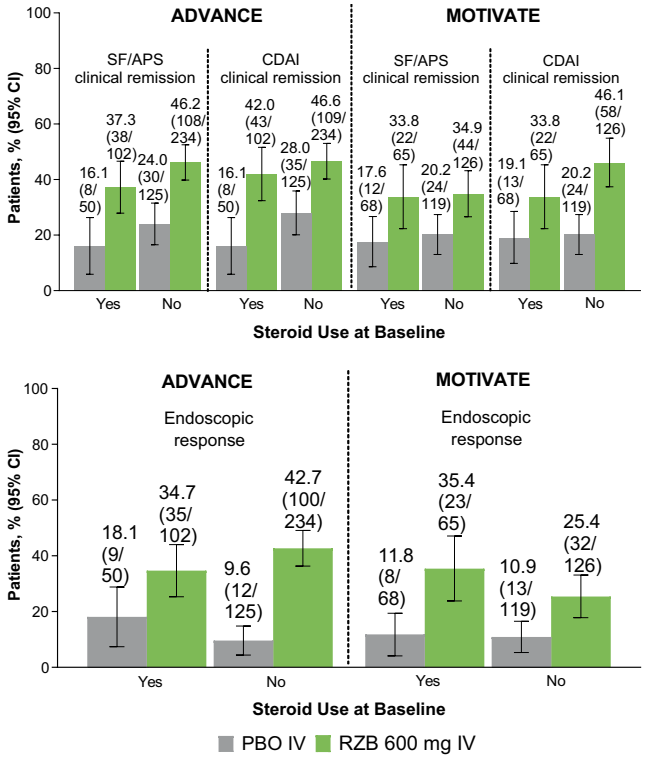

FIGURE 1 Clinical remission and endoscopic response by baseline corticosteroid use at week 12 of induction. APS, abdominal pain score; CDAI, Crohn's Disease Activity Index; IV, intravenous; PBO, placebo; RZB, risankizumab; SES-CD, Simple Endoscopic Score for Crohn's Disease; SF, stool frequency. Values above bars represent % (*n*/*N*).

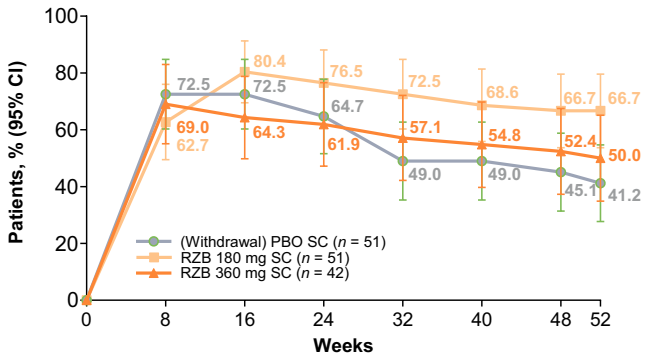

FIGURE 2 Discontinuation of corticosteroids over time during maintenance among patients taking corticosteroids at induction study baseline. PBO, placebo; RZB, risankizumab; SC, subcutaneous.

(8.4) and 1.9 (4.9) for risankizumab 180 mg, risankizumab 360 mg and (withdrawal) placebo, respectively.

Among patients taking concomitant corticosteroids at induction baseline, the proportion who discontinued corticosteroid use for 90 days and achieved clinical remission per SF/APS at week 52 of maintenance was 43.1% (22/51; $p=0.02$ vs. placebo) with risankizumab 180 mg, 34.0% (14/42; $p=0.13$ vs. placebo) with risankizumab 360 mg and 23.5% (12/51) with (withdrawal) placebo; the proportion who discontinued corticosteroid use for 90 days and achieved clinical remission per CDAI at week 52 was 52.9% (27/51; $p<0.001$ vs. placebo) with risankizumab 180 mg, 25.6% (11/42; $p=0.66$ vs. placebo) with risankizumab 360 mg and 23.5% (12/51) with (withdrawal) placebo.

Among all patients in the primary efficacy analysis of the maintenance study ($n=462$), regardless of baseline corticosteroid use, higher rates of corticosteroid-free clinical remission, endoscopic remission, endoscopic response and deep remission were observed at week 52 with risankizumab compared with (withdrawal) placebo (Figure 3).

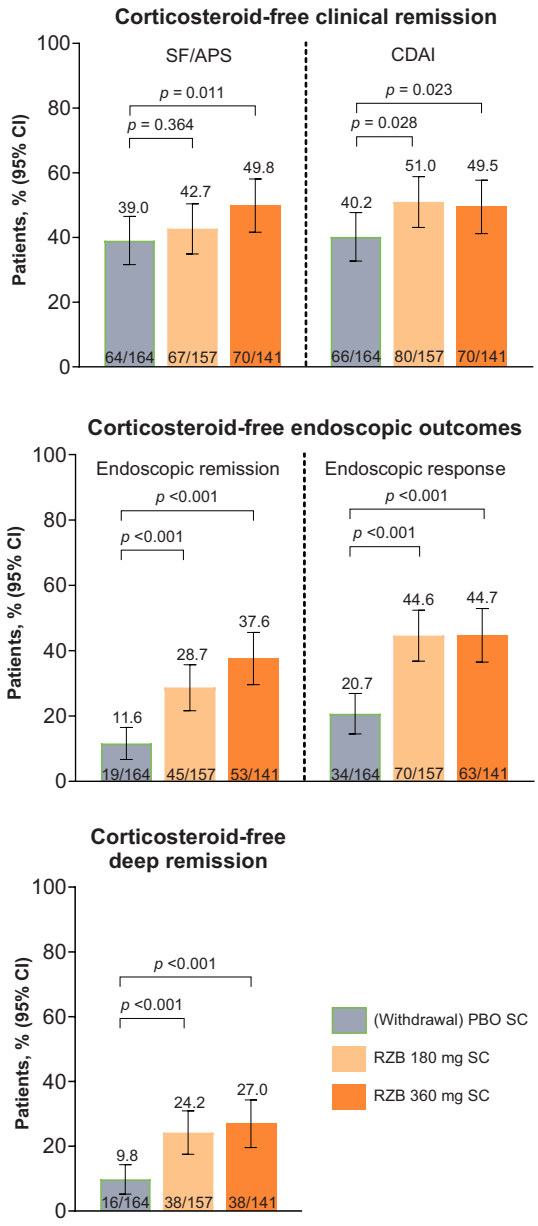

FIGURE 3 Achievement of clinical and endoscopic outcomes at week 52 with no corticosteroid use for 90 days prior to week 52. APS, abdominal pain score; CDAI, Crohn's Disease Activity Index; PBO, placebo; RZB, risankizumab; SC, subcutaneous; SES-CD, Simple Endoscopic Score for Crohn's Disease; SF, stool frequency. Values inside bars represent *n*/*N*.

Similar results were observed when corticosteroid-free was defined as no corticosteroid use at week 52 of maintenance, demonstrating that nearly all patients who achieved corticosteroid-free outcomes at week 52 of maintenance had been corticosteroid-free for at least 90 days (Figure S1). In a separate analysis assessing patients who achieved clinical remission (either per SF/APS or per CDAI), endoscopic outcomes or deep remission at week 52 of maintenance, almost all achieved these outcomes without concomitant corticosteroids (clinical remission per CDAI, 98.5% [66/67] (withdrawal) placebo, 92.0% [80/87] risankizumab 180 mg, 97.2% [69/71] risankizumab 360 mg; clinical remission per SF/APS, 98.5% [64/65] (withdrawal) placebo, 91.8% [67/73] risankizumab 180 mg, 97.2% [70/72] risankizumab 360 mg; endoscopic response, 94.4% [34/36] (withdrawal) placebo, 94.6% [70/74] risankizumab 180 mg, 96.9% [63/65] risankizumab 360 mg; endoscopic remission, 90.5% [19/21] (withdrawal) placebo, 95.7% [45/47] risankizumab 180 mg, 96.4% [53/55] risankizumab 360 mg; deep remission, 94.1% [16/17] (withdrawal) placebo, 95.0% [38/40] risankizumab 180 mg, 95.0% [38/40] risankizumab 360 mg).

3.3 | Safety

During induction, the incidence of TEAEs was similar among all treatment groups, regardless of baseline corticosteroid use (Table 2). The rate of TEAEs of special interest was low; no individual TEAE of special interest was reported in >2% of patients receiving risankizumab.

During the maintenance study, exposure-adjusted TEAE rates among patients with or without induction baseline corticosteroid use were similar (Table 3), but rates of serious TEAEs were higher in patients with concomitant corticosteroid use at induction baseline versus those without, regardless of treatment group. Regarding the areas of special interest, rates of serious infections and hepatic events were higher in patients with corticosteroid use at induction baseline versus those without. Most hepatic events were due to increased liver enzymes; events were not serious or severe and did not lead to study drug discontinuation. Overall, the extended exposure to risankizumab in maintenance did not lead to increased rates of TEAEs, regardless of corticosteroid use at induction baseline.

4 | DISCUSSION

In post hoc analyses of the ADVANCE and MOTIVATE studies, we assessed the impact of concomitant corticosteroid use on clinical and endoscopic outcomes during induction. In contrast to results from the GAIN, GEMINI 2 and GEMINI 3 studies suggesting a synergistic effect of corticosteroids and adalimumab and vedolizumab during induction, our study showed that clinical remission and endoscopic response rates were similar at week 12 of induction with IV risankizumab, regardless of concomitant corticosteroid use.[19,20] This finding is consistent with results from a meta-analysis of anti–tumour necrosis factor therapy that showed similar clinical outcomes

TABLE 2 Overview of treatment-emergent adverse events during induction by baseline corticosteroid use.

Parameter, *n* (%)	Corticosteroid use		No corticosteroid use	
	PBO (*n* = 127)	RZB 600 mg (*n* = 179)	PBO (*n* = 241)	RZB 600 mg (*n* = 354)
TEAEs	84 (66.1)	94 (52.5)	140 (58.1)	191 (54.0)
Serious TEAEs	19 (15.0)	7 (3.9)	31 (12.9)	25 (7.1)
TEAEs leading to discontinuation of study medication	13 (10.2)	1 (0.6)	16 (6.6)	10 (2.8)
Death	1 (0.8)	0	1 (0.4)	0
TEAEs of special interest				
Adjudicated MACE	0	0	0	0
Malignancies	0	0	0	0
Serious infections	2 (1.6)	2 (1.1)	10 (4.1)	2 (0.6)
Active tuberculosis	1 (0.8)	0	0	1 (0.3)
Opportunistic infections excluding herpes zoster and tuberculosis	0	0	3 (1.2)	0
Serious hypersensitivity reactions	0	0	0	1 (0.3)[a]
Adjudicated or serious anaphylactic reactions	0	0	0	0
Infusion-site reactions	2 (1.6)	1 (0.6)	2 (0.8)	4 (1.1)
Hepatic events	1 (0.8)	2 (1.1)	5 (2.1)	7 (2.0)

Note: All drugs were administered intravenously during induction.

Abbreviations: MACE, major adverse cardiovascular event; PBO, placebo; RZB, risankizumab; TEAE, treatment-emergent adverse event.

[a]As previously reported,[17] a serious hypersensitivity reaction (rash) event that occurred 80 days after the first study drug dose with accompanying liver enzyme elevations above clinical thresholds (alanine transaminase, aspartate transaminase and total bilirubin); the rash and liver enzyme elevations resolved after hospitalisation and steroid administration.

TABLE 3 Overview of treatment-emergent adverse events during maintenance by induction baseline corticosteroid use.

	Corticosteroid use			No corticosteroid use		
	PBO (*n* = 52)	RZB 180 mg (*n* = 52)	RZB 360 mg (*n* = 42)	PBO (*n* = 114)	RZB 180 mg (*n* = 107)	RZB 360 mg (*n* = 99)
Parameter, E (E/100 PY)	**PY = 40.8**	**PY = 52.3**	**PY = 34.3**	**PY = 101.7**	**PY = 98.0**	**PY = 97.2**
TEAEs	155 (379.7)	134 (256.3)	108 (314.8)	330 (324.3)	303 (309.0)	260 (267.5)
Serious TEAEs	15 (36.7)	13 (24.9)	9 (26.2)	10 (9.8)	16 (16.3)	21 (21.6)
TEAEs leading to discontinuation of study medication	2 (4.9)	0	4 (11.7)	3 (2.9)	4 (4.1)	4 (4.1)
Death	0	0	0	0	0	0
TEAEs of special interest						
Adjudicated MACE	0	0	1 (2.9)	0	0	0
Malignancies	0	0	0	1 (1.0)	0	1 (1.0)
NMSC	0	0	0	1 (1.0)	0	0
Serious infections	4 (9.8)	2 (3.8)	3 (8.7)	1 (1.0)	1 (1.0)	6 (6.2)
Active tuberculosis	0	0	0	0	0	0
Opportunistic infections excluding herpes zoster and tuberculosis	0	1 (1.9)	1 (2.9)	0	0	0
Serious hypersensitivity reactions	0	0	0	0	0	0
Adjudicated or serious anaphylactic reactions	0	0	0	0	0	0
Injection-site reactions	6 (14.7)	6 (11.5)	0	7 (6.9)	10 (10.2)	19 (19.6)
Hepatic events	1 (2.4)	0	1 (2.9)	3 (2.9)	7 (7.1)	7 (7.2)

Note: All drugs were administered subcutaneously during maintenance.

Abbreviations: E, event; MACE, major adverse cardiovascular event; NMSC, nonmelanoma skin cancer; PBO, placebo; PY, person-year; RZB, risankizumab; TEAE, treatment-emergent adverse event.

among patients with concomitant corticosteroid use versus those receiving biologic induction therapy alone.[21]

In post hoc analyses of the FORTIFY study, our results support that risankizumab can be a corticosteroid-sparing therapy. A greater proportion of patients discontinued corticosteroids during maintenance with risankizumab therapy compared with (withdrawal) placebo group starting at week 32. However, it is still worth noting that discontinuation rates of concomitant corticosteroids in the (withdrawal) placebo group during maintenance were greater than 40%, which indicates prolonged durability of risankizumab induction therapy, as supported by measurable risankizumab serum levels through 52 weeks of maintenance.[16] Among patients who discontinued corticosteroid use for 90 days, achievement of clinical remission was numerically greater among those who received risankizumab versus (withdrawal) placebo. However, statistical significance for this prespecified secondary endpoint was not met with the higher 360 mg dose, which may be due to a significant carryover from induction in the (withdrawal) placebo group, which has been observed for this agent.[16] Of note, this prespecified secondary endpoint only included patients using corticosteroids at baseline (51 and 42 patients in the 180 and 360 mg groups, respectively), and data from this small number of patients should be interpreted with caution. Among all patients, risankizumab maintenance treatment led to high rates of corticosteroid-free outcomes, regardless of baseline corticosteroid use, and nearly all patients who achieved clinical and endoscopic outcomes at week 52 of maintenance did so without concomitant corticosteroids.

Risankizumab induction and maintenance therapy was well tolerated in patients with moderately to severely active CD, with rates of TEAEs generally similar, regardless of baseline corticosteroid use and consistent with primary analyses, although the number of patients in each subgroup was small and data should therefore be interpreted with caution.[16,17] Consistent with findings of clinical trials of other biologic therapies that corticosteroid use was a risk factor for serious infections,[22,23] we noted higher rates of serious TEAEs and serious infections in patients with induction baseline corticosteroid use during the maintenance study. While corticosteroids are known to be associated with increased risk of side effects,[4] it is worth noting that patients with induction baseline corticosteroid use tended to have slightly worse CD severity based on SES-CD scores at baseline.

A strength of this analysis is that randomisation of patients in the ADVANCE and MOTIVATE studies was stratified by baseline corticosteroid use, which kept the distribution of patients with and without corticosteroid use comparable between dose groups. However, the majority of patients enrolled in the ADVANCE and MOTIVATE induction studies were not taking corticosteroids at baseline, which limited the sample size for the baseline corticosteroid use subgroup and may have increased variability in responses. The potential

corticosteroid-sparing effects of risankizumab could not be formally evaluated during induction because consistent corticosteroid therapy was required per protocol. Additionally, we assume that a durable effect of risankizumab induction therapy may have influenced the ability of patients in the (withdrawal) placebo group to remain off corticosteroids because their symptoms were controlled. Significant carryover of risankizumab from induction in the (withdrawal) placebo group may have contributed to the high rates of corticosteroid discontinuation and corticosteroid-free clinical remission seen in this group during maintenance. Similar results were observed, regardless of whether corticosteroid-free was defined as without corticosteroids for at least 90 days prior to week 52 or as without corticosteroids at week 52. As corticosteroid therapy could be modified at the investigator's discretion after the protocol-mandated corticosteroid taper, cumulative corticosteroid exposure may have varied among patients. Potential safety-related differences associated with the use of systemic versus local corticosteroids were not evaluated due to the small number of patients receiving the latter.

In summary, the efficacy of risankizumab induction therapy was independent of concomitant corticosteroid use, and risankizumab maintenance therapy was associated with high rates of corticosteroid-free clinical and endoscopic outcomes at 52 weeks. Risankizumab was also well tolerated, regardless of baseline corticosteroid use, with a safety profile that was generally similar to that observed in the primary analyses. These results support risankizumab as an effective corticosteroid-sparing treatment for patients with CD.

AUTHOR CONTRIBUTIONS

Stefan Schreiber: Conceptualization; investigation; methodology; visualization; writing – review and editing; writing – original draft. **Raymond K. Cross:** Conceptualization; investigation; methodology; visualization; writing – original draft; writing – review and editing. **Remo Panaccione:** Conceptualization; investigation; methodology; visualization; writing – original draft; writing – review and editing. **Geert D'Haens:** Conceptualization; investigation; methodology; visualization; writing – original draft; writing – review and editing. **Peter Bossuyt:** Conceptualization; investigation; methodology; visualization; writing – original draft; writing – review and editing. **Iris Dotan:** Conceptualization; investigation; methodology; visualization; writing – original draft; writing – review and editing. **Jean-Frederic Colombel:** Conceptualization; investigation; methodology; visualization; writing – original draft; writing – review and editing. **Edouard Louis:** Conceptualization; investigation; methodology; visualization; writing – original draft; writing – review and editing. **Marla C. Dubinsky:** Conceptualization; visualization; writing – original draft; writing – review and editing; investigation; methodology. **Kristina Kligys:** Conceptualization; writing – original draft; writing – review and editing; methodology; project administration; supervision; visualization. **Ezequiel Neimark:** Conceptualization; methodology; visualization; writing – original draft; writing – review and editing. **Alexandra Song:** Conceptualization; methodology; visualization; writing – original draft; writing – review and editing. **Javier Zambrano:** Conceptualization; methodology; visualization; writing – original draft; writing – review and editing. **Jasmina Kalabic:** Conceptualization; methodology; visualization; writing – original draft; writing – review and editing. **Erica Cheng:** Conceptualization; data curation; formal analysis; methodology; resources; software; validation; visualization; writing – original draft; writing – review and editing. **Yafei Zhang:** Conceptualization; data curation; formal analysis; methodology; resources; software; validation; visualization; writing – original draft; writing – review and editing. **Marc Ferrante:** Conceptualization; investigation; methodology; visualization; writing – original draft; writing – review and editing.

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DATA AVAILABILITY STATEMENT

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymised individual and trial-level data (analysis data sets), as well as other information (e.g. 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 and 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'.

AUTHORSHIP

Guarantor of the article: Dr. Stefan Schreiber.

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ORCID

Stefan Schreiber https://orcid.org/0000-0003-2254-7771
Remo Panaccione https://orcid.org/0000-0002-5247-940X
Jean-Frederic Colombel https://orcid.org/0000-0001-6472-249X
Edouard Louis https://orcid.org/0000-0002-1287-7075
Marla C. Dubinsky https://orcid.org/0000-0003-4968-5795
Marc Ferrante https://orcid.org/0000-0003-1492-0716

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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