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ORIGINAL RESEARCH—CLINICAL

Shorter Crohn's Disease Duration Is Associated With Better Clinical and Endoscopic Outcomes With Risankizumab in Phase 3 Studies

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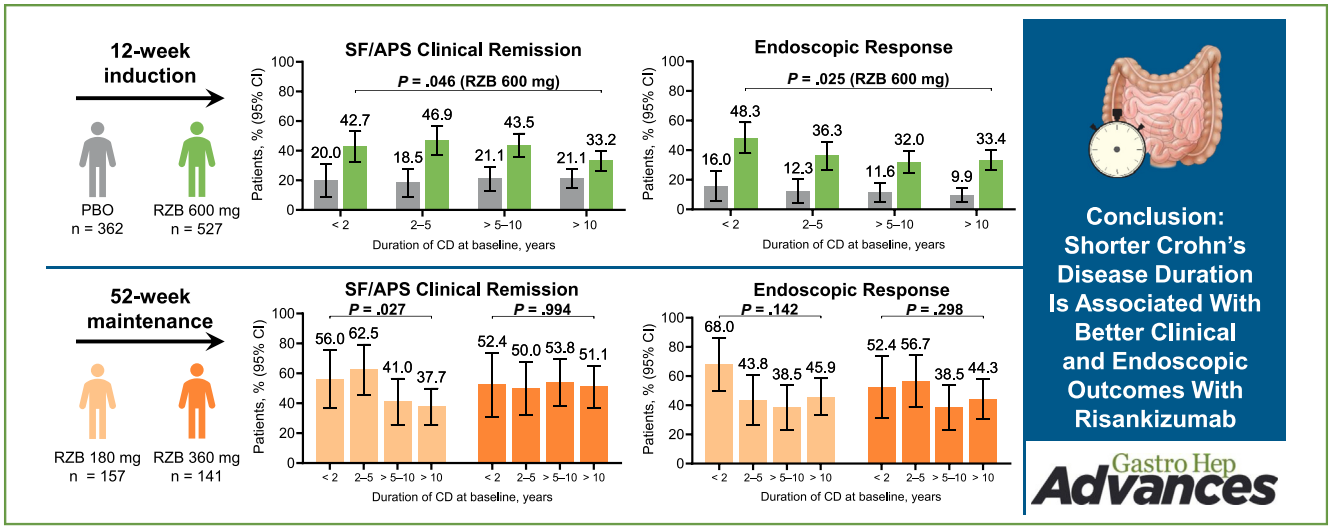

BACKGROUND AND AIMS: Early biologic therapy treatment has demonstrated better outcomes in Crohn's disease (CD). We evaluated the impact of CD duration in patients with moderately to severely active CD treated with risankizumab therapy. **METHODS:** This post hoc analysis evaluated clinical, endoscopic, and safety outcomes by baseline CD duration (<2, 2–5, >5–10, and >10 years) in patients from ADVANCE, MOTIVATE, and FORTIFY. Pooled induction analyses included patients who received intravenous 600-mg dose of risankizumab or placebo for 12 weeks. Maintenance analyses included patients who responded to induction risankizumab and received subcutaneous 180-mg or 360-mg dose of risankizumab for 52 weeks. Duration subgroups were compared using Cochrane-Armitage trend tests with nominal *P* values. **RESULTS:** Among 527

Abbreviations used in this paper: **APS, abdominal pain score; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; FCP, fecal calprotectin; hsCRP, high-sensitivity C-reactive protein; IV, intravenous; SAEs, serious adverse events; SC, subcutaneous; SES-CD, Simple Endoscopic Score for Crohn's Disease; SF, stool frequency; TEAEs, treatment-emergent adverse events.**

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patients who received risankizumab 600-mg induction therapy, higher outcome rates were observed at week 12 among patients with shorter vs longer baseline disease duration (for <2, 2–5, >5–10, and >10 years, clinical remission: 42.7%, 46.9%, 43.5%, and 33.2% [$P = .046$]; endoscopic response: 48.3%, 36.3%, 32.0%, and 33.4% [$P = .025$]). Among 298 patients receiving risankizumab (180 mg or 360 mg) maintenance therapy, shorter vs longer baseline disease duration was generally associated with numerically higher endoscopic outcome rates at week 52. Higher clinical remission and endoscopic outcome rates were generally observed with shorter disease duration with 180-mg risankizumab dose only. Adverse event rates were generally similar across duration subgroups. **CONCLUSION:** Clinical benefits of risankizumab are observed across disease duration subgroups; clinical and endoscopic outcome rates are higher with risankizumab initiation earlier in the disease course (ClinicalTrials.gov numbers: NCT03105128, NCT03104413, and NCT03105102).

Keywords: Biologics; Crohn's Disease; Disease Duration; Interleukin 23; Risankizumab

Introduction

Crohn's disease (CD) is a progressive, chronic, inflammatory bowel disorder characterized by a remitting-relapsing disease course, and subclinical, untreated inflammation can cause irreversible bowel damage.[1] The concept of early CD was introduced in 2010 and was addressed 2 years later in the publication of an international consensus.[2,3] There is accumulating evidence that early treatment with disease-modifying agents such as biologic therapies may slow or interrupt disease progression, thus improving patients' quality of life and preventing further complications, such as strictures, fistulae, hospitalizations, and surgeries.[4–6] The CALM trial was the first study to demonstrate the benefit of using tight control for patients with early CD (mean disease duration: 0.9–1.0 years).[7] Based on findings from post hoc analyses and systematic reviews, patients with shorter CD duration treated with biologic therapies experience greater improvement in symptomatic endpoints compared with patients with longer disease duration, supporting the notion that patients with early CD could greatly benefit from early initiation of biologics.[8–10]

Risankizumab is a humanized immunoglobulin G1 monoclonal antibody that specifically inhibits interleukin 23 by binding to its p19 subunit.[11] In the ADVANCE, MOTIVATE, and FORTIFY phase 3 trials, intravenous (IV) risankizumab induction therapy and subcutaneous (SC) maintenance therapy were effective and well tolerated in patients with moderately to severely active CD who had previously shown intolerance or inadequate response to conventional or biologic therapies.[12,13] We evaluated the impact of disease duration on clinical and endoscopic outcomes with risankizumab treatment in the phase 3 trials.

Methods

Study Design and Patients

Detailed descriptions of ADVANCE (NCT03105128), MOTIVATE (NCT03104413), and FORTIFY (NCT03105102) study designs, patient populations, and procedures were previously reported.[12,13]

The two phase 3, multicenter, double-blind, randomized, placebo-controlled, 12-week induction studies, ADVANCE and MOTIVATE, were performed at 297 sites in 39 countries (ADVANCE) and 214 sites in 40 countries (MOTIVATE).[12] 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 ≥1 biologic (ADVANCE and MOTIVATE) and/or conventional therapy (ADVANCE) were enrolled. Patients were randomized (2:2:1 in ADVANCE; 1:1:1 in MOTIVATE) to receive IV risankizumab (600 mg or 1200 mg) or placebo at weeks 0, 4, and 8.

Patients achieving clinical response based on patient-reported outcomes (≥30% decrease in average daily stool frequency [SF] and/or ≥30% decrease in average daily abdominal pain score [APS]) after 12 weeks of IV risankizumab induction therapy were eligible to enroll in the FORTIFY maintenance study, a phase 3, multicenter, double-blind, randomized, placebo-controlled withdrawal study conducted at 273 sites in 44 countries.[13] Patients were rerandomized (1:1:1) to receive SC risankizumab (180 mg or 360 mg) or placebo (withdrawal) every 8 weeks for 52 weeks.

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 and approved all relevant documentation. Written informed consent was obtained from all patients. All authors had access to the study data and had reviewed and approved the final manuscript.

Assessments

Clinical and endoscopic outcomes at week 12 of the ADVANCE and MOTIVATE studies and at week 52 of the FORTIFY study were evaluated by baseline CD duration (<2, 2–5, >5–10, and >10 years); a supplemental analysis evaluated the same outcomes by baseline CD duration <2 and ≥2 years. Outcomes included clinical remission per SF and APS criteria (average daily SF ≤2.8 plus average daily APS ≤1, and both not worse than baseline of the induction studies) and per Crohn's Disease Activity Index (CDAI) (defined as CDAI <150), endoscopic response (>50% decrease in Simple Endoscopic Score for Crohn's disease [SES-CD] from baseline or ≥2-point reduction from baseline for patients with isolated ileal disease and a baseline SES-CD of 4), endoscopic remission (SES-CD ≤4 and ≥2-point reduction vs baseline and no subscore >1 in any individual variable), ulcer-free endoscopy (SES-CD ulcerated surface subscore of 0 in patients with SES-CD ulcerated surface subscore ≥1 at baseline), enhanced clinical response (≥60% decrease in average daily SF and/or ≥35% decrease in average daily APS and both not worse than at baseline of the induction studies, and/or clinical remission), and deep remission (CDAI clinical remission and endoscopic remission;

assessed during maintenance only). Additionally, outcomes within each disease duration subgroup were evaluated by patients' prior biologic experience (inadequate response/intolerance to biologic therapies [Bio-IR] vs non–Bio-IR status). Inflammatory biomarker outcomes at week 12 included normalization of high-sensitivity C-reactive protein (hsCRP; ≤5 mg/L) or fecal calprotectin (FCP; ≤250 mg/kg) and achievement of ≥50% decrease in hsCRP or FCP by baseline disease duration. Median changes from baseline in hsCRP or FCP during induction were also assessed by baseline disease duration.

Reports of treatment-emergent adverse events (TEAEs), findings from standard laboratory tests, results from physical examinations, and data on vital sign measurements were collected throughout the study and tabulated using MedDRA system organ class and preferred terms (version 23.1).

Statistical Analysis

Induction study efficacy and safety analyses were performed on pooled data from the ADVANCE and MOTIVATE studies, which included randomized patients in the intent-to-treat population who received at least 1 dose of IV risankizumab (600 mg) or placebo for 12 weeks and had eligible SES-CD scores of ≥6 (or ≥4 for isolated ileal disease) at baseline; data for patients receiving the risankizumab (1200 mg) induction dose are not reported for induction efficacy analyses as this dose did not demonstrate a treatment benefit over the 600 mg dose in the primary analyses.[12] Maintenance efficacy analyses were limited to patients who achieved clinical response to IV risankizumab for 1 induction period of 12 weeks in the ADVANCE and MOTIVATE studies and received ≥1 dose of SC risankizumab (either 180 mg or 360 mg) in the FORTIFY study. Patients randomized to placebo (withdrawal of risankizumab) were not included in the maintenance efficacy analyses. Continuous outcomes with multiple post-baseline measurements were analyzed using a mixed-effect model for repeated measures; an analysis of a covariance model was used to analyze continuous outcomes with only 1 post-baseline measurement. Cochran-Armitage trend tests were used to evaluate trends in the achievement of outcomes among groups with increasing disease duration. Two-sided tests for statistical significance were used for all treatment comparisons; all *P* values are nominal. For categorical endpoints, missing data were imputed using nonresponder imputation incorporating multiple imputations to handle missing data due to COVID-19. Safety in the FORTIFY study was analyzed in all patients who received IV risankizumab for only 1 induction period and who received ≥1 dose of the study drug (SC risankizumab or placebo). TEAEs were defined as events that began on or after the first dose of the study drug through 140 days after the last dose administration.

Results

Patients

Induction study analyses included 889 patients randomized to receive 600-mg risankizumab dose (n = 527) or placebo (n = 362; Table 1). Of these, 15.6% of patients had disease duration <2 years, and the majority (66.0%) of patients had disease duration >5 years. Demographic and baseline disease characteristics were generally similar across disease duration groups. As expected, most patients with disease duration <2 years had no history of biologic therapy failure, while most patients with longer disease duration had experienced inadequate response to or failed ≥1 biologic therapy, and the percentage of patients who had failed ≥1 biologic therapy increased with longer disease duration.

Efficacy

Induction: week 12. At week 12, significantly higher rates of clinical remission (per SF/APS or CDAI), CDAI clinical response, enhanced clinical response, endoscopic response, endoscopic remission, and ulcer-free endoscopy (SES-CD ulcerated surface subscore of 0; a more stringent endpoint than endoscopic remission) were achieved with risankizumab (600 mg) compared with placebo across all disease duration subgroups ($P < .05$; Figure 1 and Figure A1). Except for SF/APS clinical remission rates, which were generally higher for risankizumab-treated patients with shorter vs longer disease duration (Cochran-Armitage test, $P < .05$), there were no clear trends for clinical outcomes across disease duration subgroups. Response rates for all endoscopic outcomes were higher among risankizumab-treated patients with shorter vs longer disease duration (Cochran-Armitage test, $P < .05$); similar trends across disease duration subgroups were also observed for patients who received placebo during induction. Similar results were observed in the supplemental analysis by comparing the <2 and ≥2 years subgroups; endoscopic outcome rates were greater for patients with disease duration <2 vs ≥2 years, while clinical outcomes were generally similar between disease duration subgroups (Figures A2 and A3).

Maintenance: week 52. Patients with shorter disease duration treated with risankizumab (180 mg or 360 mg) generally had numerically higher rates of all endoscopic outcomes evaluated relative to those with longer disease duration (Figure 2 and Figure A4). In contrast, clinical remission rates were similar across disease duration subgroups for patients treated with risankizumab (360 mg). In the risankizumab 180-mg dose group, higher rates were observed with shorter disease duration for several clinical and endoscopic outcomes but not for endoscopic response, CDAI clinical response, and enhanced clinical response (Cochran-Armitage test, $P < .05$). No trends were observed in the risankizumab 360-mg dose group. Among patients with disease duration >10 years, numerically higher response rates were generally observed across most outcomes with risankizumab 360-mg vs risankizumab 180-mg dose groups. In the supplemental <2 vs ≥2 years analysis, a numerically greater proportion of patients with disease duration <2 years achieved clinical and endoscopic outcomes with risankizumab (180 mg or 360 mg) treatment relative to those with disease duration ≥2 years (Figures A5 and A6).

Table 1. Baseline Demographics and Characteristics at Induction by Baseline Disease Duration[a]

	Crohn's disease duration							
	<2 y		2–5 y		>5–10 y		>10 y	
Parameter	PBO n = 50	RZB 600 mg n = 89	PBO n = 65	RZB 600 mg n = 98	PBO n = 95	RZB 600 mg n = 147	PBO n = 152	RZB 600 mg n = 193
Female, n (%)	23 (46.0)	42 (47.2)	36 (55.4)	47 (48.0)	38 (40.0)	64 (43.5)	78 (51.3)	93 (48.2)
Age, y, mean (SD)	35.9 (12.4)	38.5 (13.8)	36.5 (13.4)	33.8 (12.9)	32.6 (12.0)	36.9 (13.4)	43.3 (13.0)	43.5 (12.2)
Weight, kg, mean (SD)	69.0 (16.2)	69.3 (21.0)	70.7 (18.6)	70.6 (20.0)	70.3 (19.8)	69.8 (15.4)	73.8 (18.7)	72.7 (19.1)
Corticosteroid use, n (%)	19 (38.0)	30 (33.7)	21 (32.3)	31 (31.6)	28 (29.5)	45 (30.6)	50.0 (32.9)	61 (31.6)
Immunomodulator use, n (%)	11 (22.0)	26 (29.2)	20 (30.8)	24 (24.5)	20 (21.1)	41 (27.9)	31 (20.4)	33 (17.1)
Biologic failure history, n (%)								
0	25 (50.0)	58 (65.2)	17 (26.2)	21 (21.4)	16 (16.8)	29 (19.7)	20 (13.2)	33 (17.1)
1	18 (36.0)	24 (27.0)	30 (46.2)	46 (46.9)	33 (34.7)	66 (44.9)	48 (31.6)	56 (29.0)
>1	7 (14.0)	7 (7.9)	18 (27.7)	31 (31.6)	46 (48.4)	52 (35.4)	84 (55.3)	104 (53.9)
FCP, mg/kg, mean (SD)	2377 (2630)	1645 (1974)	2970 (5653)	2402 (3849)	2815 (4753)	2060 (2233)	2331 (4485)	1861 (3259)
hsCRP, mg/L, mean (SD)	17.9 (24.0)	16.9 (24.1)	19.2 (26.7)	19.3 (25.7)	24.3 (26.0)	22.1 (28.1)	14.6 (20.0)	16.2 (27.0)
CDAI, mean (SD)	318.1 (47.8)	312.4 (59.3)	330.7 (75.7)	309.0 (66.0)	314.3 (60.4)	310.7 (61.9)	318.2 (67.4)	311.8 (63.8)
SES-CD, mean (SD)	14.6 (7.6)	13.8 (7.7)	13.4 (6.9)	15.3 (7.6)	15.6 (7.9)	14.4 (7.6)	14.1 (7.4)	14.6 (7.7)
Average daily SF, mean (SD)	5.5 (2.9)	5.2 (2.7)	6.5 (2.8)	5.9 (2.2)	5.8 (2.6)	5.6 (2.6)	6.7 (2.9)	6.5 (3.3)
Average daily APS, mean (SD)	2.0 (0.5)	1.9 (0.6)	1.9 (0.5)	1.8 (0.6)	1.9 (0.5)	1.9 (0.5)	1.8 (0.6)	1.8 (0.5)

Drugs were administered intravenously during induction.
PBO, placebo; RZB, risankizumab; SD, standard deviation.
[a]Baseline characteristics were pooled from the ADVANCE and MOTIVATE induction studies.

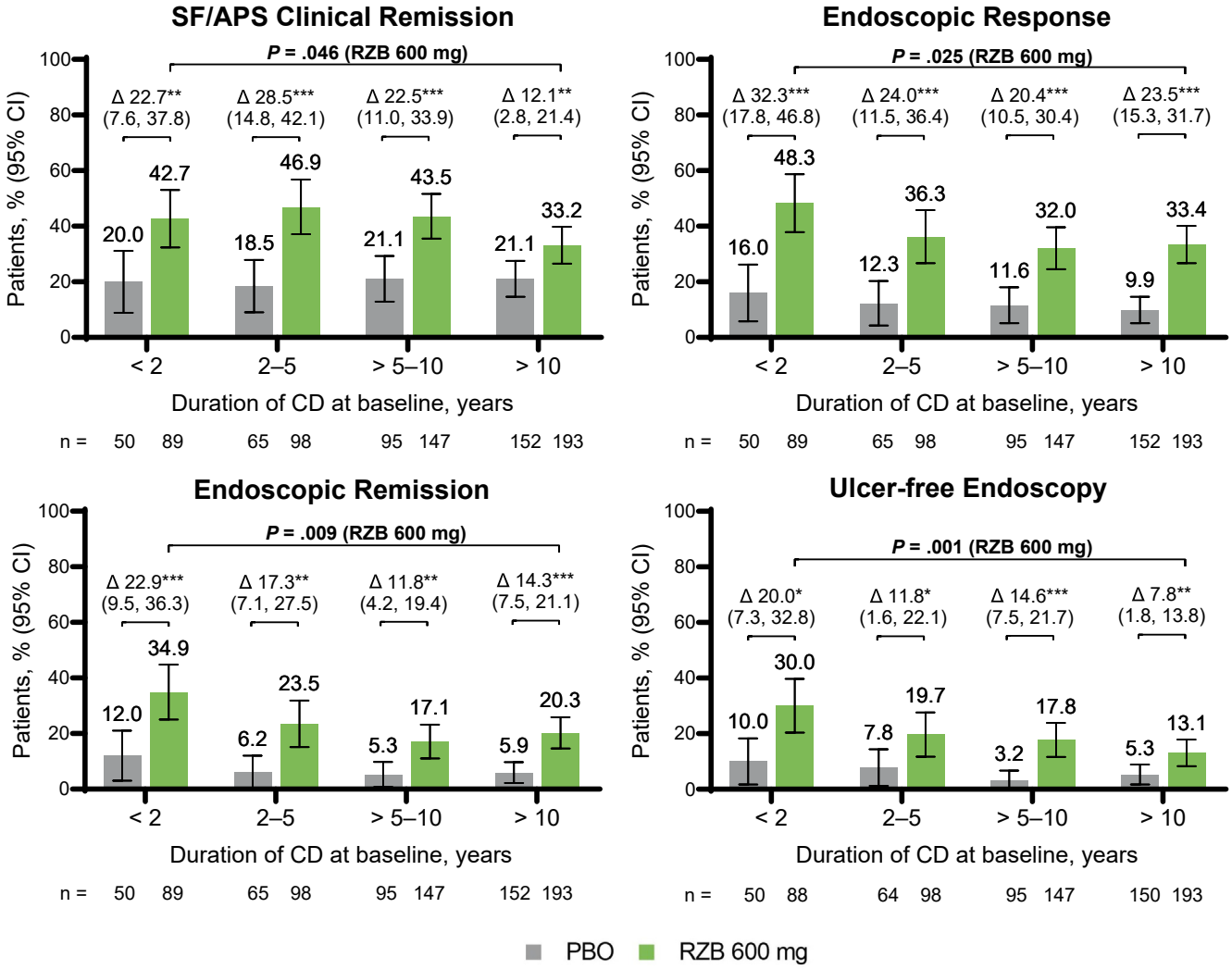

Figure 1. Clinical remission and endoscopic outcomes at week 12 of induction by baseline disease duration. All nominal *P* values: **P* ≤ .05; ***P* ≤ .01; ****P* < .001 vs PBO. Differences vs PBO (Δ) were calculated as risankizumab−placebo, and 95% CIs were calculated using normal approximation to the binomial distribution. Nominal *P* values above brackets were calculated by Cochran-Armitage trend tests. Drugs were administered intravenously during induction. APS, abdominal pain score; CD, Crohn's disease; PBO, placebo; SF, stool frequency; RZB, risankizumab.

Response by Bio-IR status. Across disease duration subgroups, numerically higher rates of SF/APS clinical remission, endoscopic response, endoscopic remission, and ulcer-free endoscopy were achieved with 600-mg risankizumab dose compared with placebo (Table A1). Among patients with baseline disease duration <2 years (n = 139), 40.3% of patients were Bio-IR, and generally similar clinical and endoscopic outcomes were observed with 600-mg risankizumab dose at the end of induction at week 12, regardless of Bio-IR status, although the number of patients in each subgroup was small and data should be interpreted with caution.

Inflammatory biomarkers. Of patients with elevated hsCRP at baseline, a greater proportion of patients treated with 600-mg risankizumab dose achieved ≥50% decrease in hsCRP or normalization of hsCRP at week 12 compared with those receiving placebo across all disease duration subgroups (Figure 3; $P < .001$). Among those with elevated FCP at baseline, a greater proportion of patients treated with 600-mg risankizumab dose achieved ≥50% decrease in FCP or normalization of FCP at week 12 compared with those receiving placebo across all disease duration subgroups. Similar results were observed in the supplemental <2 vs ≥2 years analysis (Figure A7).

At week 12 of induction, significantly greater reductions in hsCRP levels were observed among patients treated with 600-mg dose of risankizumab compared with those receiving placebo across all disease duration subgroups (Figure A8; $P < .001$). Similarly, numerically greater reductions in FCP levels were observed with 600-mg risankizumab dose compared with placebo across all disease duration subgroups; significant reductions in FCP were observed among patients with disease durations of <2 and >10 years ($P \leq .001$). No clear relationship between

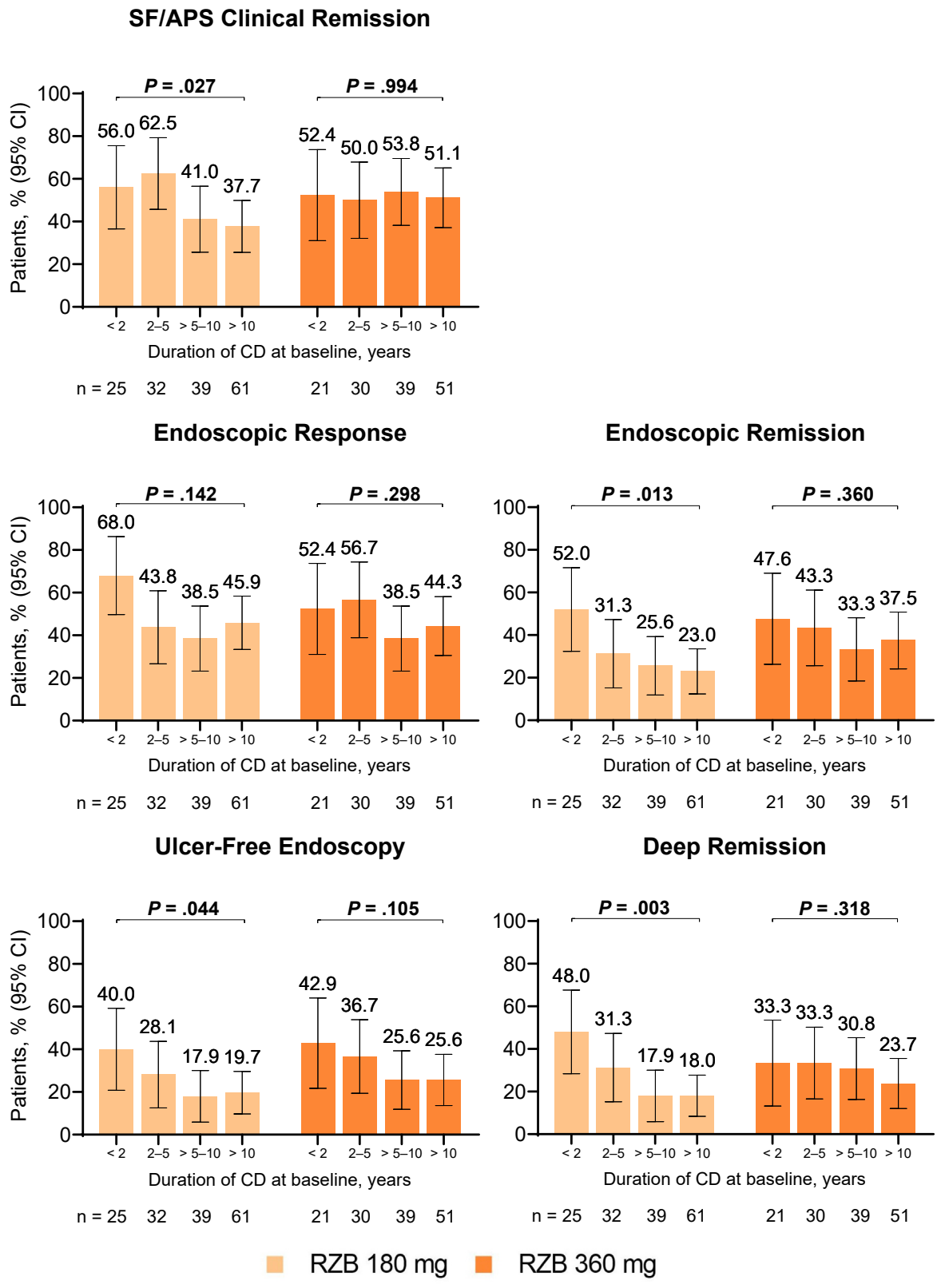

Figure 2. Clinical remission and endoscopic outcomes at week 52 of maintenance by baseline disease duration. Drugs were administered subcutaneously during maintenance. Nominal *P* values above brackets were calculated by Cochran-Armitage trend tests. APS, abdominal pain score; CD, Crohn's disease; RZB, risankizumab; SF, stool frequency.

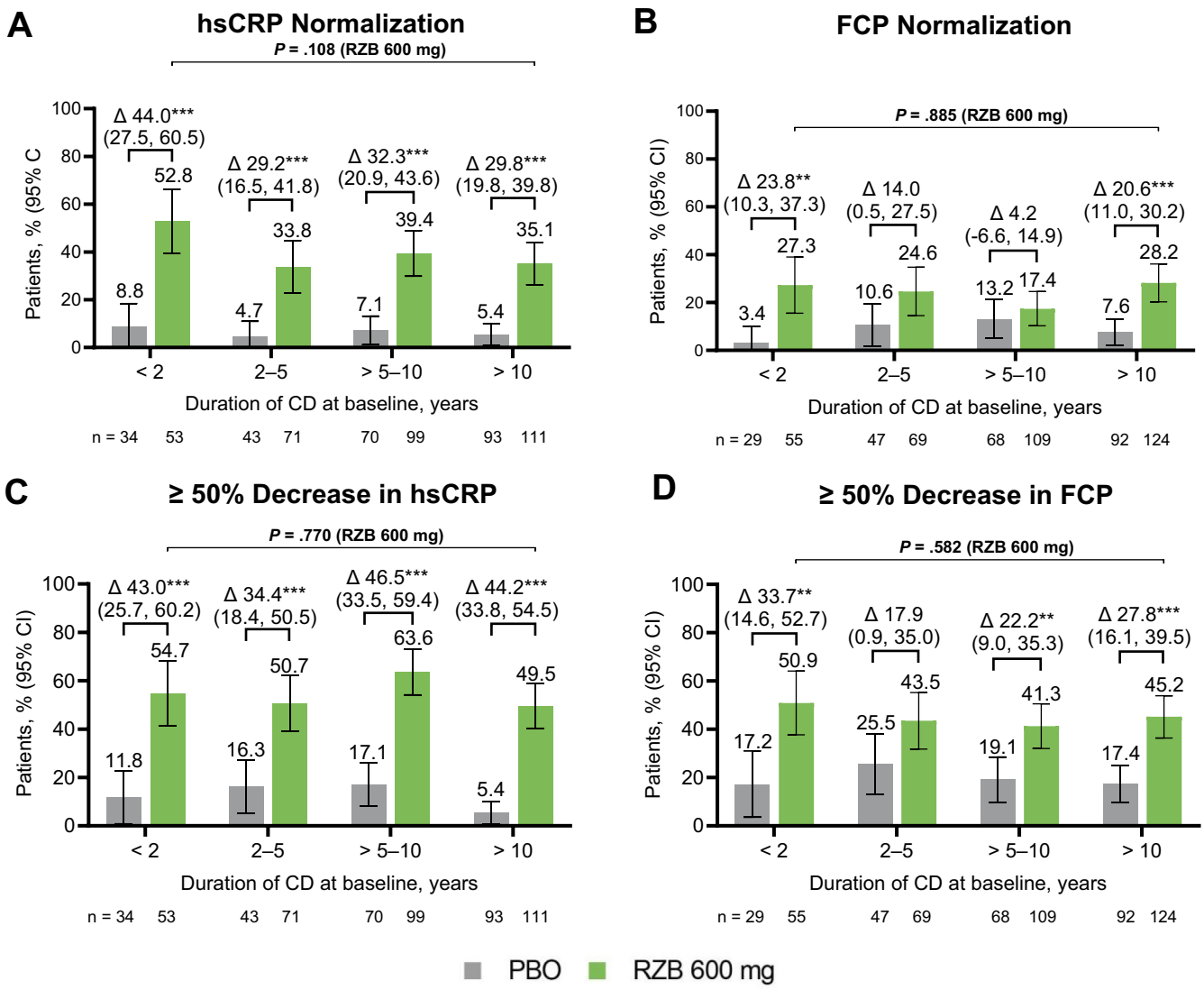

Figure 3. Achievement of (A) hsCRP normalization at week 12 of induction in patients with elevated hsCRP at baseline, (B) FCP normalization at week 12 of induction in patients with elevated FCP at baseline, (C) ≥50% decrease in hsCRP at week 12 of induction in patients with elevated hsCRP at baseline, (D) ≥50% decrease in FCP at week 12 of induction in patients with elevated FCP at baseline. Drugs were administered intravenously during induction. All nominal *P* values: $^{**}P \leq .01$; $^{***}P < .001$ vs PBO. Differences vs PBO (Δ) were calculated as risankizumab−placebo, and 95% CIs were based on Wald limits without continuity correction. Nominal *P* values above brackets were calculated by Cochran-Armitage trend tests. FCP, fecal calprotectin; hsCRP, high-sensitivity C-reactive protein; PBO, placebo; RZB, risankizumab.

baseline duration of disease and improvement in hsCRP or FCP levels was observed.

Safety

The overall incidence of TEAEs and TEAEs of safety interest was similar among all treatment groups during the induction studies, regardless of disease duration (Table 2). Patients randomized to placebo, regardless of baseline disease duration, experienced greater rates of serious adverse events (SAEs) than did patients treated with risankizumab.

In the maintenance study, exposure-adjusted TEAE rates remained similar across disease duration subgroups (Table 3). Rates of SAEs were low across disease duration subgroups. Regarding the areas of safety interest, incidence of TEAEs remained numerically low and stable.

Discussion

These post hoc analyses using data from the ADVANCE, MOTIVATE, and FORTIFY studies are the first to show an association between early risankizumab treatment and improved efficacy outcomes in patients with CD. Greater clinical and endoscopic efficacy with risankizumab treatment vs placebo was observed at week 12 across all disease duration subgroups, with generally higher efficacy rates among patients with shorter disease duration. Interestingly,

Table 2. Treatment-Emergent Adverse Events During Induction by Baseline Disease Duration

	Crohn's disease duration							
	<2 y		2–5 y		>5–10 y		>10 y	
Parameter, n (%)	PBO n = 50	RZB 600 mg n = 89	PBO n = 65	RZB 600 mg n = 98	PBO n = 98	RZB 600 mg n = 150	PBO n = 155	RZB 600 mg n = 196
AE	28 (56.0)	49 (55.1)	37 (56.9)	47 (48.0)	61 (62.2)	75 (50.0)	98 (63.2)	114 (58.2)
Serious AE	5 (10.0)	2 (2.2)	7 (10.8)	7 (7.1)	16 (16.3)	9 (6.0)	22 (14.2)	14 (7.1)
AE leading to discontinuation of study drug	4 (8.0)	2 (2.2)	4 (6.2)	3 (3.1)	9 (9.2)	2 (1.3)	12 (7.7)	4 (2.0)
Death[a]	0	0	0	0	1 (1.0)	0	1 (0.6)	0
TEAEs of safety interest								
Adjudicated MACE	0	0	0	0	0	0	0	0
Malignancies	0	0	0	0	0	0	0	0
Serious infections	1 (2.0)	1 (1.1)	2 (3.1)	1 (1.0)	4 (4.1)	0	5 (3.2)	2 (1.0)
Active TB	1 (2.0)	1 (1.1)	0	0	0	0	0	0
Opportunistic infections excluding herpes zoster and TB	0	0	1 (1.5)	0	0	0	2 (1.3)	0
Serious hypersensitivity reactions	0	1 (1.1)	0	0	0	0	0	0
Adjudicated or serious anaphylactic reaction	0	0	0	0	0	0	0	0

Drugs were administered intravenously during induction.
AE, adverse event; MACE, major adverse cardiovascular event; PBO, placebo; RZB, risankizumab; TB, tuberculosis; TEAE, treatment-emergent adverse event.
[a]Patient deaths in the PBO arm were assessed with no reasonable possibility of relationship to the study drug.

Table 3. Treatment-Emergent Adverse Events During Maintenance by Baseline Disease Duration

	Crohn's disease duration											
	<2 y			2–5 y			>5–10 y			>10 y		
Parameter, E (E/100 PY)	RZB 180 mg n = 25 PY: 24.0	RZB 360 mg n = 21 PY: 19.1	PBO n = 35 PY: 29.7	RZB 180 mg n = 32 PY: 32.0	RZB 360 mg n = 30 PY: 28.2	PBO n = 28 PY: 25.7	RZB 180 mg n = 40 PY: 37.3	RZB 360 mg n = 39 PY: 35.5	PBO n = 39 PY: 34.4	RZB 180 mg n = 62 PY: 57.0	RZB 360 mg n = 51 PY: 48.7	PBO n = 64 PY: 52.8
AE	50 (207.9)	58 (303.6)	112 (377.7)	76 (237.6)	81 (286.8)	84 (326.3)	128 (343.5)	75 (211.3)	103 (299.7)	183 (320.9)	154 (316.5)	186 (352.2)
Serious AE	3 (12.5)	0	6 (20.2)	5 (15.6)	4 (14.2)	4 (15.5)	8 (21.5)	13 (36.6)	7 (20.4)	13 (22.8)	13 (26.7)	8 (15.2)
AE leading to discontinuation of study drug	0	0	2 (6.7)	0	1 (3.5)	0	2 (5.4)	2 (5.6)	1 (2.9)	2 (3.5)	5 (10.3)	2 (3.8)
Death	0	0	0	0	0	0	0	0	0	0	0	0
TEAEs of safety interest												
Adjudicated MACE	0	0	0	0	0	0	0	1 (2.8)	0	0	0	0
Malignancies[a]	0	0	0	0	0	0	0	0	1 (2.9)	0	1 (2.1)	0
Serious infections	0	0	1 (3.4)	0	2 (7.1)	1 (3.9)	1 (2.7)	4 (11.3)	1 (2.9)	2 (3.5)	3 (6.2)	2 (3.8)
Active TB	0	0	0	0	0	0	0	0	0	0	0	0
Opportunistic infections excluding herpes zoster and TB	0	0	0	0	0	0	1 (2.7)	0	0	0	1 (2.1)	0
Serious hypersensitivity reactions	0	0	0	0	0	0	0	0	0	0	0	0
Adjudicated or serious anaphylactic reaction	0	0	0	0	0	0	0	0	0	0	0	0

Drugs were administered subcutaneously during maintenance.

AE, adverse event; E, event; HER2, human epidermal growth factor receptor 2; MACE, major adverse cardiovascular event; PBO, placebo; PY, patient-years; RZB, risankizumab; TB, tuberculosis; TEAE, treatment-emergent adverse event.

[a]One patient who received PBO was diagnosed with basal cell carcinoma; 1 patient who received 360-mg RZB dose was diagnosed with HER2+ breast cancer.

patients who were randomized to placebo during induction shared a similar pattern (most notably for endoscopic outcomes), which supports the hypothesis that some patients with early-stage CD may achieve remission during the natural disease course; this is reminiscent of results observed in a meta-analysis of other clinical trials showing greater remission and response with shorter disease duration among patients receiving placebo.[8] While efficacy rates were lower in the longest disease duration subgroup (>10 years), a substantial benefit over placebo persisted at week 12, with approximately one-third of patients achieving SF/APS clinical remission and endoscopic response. Numerically higher response rates were also observed at week 52 in patients with shorter disease duration, regardless of risankizumab dose. Interestingly, numerically higher response rates were observed at week 52 with 360-mg risankizumab dose relative to 180-mg risankizumab dose in the longer disease duration subgroup, suggesting a benefit of the 360-mg risankizumab dose, especially for patients with longer disease duration. The fact that all patients in the maintenance study were responders to induction therapy may also partially explain the lack of significant effect of disease duration on efficacy outcomes with 360-mg risankizumab maintenance treatment. Another explanation could be that patients with refractory disease achieved better clinical and endoscopic outcomes with 360-mg risankizumab dose vs 180-mg risankizumab dose given the dose–response relationship observed for the more stringent, objective endoscopic and composite endpoints[13]; thus, 360-mg risankizumab therapy resulted in comparable outcome rates, regardless of disease duration. Overall, our results are consistent with findings from previous observational and post hoc analyses that indicate that early initiation of biologic treatment can lead to favorable clinical and endoscopic outcomes; however, comparisons are limited due to different study designs.[9,10,14,15]

Physicians' abilities to treat beyond symptom relief to achieve mucosal healing and bowel preservation may alter the natural course of CD in patients with early CD.[16] Our findings support that early risankizumab treatment is associated with mucosal healing, as numerically greater proportions of patients with early disease duration achieved improved endoscopic outcomes than did those who had longer disease duration. This pattern is consistent with results from exploratory analysis of EXTEND trial data and post hoc analysis of the SONIC trial, which reported higher composite remission rates with biologic therapy among patients with shorter CD duration.[5,17]

Surrogate inflammation biomarkers are commonly used as predictive monitoring tools to inform clinicians whether patients have successfully responded to therapy or are likely to experience relapse.[18] A benefit of risankizumab over placebo was observed for inflammatory biomarker outcomes across all disease duration subgroups. However, in contrast to the clear association between shorter baseline CD duration and higher response rates in clinical and endoscopic outcomes during induction, biomarker responses were generally similar across all disease duration subgroups. Despite the absence of an association between biomarkers and disease duration, earlier initiation of therapy may still be crucial to avoid persistent inflammation and preserve mucosal integrity, though evidence of this mechanism is still lacking. Biomarker responses during maintenance are not reported due to small sample sizes; further studies are needed to assess the long-term effects of maintenance therapy on biomarkers by disease duration.

It has been documented in the literature that prior exposure to biologics is associated with reduced odds of achieving clinical remission.[19] Given that prior exposure to biologics is also a proxy for disease duration, we focused our assessment of the efficacy of risankizumab in biologic-experienced vs biologic-naïve patients on those with <2 years of CD duration, as these patients would be expected to have less exposure to prior treatments and represent a more balanced proportion of patients classified as Bio-IR vs non–Bio-IR. Lower rates of clinical response are typically expected in patients with refractory CD; however, among patients with CD duration <2 years, clinical and endoscopic outcomes were achieved by similar proportions of Bio-IR and non–Bio-IR patients after 12 weeks of risankizumab induction therapy. In contrast to previous findings that showed no apparent confounding effect of prior biologics on the relationship between disease duration and treatment effect,[8] these results may suggest a confounding influence of disease duration on efficacy among patients with CD who have received previous biologic therapies. These interpretations are limited by the small sample size, which also prevents us from reporting maintenance data by Bio-IR status. Further studies are needed to assess long-term efficacy based on Bio-IR status, particularly in patients with shorter disease duration.

Risankizumab induction and maintenance therapy was well tolerated in patients with moderately to severely active CD, with rates of adverse events generally similar to or lower than adverse event rates reported for placebo across CD duration subgroups; these findings are consistent with those seen in primary analyses.[12,13] Although rates of SAEs were low in the maintenance study, increasing rates were observed in patients with longer disease duration (>5 years); however, this trend was inconsistent between dose groups. These rates might be explained by the baseline demographics and disease characteristics of these patients, as they tended to be older, with greater exposure to previous biologic therapies.

A limitation of this post hoc analysis is that patients were not prospectively stratified by disease duration. As a result, most patients (66%) were in the longer disease duration subgroups (>5 years), and sample size was limited in the shorter duration subgroups (<2 and 2−5 years), which may have resulted in more variability in responses for the shorter duration subgroups. Secondly, the Cochran-Armitage trend test does not identify differences between individual disease duration subgroups or disease duration cutoffs associated with maximum efficacy. These analyses

did not include adjustments for other potential factors that could have confounded the relationship between disease duration and clinical and endoscopic outcomes, such as prior biologic use. Further research into the effect of this and other potential confounding factors that may affect treatment outcomes is warranted. Lastly, the prolonged durability of risankizumab induction therapy may have resulted in a considerable carryover effect during maintenance that limits interpretations of outcomes by disease duration.

The results from this post hoc analysis showed an association between a shorter baseline CD duration and greater rates of achievement of clinical and endoscopic outcomes, supporting the potential value of earlier introduction of risankizumab therapy for better treatment outcomes. Risankizumab induction and maintenance therapy were well tolerated, with a safety profile that was generally similar across CD duration subgroups. In summary, risankizumab is efficacious across a wide range of CD durations but given the favorable risk-benefit profile in patients with early CD, earlier introduction of risankizumab therapy to achieve improved outcomes in patients with moderately to severely active CD should be considered. The effect of early risankizumab therapy on disease modification remains to be demonstrated. Future studies are needed to clarify the role of early risankizumab therapy in altering the course of disease progression.

Supplementary Materials

Material associated with this article can be found in the online version at https://doi.org/10.1016/j.gastha.2024.02.008.

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Ethical Statement:
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 and approved all relevant documentation. Written informed consent was obtained from all patients.

Data Transparency Statement:
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, and execution of a data sharing agreement. 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 then select "Home": https://vivli.org/ourmember/abbvie/.

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