Effect of risankizumab on health-related quality of life in patients with Crohn's disease: Results from phase 3 MOTIVATE, ADVANCE, and FORTIFY clinical trials

Running title (≤40 characters): Effect of risankizumab in Crohn's disease

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SUMMARY (≤250 WORDS)

Background: Crohn's disease has a substantial negative impact on health-related quality of life (HRQoL).

Aim: To examine the effects of risankizumab on HRQoL in Crohn's disease.

Methods: We analysed data from patients with Crohn's disease from 12-week induction trials ADVANCE (N=850) and MOTIVATE (N=569) with risankizumab 600 mg or 1200 mg intravenous (IV) versus placebo IV and a 52-week maintenance trial FORTIFY (N=462) with risankizumab 180 mg or 360 mg subcutaneous (SC) versus placebo SC. Outcomes included Inflammatory Bowel Disease Questionnaire (IBDQ), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), 36-item Short Form Health Survey (SF-36), EuroQol 5-Dimension-5-Level (EQ-5D-5L) and work productivity. The mean change and percentages of patients achieving clinically meaningful improvement in all outcomes were determined at Weeks 12 and 52.

Results: At Week 12, more patients in the risankizumab 600 mg or 1200 mg groups versus placebo achieved IBDQ response (ADVANCE: 70.2%, 75.5% versus 47.8%, $p \leq 0.001$; MOTIVATE: 61.7%, 68.5% versus 48.2%, $p \leq 0.01$) and FACIT-F response (ADVANCE: 51.3%, 48.0% versus 35.7%, $p \leq 0.01$; MOTIVATE: 44.2%, 49.1% versus 33.7%, $p < 0.05$). These improvements persisted at Week 52 with risankizumab maintenance treatment. Similar trends were observed for SF-36 physical and mental component summary scores, EQ-5D-5L and activity impairment within work productivity measures.

Conclusions: Risankizumab induction therapy (600 mg IV or 1200 mg IV) led to clinically meaningful improvements in disease-specific and general patient-reported outcomes, including

fatigue, in patients with moderate to severe Crohn's disease. These improvements were sustained after 52 weeks of risankizumab (180 mg SC or 360 mg SC) maintenance therapy.

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INTRODUCTION

Crohn's disease is a chronic, disabling, inflammatory disease affecting the gastrointestinal tract that is progressive in nature with alternating periods of activity and remission.[1,2] Crohn's disease has a substantial negative impact on health-related quality of life (HRQoL), including psychological, social, and work-related issues.[3-8] The BIRD study, a national survey of a large cohort of French patients with inflammatory bowel disease (IBD), showed that approximately half of patients had poor HRQoL, severe fatigue, and severe work impairment, and one-third had moderate to severe disability.[9] Poor HRQoL and fatigue have been shown to be strongly associated with loss of work productivity in employed patients with IBD.[10] However, fatigue related to Crohn's disease and its treatment has not been extensively reported from pivotal trials of drug development.

Treatment targets in IBD now include measures of HRQoL and disability.[11-13] Per the STRIDE-II and SPIRIT initiatives, current recommended treatment targets for patients with Crohn's disease include early symptom improvement (clinical response), followed by intermediate targets of more stringent symptom control (clinical remission) and decreases in serum levels of inflammatory biomarkers (i.e., serum C-reactive protein and fecal calprotectin), with the ultimate long-term goals of endoscopic healing and a return to normal HRQoL.[11,12,14] Beyond mucosal healing, patient-reported outcomes are becoming important measures to assess the benefit of treatment in Crohn's disease. These measures aid in identifying an individual patient's illness perceptions, are strongly associated with the patient's quality of life, and foster shared decision-making between patients and physicians, which is required for the successful long-term management of Crohn's disease.[14-16]

Risankizumab, a humanised immunoglobulin G1 monoclonal antibody directed against interleukin-23 p19, is currently being investigated in the treatment of Crohn's disease. Primary clinical and endoscopic results of the phase 3 induction (ADVANCE and MOTIVATE) and maintenance (FORTIFY) studies have been reported.[17,18] Results of the induction trials demonstrated that risankizumab induction treatment reduced the signs and symptoms of Crohn's disease and resulted in the resolution of mucosal inflammation as evaluated by endoscopic measures.[17] The maintenance trial showed that the effects of risankizumab treatment persisted through Week 52 in patients who were clinical responders to induction treatment.[18]

In this study, we present the effects of induction and maintenance treatment with risankizumab on HRQoL and work productivity in patients with Crohn's disease. Specifically, we evaluated the effect of risankizumab on disease-specific and general health patient-reported outcomes in patients with moderate to severe Crohn's disease.

METHODS

Study design and patients

The detailed study designs and primary results from the ADVANCE, MOTIVATE, and FORTIFY trials have previously been reported.[17,18] ADVANCE was conducted at 297 sites in 39 countries and MOTIVATE was conducted at 214 sites in 40 countries. ADVANCE (NCT03105128) and MOTIVATE (NCT03104413) were phase 3, double-blind, randomised clinical trials (RCTs) that evaluated the efficacy and safety of risankizumab as induction therapy in patients with moderate to severe Crohn's disease. Patients participating in these RCTs were ≥16 to ≤80 years

of age with moderate to severe Crohn's disease, defined as Crohn's Disease Activity Index [CDAI] 220-450, average daily soft stool frequency ≥4 and/or daily abdominal pain score ≥2, and endoscopic evidence of mucosal inflammation (Simple Endoscopic Score for Crohn's disease [SES-CD] ≥6 [≥4 for isolated ileal disease] excluding the narrowing component). Eligible patients in ADVANCE had a demonstrated inadequate response or intolerance to biologic therapy and/or to conventional therapy, whereas all of those in MOTIVATE had a demonstrated inadequate response to biologic therapy. Patients were randomised (using Interactive Response Technology) 2:2:1 in ADVANCE and 1:1:1 in MOTIVATE to receive IV risankizumab 600 mg, 1200 mg, or placebo at Weeks 0, 4, and 8. In both studies, randomisation was stratified by number of prior biologics failed, baseline corticosteroid use, and baseline SES-CD. In MOTIVATE, the percentage of enrolled patients who failed ustekinumab was capped at 20%. Co-primary endpoints in both RCTs were clinical remission (per CDAI <150 or average daily stool frequency ≤2.8 and daily abdominal pain score ≤1, not worse than baseline for both) and endoscopic response (decrease in SES-CD >50% from baseline [or for patients with isolated ileal disease and a baseline SES-CD of 4, an at least a 2-point reduction from baseline]) at Week 12.

FORTIFY (NCT03105102) was a 52-week, phase 3, double-blind, re-randomised responder withdrawal study evaluating the efficacy and safety of continuing risankizumab as subcutaneous (SC) maintenance therapy versus withdrawal in patients who previously achieved a clinical response to 12 weeks of IV risankizumab induction therapy in ADVANCE and MOTIVATE. IV risankizumab responders were re-randomised (using Interactive Response Technology) 1:1:1 to receive risankizumab 360 mg SC, risankizumab 180 mg SC, or placebo SC (withdrawal from IV risankizumab) every eight weeks for 52 weeks. For patients receiving

concomitant corticosteroids during the induction studies, tapering was mandatory starting at Week 0 of the maintenance study. Initiation of, increase in dose, or decrease in dose of other concomitant Crohn's disease medications (i.e., aminosalicylates, oral locally acting corticosteroids, or immunomodulators) was prohibited during the maintenance study. Rescue treatment (open-label risankizumab 1200 mg IV for one dose followed by 360 mg SC every eight weeks) was available for all patients meeting criteria of increased symptoms and objective confirmation of disease activity. Co-primary endpoints in the maintenance study were clinical remission (defined by CDAI or stool frequency/abdominal pain score) and endoscopic response at week 52.

All three RCTs were conducted according to the International Counsel for Harmonisation (ICH) guidelines and the principles of the Declaration of Helsinki. All patients provided written informed consent. The trial protocols were each approved by independent ethics committees and institutional review boards.

Outcomes

In the present study, we examined the effect of risankizumab induction and maintenance treatment on HRQoL using disease-specific and general patient-reported outcomes. We evaluated the change from induction baseline to Weeks 12 and 52 for all outcomes in patients treated with risankizumab versus those receiving placebo. To assess clinically meaningful improvements in HRQoL, we determined the percentage of patients who achieved a meaningful within-person change (MWPC) from induction baseline for all patient-reported outcomes at Weeks 12 and 52.

Disease-specific HRQoL outcomes

The Inflammatory Bowel Disease Questionnaire (IBDQ) is a validated and widely used disease-specific questionnaire[19-21] evaluating IBD across four dimensions: bowel symptoms, such as loose stools and abdominal pain; systemic symptoms, such as weight loss and altered sleep patterns; social function, such as interpersonal interactions and the need to cancel social events; and emotional function, such as anger, depression, and embarrassment. IBDQ total score ranges from 32 to 224, with higher scores indicating better HRQoL. IBDQ response was defined as a ≥ 16-point increase from induction baseline in IBDQ total score;[22] IBDQ remission was defined as a total score ≥170.[23]

Crohn's symptom severity

The Crohn's symptom severity (CSS) questionnaire is a new measure that was developed based on best practice guidelines[24,25] of patient-reported outcome development and has a recall period of seven days compared with 14 days in the IBDQ.[26] The CSS is a 14-item questionnaire designed to assess the severity of symptoms of associated Crohn's disease and their impact on sleep and energy. Symptoms evaluated include bowel movement frequency, passing large amounts of gas, abdominal pain, feeling tired or lacking energy, nausea, loss of appetite, joint pain, difficulty sleeping, bloating, diarrhea, bloody stools, constipation, vomiting, and stomach gurgling or growling. Patients rated the first 8 items of the CSS as 'not at all', 'a little bit', or 'very much' and the last 6 items as 'never', rarely', or 'always' to assess the impact or frequency and intensity of individual symptoms. The total score for the CSS is calculated by summing the individual item scores. The CSS ranges from 14 to 70, with higher scores indicating greater

severity. MWPC threshold for CSS was defined as ≥9-point increase in CSS score and was derived from anchor-based analysis (see Appendix 1 for details).

General HRQoL outcomes

The 36-item Short Form Survey (SF-36) is a commonly used generic measure of HRQoL[27] that has been used in clinical trials to evaluate clinically meaningful changes in HRQoL.[28] The questionnaire has 36 items across eight domains: physical function, role limitations resulting from physical health problems, bodily pain, general health perceptions, vitality, social functioning, role limitations resulting from emotional problems, and general mental health. The domain scores can be combined to calculate two summary scores: physical component summary (PCS) and mental component summary (MCS) scores, with greater scores indicative of better HRQoL. PCS and MCS scores are reported as a norm-based metric with a score of 50 representing the mean score of the US general population.[28] MWPC thresholds were ≥4.1 and ≥3.9 points for SF-36 PCS and SF-36 MCS, respectively.[28]

The EuroQol 5-Dimension 5-Level (EQ-5D-5L) is a self-reported, standardised, non-disease-specific measure[29] evaluating health status and HRQoL. EQ-5D-5L consists of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression assessed at five levels ranging from ’no problems‘ to ’extreme problems‘. The measure includes a visual analogue scale (VAS) that is rated on a scale from 0 (worst imaginable health) to 100 (best imaginable health). MWPC threshold was defined as ≥9.2-point increase from induction baseline for EQ-5D-5L VAS.[28]

Fatigue

The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) is a symptom-specific subscale of FACIT composed of 13 fatigue-related questions.[30] The FACIT-F questionnaire was developed to measure fatigue in patients with chronic illness and has been validated with good internal consistency, reproducibility, and sensitivity in patients with Crohn's disease.[31] The FACIT-F score ranges from 0 – 52, with higher scores indicating less fatigue. The MWPC threshold for FACIT-F, defined as a ≥9-point increase in FACIT-F total score from induction baseline, was derived from anchor-based analyses (see Appendix 1 for details).

Work productivity

The Work Productivity and Activity Impairment questionnaire in Crohn's disease (WPAI-CD) has been validated in patients with Crohn's disease and evaluates the impact of Crohn's disease on work productivity and performance of daily activities.[32] WPAI-CD consists of four domains: work time missed, impairment while working, overall work impairment, and activity impairment. Scores are reported as impairment percentages with higher scores indicating less work productivity and greater activity impairment. MWPC thresholds for WPAI-CD domains were ≥ 6.5% for work time missed, ≥6.1% for impairment while working, ≥7.3% for overall work impairment, and ≥8.5% for activity impairment.[33]

Statistical analysis

For the induction and maintenance studies, sample size calculation was determined to detect a treatment difference in the co-primary endpoints. The co-primary endpoints were the percentage of patients with clinical remission and the percentage with endoscopic response at

Week 12 in the induction trials and at Week 52 in the maintenance trial. The sample size for each study was calculated to provide >87% power to detect anticipated treatment differences in each co-primary endpoint between risankizumab and placebo using a Fisher's exact test at a two-sided significance level of 0.025 in induction studies and 0.05 in maintenance study, respectively (see Appendix 1 for assumptions regarding power calculations).

For the induction studies, the population analysed at Week 12 included all randomised patients who received at least one dose of IV study drug during the 12-week induction period and had an eligible SES-CD of ≥6 (≥4 for isolated ileal disease) at baseline. For the maintenance study, the population analysed at Week 52 included re-randomised patients who achieved a clinical response after receiving IV risankizumab for 12 weeks in the induction studies, had at least one dose of study drug in the maintenance study and had an eligible SES-CD of ≥6 (≥4 for isolated ileal disease) at induction baseline.

All analyses were performed using SAS Version 9.4 or later (SAS Institute Inc., Cary, NC 27513). Demographics and baseline or disease characteristics were summarised by treatment group. Categorical variables were summarised with the number and percentage of patients and continuous variables with means and standard deviations.

At Week 12, least squares (LS) mean changes from induction baseline, along with 95% confidence intervals (CIs) and *p*-values, were based on mixed-effects repeated measures model (MMRM) analysis with categorical fixed effects of treatment, visit, and treatment-by-visit interaction. Stratification factors included in the model were the number of prior biologics failed (0, 1, >1 for ADVANCE and ≤1, >1 for MOTIVATE), baseline corticosteroid use (yes or no),

and the continuous fixed covariate of the baseline value of the corresponding patient-reported outcome measurement.

At Week 52, the 95% CIs for within group LS means, adjusted treatment differences, and *p*-values were calculated using analysis of covariance with the following strata: endoscopic response at Week 0 (yes or no), clinical remission status at Week 0 (yes or no), last IV dose during risankizumab induction period (1200 mg IV or 600 mg IV), and induction baseline and Week 0 (i.e., maintenance baseline) patient-reported outcome scores as covariates for the comparison of two treatment groups versus placebo. Approximately 24% and 21% of patients in the risankizumab 180 mg and 360 mg groups, respectively, and 40% of patients in the placebo group received rescue therapy of risankizumab due to worsening symptoms and elevated inflammation markers. Data for these patients were censored and excluded from the primary analysis of continuous variables. A sensitivity analysis was performed to evaluate the treatment effect in continuous variables at Week 52 when data from censored patients remained in the analysis. For analysis of binary variables, patients who were censored during the maintenance trial were considered non-responders.

The percentage of patients who achieved IBDQ response and IBDQ remission were calculated at Weeks 4, 12 and 52. The percentage of patients who achieved MWPC in FACIT-F, CSS, SF-36 PCS and MCS, EQ-5D-5L VAS, and WPAI-CD was calculated at Weeks 12 and 52. The 95% CIs for response rates were based on Student's t-distribution if there were missing data because of COVID-19 or the normal approximation to the binomial distribution if there were no data missing because of COVID-19. At Week 12, the 95% CIs and *p*-values for between group

differences were calculated with the Cochran-Mantel-Haenszel test adjusted for the number of prior biologics failed and baseline corticosteroid use. At Week 52, the 95% CIs and *p*-values for between group differences were adjusted for endoscopic response and clinical remission status at Week 0, and last IV dose during risankizumab induction periods (1200 mg or 600 mg). The calculations were based on non-responder imputation incorporating multiple imputation to handle missing data because of COVID-19 or non-responder imputation only if there were no data missing because of COVID-19.

RESULTS

Study population

A total of 850 patients (placebo: 175; risankizumab 600 mg IV: 336; risankizumab 1200 mg IV: 339) participated in the ADVANCE induction trial. Induction baseline characteristics and patient-reported outcome scores were well-balanced across the treatment groups (Tables 1). In ADVANCE, 28.1% of patients previously failed treatment with one biologic therapy and 29.6% with more than one biologic therapy.

A total of 569 patients (placebo: 187; risankizumab 600 mg IV: 191; risankizumab 1200 mg IV: 191) participated in the MOTIVATE induction trial. Induction baseline characteristics and patient-reported outcome scores were well-balanced across the treatment groups (Table 1). All patients enrolled in MOTIVATE had demonstrated intolerance and/or inadequate response to biologic therapy with 52.9% of the patients previously failing treatment with more than one biologic therapy.

Baseline patient-reported outcome scores indicate a substantial impact of Crohn's disease on patients' HRQoL in both induction studies. Mean IBDQ total scores at induction baseline ranged from 120 to 124 and from 115 to 122 across the treatment groups in ADVANCE and MOTIVATE, respectively, which are much lower than the IBDQ remission threshold score of 170 (Table 1). Mean SF-36 PCS and MCS scores at induction baseline were approximately 38 across treatment groups in both studies, which is below the normal score of 50.

A total of 462 patients were clinical responders after 12-week induction with risankizumab IV and entered the FORTIFY maintenance study; 164 were assigned to withdrawal placebo SC, 157 to risankizumab 180 mg SC, and 141 to risankizumab 360 mg SC. Mean IBDQ scores at Week 0 of maintenance phase ranged from 175 to 181 across the treatment groups, indicating substantial improvement with risankizumab induction treatment. Mean FACIT-F scores also improved, ranging from 22 to 26 across treatment groups at induction baseline and from 39 to 41 at Week 0 of maintenance treatment.

Change in disease specific and general HRQoL outcome scores

Mean change from induction baseline to Weeks 12 and 52 in IBDQ total and domain scores, CSS, SF-36 PCS, SF-33 MCS, EQ-5D-5L, FACIT-F, and WPAI-CD are provided in Appendix Tables 1 and 2. Numerical improvements in mean change from induction baseline to Week 12 were observed with risankizumab 600 mg IV and risankizumab 1200 mg IV in all scores. These improvements were statistically significant for most outcomes (Appendix Table 1). Improvements in outcome scores reported at Week 12 persisted during maintenance treatment (Appendix Table 2) although the adjusted treatment differences tended to be small

and were generally not statistically significant. In a sensitivity analysis when censored data remained in the analysis (Appendix Table 3), the adjusted treatment difference between the risankizumab and placebo groups was greater than that observed in the primary analysis where data were censored (Appendix Table 2).

Disease-specific HRQoL outcomes: meaningful within person change

Inflammatory Bowel Disease Questionnaire

Week 12

Regarding improvement in quality of life, more risankizumab-treated (both doses) patients achieved an IBDQ response (increase of ≥16 points) compared with those receiving placebo at Week 12 in the induction trials (600 mg IV and 1200 mg IV versus placebo IV): ADVANCE: 70.2% and 75.5% versus 47.8%, $p<0.001$; MOTIVATE: 61.7% and 68.5% versus 48.2%, $p\leq0.01$ (Figure 1A). These improvements were observed as early as Week 4, with at least 61% of risankizumab-treated patients achieving IBDQ response. In addition, more risankizumab-treated patients achieved IBDQ remission (≥170) at Week 12 (ADVANCE: 44.5% and 51.7% versus 29.8%, $p\leq0.01$; MOTIVATE: 38.8% and 44.7% versus 26.7%, $p\leq0.01$). At least 25% of risankizumab-treated patients achieved IBDQ remission at Week 4 (Figure 1B).

Week 52

Patients who achieved clinical response to 12-week induction therapy were re-randomised to receive either risankizumab 180 mg SC or 360 mg SC or were withdrawn from risankizumab and received placebo SC (withdrawal placebo SC).

The percentage of risankizumab-treated patients who achieved IBDQ response and remission after 12 weeks of induction treatment persisted with 52 weeks of maintenance treatment (Figure 1). More patients achieved IBDQ response and remission after 52 weeks of maintenance treatment with risankizumab SC compared to withdrawal placebo SC (180 mg SC and 360 mg SC versus withdrawal placebo SC — IBDQ response: 70.7% and 65.7% versus 50.0%, $p \leq 0.01$; IBDQ remission: 59.2% and 57.2% versus 39.5%, $p < 0.001$).

Crohn's symptom severity

Week 12

Clinically meaningful improvements in Crohn's disease-related symptoms that have an impact on HRQoL were observed during induction with risankizumab. The percentage of patients who achieved MWPC thresholds in CSS at Week 12 was greater in both risankizumab groups compared with placebo (Figure 2A). At least 48% of patients achieved an increase of ≥9 points from induction baseline in CSS scores, compared with approximately one-third of patients receiving placebo.

Week 52

Among clinical responders to risankizumab induction therapy, clinically meaningful improvements in CSS persisted at Week 52. The percentage of patients who achieved MWPC threshold in CSS at Week 52 was numerically greater in both risankizumab SC groups compared with withdrawal placebo SC (Figure 2A). At least 57% of risankizumab-treated patients achieved an increase of ≥9 points from induction baseline in CSS scores, compared with 44% of patients receiving placebo.

General HRQoL outcomes: meaningful within person change

SF-36 PCS, SF-36 MCS, and EQ-5D-5L scores

Week 12

The percentage of patients who achieved MWPC thresholds in SF-36 PCS, SF-36 MCS, and EQ-5D-5L at Week 12 in the induction trials was numerically greater in both risankizumab groups compared with placebo (Figure 3). At Week 12, at least 56% of risankizumab-treated patients achieved an increase of ≥4.1 points from induction baseline in SF-36 PCS, compared with approximately 45% of patients receiving placebo (Figure 3A). Similar results were reported for SF-36 MCS (Figure 3B) and EQ-5D-5L VAS (Figure 3C).

Week 52

Clinically meaningful improvements in SF-36 PCS, SF-36 MCS, and EQ-5D-5L VAS in patients who responded to induction therapy persisted with 52 weeks of maintenance treatment. At least 61% of risankizumab-treated patients achieved an increase of ≥4.1 points from induction baseline in SF-36 PCS, compared with 46% of patients receiving placebo (Figure 3A). Similar results were reported for SF-36 MCS (Figure 3B) and EQ-5D-5L VAS (Figure 3C).

Fatigue

Week 12

Clinically meaningful improvements were observed in FACIT-F. The percentage of patients who achieved MWPC thresholds in FACIT-F at Week 12 was greater in both risankizumab groups compared with placebo. At least 44% of patients achieved an increase of ≥9 points from

induction baseline in FACIT-F compared with approximately one-third of patients receiving placebo (Figure 2B).

Week 52

Among clinical responders to risankizumab induction therapy, clinically meaningful improvements in FACIT-F persisted at Week 52. The percentage of patients who achieved MWPC threshold in FACIT-F at Week 52 was greater in the risankizumab 180 mg SC group compared with withdrawal placebo SC (Figure 2B). At least 46% of risankizumab-treated patients achieved an increase of ≥9 points from induction baseline in FACIT-F compared with 38% of patients receiving placebo.

WPAI-CD

Week 12

Clinically meaningful improvements were reported for impairment while working and activity impairment. A greater percentage of patients achieved MWPC thresholds in impairment while working and activity impairment at Week 12 (Appendix Figure 1) in risankizumab-treated patients compared with placebo. At least 46% of risankizumab-treated patients achieved ≥6.1% improvement from induction baseline in impairment while working compared with approximately 35% of those who received placebo (Appendix Figure 1C). Regarding activity impairment, at least 63% of risankizumab-treated patients achieved ≥8.5% improvement from induction baseline compared with at least 45% of those receiving placebo (Appendix Figure 1D). Improvement was observed in all four domains, including work time missed and impairment while working when combining the two induction studies in the analyses (Appendix Table 4).

Week 52

Clinically meaningful improvements in activity impairment achieved during risankizumab induction treatment persisted at Week 52 with both doses of risankizumab, whereas impairment while working was significant only with risankizumab 180 mg SC (Appendix Figure 1).

DISCUSSION

The present study demonstrated the positive impact of risankizumab on disease specific and general HRQoL measures, as well as fatigue and work productivity, all of which are of particular relevance to patients with Crohn's disease. Significant and clinically meaningful improvements in IBDQ, FACIT-F, CSS, SF-36 PCS, SF-36 MCS, EQ-5D-5L, and WPAI-CD, were observed with 12-week induction treatment with risankizumab (600 mg IV and 1200 mg IV) compared with placebo, and these improvements were sustained with risankizumab maintenance treatment (180 mg SC or 360 mg SC) at Week 52. These findings are important as they demonstrate movement toward normal quality of life with risankizumab treatment in patients with Crohn's disease. In this study, general HRQoL was improving close to normalcy as demonstrated by the change in SF-36 PCS in patients, which was approaching the normative value of 50 in patients treated with both doses of risankizumab maintenance treatment at Week 52.

Unique measurements examined in this study were fatigue assessed by FACIT-F and sleep and energy, which are captured in the CSS. Patients with Crohn's disease often report fatigue as a debilitating, burdensome symptom that has a detrimental effect on HRQoL.[3-8] A recent systematic review and meta-analysis found that 47% of patients with IBD reported experiencing

fatigue.[34] In addition, fatigue was highly prevalent (72%) in patients with active disease and was still present in almost half of patients who were in remission.[34] The presence of fatigue may be associated with active disease, psychological distress, such as anxiety and/or depression, anemia, sleep disturbances, altered gut microbiome, vitamin and mineral deficiencies, and medication adverse effects.[35-37] In this study, fatigue was significantly improved with both doses of risankizumab, with approximately half of the risankizumab-treated patients achieving clinically meaningful improvement. This improvement in FACIT-F score was maintained at Week 52. The CSS captures a number of gastrointestinal symptoms, as well as the related impact of Crohn's disease on sleep and energy levels that have been identified as important from the patient perspective.[23,38-40] Significant improvement in CSS score was observed in risankizumab-treated patients after induction. These improvements were maintained with risankizumab treatment during maintenance and indicate marked improvement in symptoms that patients consider most bothersome.

It is important to keep in mind the re-randomised responder-withdrawal study design of the maintenance study and the pharmacokinetic and pharmacodynamic profile of risankizumab when interpreting the results. Because of the continuous nature of the induction-to-maintenance treatments, responders who were randomised to the placebo SC in the maintenance study were withdrawal patients who still had residual risankizumab exposure from earlier IV induction treatment. Residual exposure from induction treatment was previously shown to last for approximately 16–24 weeks.[18] While the 52-week duration of the maintenance study was sufficient for drug washout in the withdrawal placebo SC group and for the risankizumab SC groups to reach steady state, a prolonged duration of the

pharmacodynamic effects of risankizumab, which exceeded the duration of pharmacokinetic effects, was previously reported.[18] Mean serum interleukin-22 levels showed that the interleukin-23 pathway in patients in the withdrawal placebo SC group remained suppressed through Week 52 compared with levels at the induction baseline.[18] The prolonged effect of risankizumab may explain why the adjusted treatment difference in patient-reported outcomes between risankizumab SC and withdrawal placebo SC at Week 52 are not statistically significant.

In addition, in the analysis of continuous variable of patient-reported outcomes, patients who had worsening symptoms and received rescue medication or Crohn's disease-related corticosteroid were censored and not included in the Week 52 analysis to avoid an impact of rescue therapy/corticosteroid use on the outcomes assessed. However, this approach could also pose a potential bias such that patients who remained in the Week 52 analyses were more likely to have better clinical and patient-reported outcomes, and thus underestimate the true treatment effect. In the sensitivity analysis, we included patients who were censored in the Week 52 analysis and observed that the outcomes in the withdrawal placebo group were in general worse than those in primary analysis, indicating the difference between patients who were censored and not censored. Note that the approach taken in the sensitivity analysis might also underestimate the true treatment effect as outcomes are expected to be worse if none of the placebo patients received rescue therapy. The significant treatment effects observed in the sensitivity analysis of continuous variables were also more aligned with the results from non-responder imputation analyses for the binary variable outcomes, which might be a better approach to evaluate the treatment effect.

The economic burden of Crohn's disease is substantial[41] and may include costs associated with treating a number of chronic comorbid conditions or complications, such as bowel obstruction, anemia, colorectal cancer, fatigue, and anxiety/depression, as well as costs associated with impaired work productivity.[41-45] Loss of work productivity can result from absenteeism, short- and long-term disability, unemployment, early retirement, and/or reduced productivity while working because of symptoms from Crohn's disease. Based on the reduction in overall work impairment after treatment with risankizumab compared with the withdrawal placebo group, and an average hourly wage of $31.03 in the US in November 2021,[46] an estimated savings of $4841 to $6454 per patient per year could be achieved with risankizumab maintenance treatment. Similarly, in European countries, using an average hourly wage of €28.5 in 2020,[47] the estimated savings would be €4446 to €5928 per patient per year.

An important strength of this study is that HRQoL was comprehensively measured, including many different aspects important to patients with Crohn's disease. In addition, this study evaluates a large sample size and assesses longitudinal follow-up over 52 weeks. A few limitations should be considered when interpreting the results, especially in the maintenance phase. The treatment effect on continuous patient-reported outcomes at Week 52 in the risankizumab versus withdrawal placebo groups might be underestimated due to the prolonged effect of risankizumab and exclusion of censored data. The non-responder imputation on binary variables might be a more appropriate analysis to address the disproportional difference in censored data and could represent a meaningful within-patient change assessment. Lastly, these results were obtained in patients with Crohn's disease who were enrolled in a clinical trial and may not be generalisable to all patients.

Conclusions

Risankizumab induction therapy (600 mg IV or 1200 mg IV) led to significant improvements in disease-specific and general patient-reported outcomes, including fatigue, in patients with moderate to severe Crohn's disease with a documented inadequate response to conventional or biologic therapy. These improvements were sustained after 52 weeks of risankizumab (180 mg SC or 360 mg SC) maintenance therapy.

STATEMENT OF INTERESTS

Declaration of personal interests:

Laurent Peyrin-Biroulet received personal fees from Galapagos, AbbVie, Janssen, Genentech, Ferring, Tillots, Celltrion, Takeda, Pfizer, Index Pharmaceuticals, Sandoz, Celgene, Biogen, Samsung Bioepis, Inotrem, Allergan, MSD, Roche, Arena, Gilead, Amgen, BMS, Vifor, Norgine, Mylan, Lilly, Fresenius Kabi, OSE Immunotherapeutics, Enthera, Theravance, Pandion Therapeutics, Gossamer Bio, Viatris, Thermo Fisher. Grants from Abbvie, MSD, Takeda, Fresenius Kabi; has stock options with CTMA.

Subrata Ghosh served as a steering committee member for Pfizer, Janssen, AbbVie, BMS, Celgene, and Boehringer-Ingelheim; and received speaker honorarium from AbbVie, Celltrion, Galapagos, Gilead, Janssen, Takeda, Shield, Ferring, Falk Pharma, and Pfizer.

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AUTHORSHIP STATEMENT

All authors had access to relevant data, contributed to the development of the article, and maintained control over the final content. All authors approved the final version of the article including the authorship list. No honoraria or payments were made for authorship.

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Involved in drafting or revising critically for important intellectual content: Laurent Peyrin Biroulet, Subrata Ghosh, Julian Panes, Edouard Louis, Edward V Loftus, Kori Wallace, Scott D Lee, Sofie Berg, Jenny Griffith, Wan-Ju Lee.

DATA AVAILABILITY 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 (e.g., protocols and Clinical Study Reports), 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.

This 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 and 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://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

ETHICAL COMPLIANCE

All three RCTs were conducted according to the International Counsel for Harmonisation (ICH) guidelines and the principles of the Declaration of Helsinki. All patients provided written informed consent. The trial protocols were each approved by independent ethics committees and institutional review boards.

REFERENCES

1. Noor NM, Verstockt B, Parkes M, Lee JC. Personalised medicine in Crohn's disease. *Lancet Gastroenterol Hepatol.* 2020;5(1):80-92.
2. Torres J, Mehandru S, Colombel JF, Peyrin-Biroulet L. Crohn's disease. *Lancet.* 2017;389(10080):1741-1755.
3. Bernstein CN, Hitchon CA, Walld R, et al. Increased burden of psychiatric disorders in inflammatory bowel disease. *Inflamm Bowel Dis.* 2019;25(2):360-368.
4. Knowles SR, Graff LA, Wilding H, Hewitt C, Keefer L, Mikocka-Walus A. Quality of life in inflammatory bowel disease: a systematic review and meta-analyses-part I. *Inflamm Bowel Dis.* 2018;24(4):742-751.
5. Knowles SR, Keefer L, Wilding H, Hewitt C, Graff LA, Mikocka-Walus A. Quality of life in inflammatory bowel disease: a systematic review and meta-analyses-part II. *Inflamm Bowel Dis.* 2018;24(5):966-976.
6. Sands BE, Han C, Gasink C, et al. The effects of ustekinumab on health-related quality of life in patients with moderate to severe Crohn's disease. *J Crohns Colitis.* 2018;12(8):883-895.
7. Feagan BG, Reilly MC, Gerlier L, Brabant Y, Brown M, Schreiber S. Clinical trial: the effects of certolizumab pegol therapy on work productivity in patients with moderate-to-severe Crohn's disease in the PRECiSE 2 study. *Aliment Pharmacol Ther.* 2010;31(12):1276-1285.
8. Loftus EV, Feagan BG, Colombel JF, et al. Effects of adalimumab maintenance therapy on health-related quality of life of patients with Crohn's disease: patient-reported outcomes of the CHARM trial. *Am J Gastroenterol.* 2008;103(12):3132-3141.
9. Williet N, Sarter H, Gower-Rousseau C, et al. Patient-reported Outcomes in a French Nationwide Survey of Inflammatory Bowel Disease Patients. *J Crohns Colitis.* 2017;11(2):165-174.
10. van Gennep S, Gielen ME, Rietdijk ST, et al. Work productivity loss is determined by fatigue and reduced quality of life in employed inflammatory bowel disease patients: a

prospective multicentre cohort study. *Eur J Gastroenterol Hepatol.* 2021;33(1S Suppl 1):e594-e602.

11. Le Berre C, Peyrin-Biroulet L. Selecting End Points for Disease-Modification Trials in Inflammatory Bowel Disease: the SPIRIT Consensus From the IOIBD. *Gastroenterology.* 2021;160(5):1452-1460.e1421.
12. Le Berre C, Ricciuto A, Peyrin-Biroulet L, Turner D. Evolving short- and long-term goals of management of IBD: getting it right, making it last. *Gastroenterology.* 2021.
13. Gower-Rousseau C, Sarter H, Savoye G, et al. Validation of the Inflammatory Bowel Disease Disability Index in a population-based cohort. *Gut.* 2017;66(4):588-596.
14. Turner D, Ricciuto A, Lewis A, et al. STRIDE-II: An update on the selecting therapeutic targets in inflammatory bowel disease (STRIDE) initiative of the international organization for the study of IBD (IOIBD): determining therapeutic goals for treat-to-target strategies in IBD. *Gastroenterology.* 2021;160(5):1570-1583.
15. Tran F, Schirmer JH, Ratjen I, et al. Patient reported outcomes in chronic inflammatory diseases: current state, limitations and perspectives. *Front Immunol.* 2021;12:614653.
16. Rochelle TL, Fidler H. The importance of illness perceptions, quality of life and psychological status in patients with ulcerative colitis and Crohn's disease. *J Health Psychol.* 2013;18(7):972-983.
17. D'Haens G, Panaccione R, Baert F, et al. Risankizumab as induction therapy for Crohn's disease. *Lancet.* 2022;In press.
18. Ferrante M, Panaccione R, Baert F, et al. Risankizumab as maintenance therapy for moderately to severely active Crohn's disease: results from the phase 3 FORTIFY maintenance trial. *Lancet.* 2022;In press.
19. Guyatt G, Mitchell A, Irvine EJ, et al. A new measure of health status for clinical trials in inflammatory bowel disease. *Gastroenterology.* 1989;96(3):804-810.
20. Irvine EJ, Feagan B, Rochon J, et al. Quality of life: a valid and reliable measure of therapeutic efficacy in the treatment of inflammatory bowel disease. Canadian Crohn's Relapse Prevention Trial Study Group. *Gastroenterology.* 1994;106(2):287-296.

21. Alrubaiy L, Rikaby I, Dodds P, Hutchings HA, Williams JG. Systematic review of health-related quality of life measures for inflammatory bowel disease. *J Crohns Colitis.* 2015;9(3):284-292.
22. Irvine EJ. Development and subsequent refinement of the inflammatory bowel disease questionnaire: a quality-of-life instrument for adult patients with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr.* 1999;28(4):S23-27.
23. Williet N, Sandborn WJ, Peyrin-Biroulet L. Patient-reported outcomes as primary end points in clinical trials of inflammatory bowel disease. *Clin Gastroenterol Hepatol.* 2014;12(8):1246-1256.e1246.
24. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for industry—Patient reported outcome measures: Use in medical product development to support labeling claims. 2009. Available at: http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf. Accessed December 20, 2021.
25. European Medicines Agency. Guideline on the development of new medicinal products for the treatment of Crohn's disease. 2018. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-development-new-medicinal-products-treatment-crohns-disease-revision-2_en.pdf. Accessed December 20, 2021.
26. Fletcher J, Cooper SC, Swift A. Patient-reported outcomes in inflammtory bowel disease: a measurement of effect in research and clinical care. *Gastroenterol Insights.* 2021;12:225-237.
27. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care.* 1992;30(6):473-483.
28. Coteur G, Feagan B, Keininger DL, Kosinski M. Evaluation of the meaningfulness of health-related quality of life improvements as assessed by the SF-36 and the EQ-5D VAS in patients with active Crohn's disease. *Aliment Pharmacol Ther.* 2009;29(9):1032-1041.

29. Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res.* 2013;22(7):1717-1727.
30. Functional Assessment of Chronic Illness Therapy – Fatigue Scale. Available at: https://www.facit.org/measures/FACIT-Fatigue. Accessed June 13, 2022.
31. Tinsley A, Macklin EA, Korzenik JR, Sands BE. Validation of the functional assessment of chronic illness therapy-fatigue (FACIT-F) in patients with inflammatory bowel disease. *Aliment Pharmacol Ther.* 2011;34(11-12):1328-1336.
32. Reilly MC, Gerlier L, Brabant Y, Brown M. Validity, reliability, and responsiveness of the work productivity and activity impairment questionnaire in Crohn's disease. *Clin Ther.* 2008;30(2):393-404.
33. Sandborn WJ, Reilly MC, Brown MCJ, Brabant Y, Gerlier L. Minimally important difference for WPAI:CD scores: defining relevant impact on work productiviity in active Crohn's disease. *Am J Gastroenterol.* 2007;102:S472.
34. D'Silva A, Fox DE, Nasser Y, et al. Prevalence and risk factors for fatigue in adults with inflammatory bowel disease: a systematic review with meta-analysis. *Clin Gastroenterol Hepatol.* 2021.
35. Truyens M, De Ruyck E, Gonzales GB, Bos S, Laukens D, De Vos M. Prevalence of fatigue and unrecognized depression in patients with inflammatory bowel disease in remission under immunosuppressants and biologicals. *J Clin Med.* 2021;10(18).
36. Nocerino A, Nguyen A, Agrawal M, Mone A, Lakhani K, Swaminath A. Fatigue in inflammatory bowel diseases: etiologies and management. *Adv Ther.* 2020;37(1):97-112.
37. Borren NZ, van der Woude CJ, Ananthakrishnan AN. Fatigue in IBD: epidemiology, pathophysiology and management. *Nat Rev Gastroenterol Hepatol.* 2019;16(4):247-259.
38. Dulai PS, Jairath V, Khanna R, et al. Development of the symptoms and impacts questionnaire for Crohn's disease and ulcerative colitis. *Aliment Pharmacol Ther.* 2020;51(11):1047-1066.

39. Higgins PDR, Harding G, Leidy NK, et al. Development and validation of the Crohn's disease patient-reported outcomes signs and symptoms (CD-PRO/SS) diary. *J Patient Rep Outcomes.* 2017;2(1):24.
40. Farrell D, McCarthy G, Savage E. Self-reported symptom burden in individuals with inflammatory bowel disease. *J Crohns Colitis.* 2016;10(3):315-322.
41. Manceur AM, Ding Z, Muser E, et al. Burden of Crohn's disease in the United States: long-term healthcare and work-loss related costs. *J Med Econ.* 2020;23(10):1092-1101.
42. Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG clinical guideline: management of Crohn's disease in adults. *Am J Gastroenterol.* 2018;113(4):481-517.
43. van Gennep S, Evers SW, Rietdijk ST, et al. High disease burden drives indirect costs in employed inflammatory bowel disease patients: The WORK-IBD study. *Inflamm Bowel Dis.* 2021;27(3):352-363.
44. Gibson TB, Ng E, Ozminkowski RJ, et al. The direct and indirect cost burden of Crohn's disease and ulcerative colitis. *J Occup Environ Med.* 2008;50(11):1261-1272.
45. Park KT, Ehrlich OG, Allen JI, et al. The cost of inflammatory bowel disease: an initiative from the Crohn's & Colitis Foundation. *Inflamm Bowel Dis.* 2020;26(1):1-10.
46. US Bureau of Labor Statistics. Average hourly and weekly earnings of all employees on private nonfram payrolls by industry section, seasonly adjusted. Available at: https://www.bls.gov/news.release/empsit.t19.htm# Accessed December 16, 2021.
47. Clark D. Hourly labor cost in European countries 2020. Available at: https://www.statista.com/statistics/1211601/hourly-labor-cost-in-europe/. Accessed December 16, 2021.

TABLES

Table 1 Baseline characteristics

	ADVANCE			MOTIVATE		
	PBO IV N = 175	**RZB 600 mg IV N = 336**	**RZB 1200 mg IV N = 339**	**PBO IV N=187**	**RZB 600 mg IV N = 191**	**RZB 1200 mg IV N = 191**
Age (years), mean ± SD	37.1 ± 13.4	38.3 ± 13.3	37.0 ± 13.2	39.3 ± 13.5	40.2 ± 13.6	39.3 ± 12.9
Male, n (%)	88 (50.3)	189 (56.3)	183 (54.0)	99 (52.9)	92 (48.2)	102 (53.4)
Race						
White, n (%)	134 (76.6)	258 (76.8)	247 (72.9)	162 (86.6)	176 (92.1)	168 (88.0)
Asian, n (%)	31 (17.7)	65 (19.3)	74 (21.8)	15 (8.0)	8 (4.2)	14 (7.3)
Black or African American, n (%)	9 (5.1)	9 (2.7)	13 (3.8)	7 (3.7)	7 (3.7)	8 (4.2)
Native Hawaiian or other Pacific Islander	1 (0.6)	0	1 (0.3)	2 (1.1)	0	0
Multiple	0	4 (1.2)	4 (1.2)	1 (0.5)	0	1 (0.5)
CD duration (years), mean ± SD	8.2 ± 7.1	9.0 ± 8.8	8.9 ± 8.4	12.5 ± 9.7	10.9 ± 7.7	11.8 ± 9.1
CD location, n (%)						
Ileal only	19 (10.9)	52 (15.5)	54 (15.9)	26 (13.9)	33 (17.3)	21 (11.0)
Colonic only	70 (40.0)	115 (34.2)	118 (34.8)	73 (39.0)	75 (39.3)	74 (38.7)
Ileal-colonic	86 (49.1)	169 (50.3)	167 (49.3)	88 (47.1)	83 (43.5)	96 (50.3)
Baseline CDAI, mean ± SD	319.2 ± 59.4	311.2 ± 62.4	311.5 ± 68.4	319.6 ± 69.8	310.7 ± 63.6	312.5 ± 61.2
Baseline corticosteroid use, n (%)	50 (28.6)	102 (30.4)	101 (29.8)	68 (36.4)	65 (34.0)	62 (32.5)

	ADVANCE			MOTIVATE		
	PBO IV N = 175	**RZB 600 mg IV N = 336**	**RZB 1200 mg IV N = 339**	**PBO IV N=187**	**RZB 600 mg IV N = 191**	**RZB 1200 mg IV N = 191**
Failed >1 prior biologics, n (%)	56 (32.0)	95 (28.3)	101 (29.8)	99 (52.9)	99 (51.8)	103 (53.9)
IBDQ total score	122.7 ± 32.5	119.7 ± 31.3	123.9 ± 32.7	115.0 ± 31.9	119.4 ± 28.7	122.0 ± 31.2
IBDQ domain scores						
Bowel symptom	39.2 ± 9.9	38.5 ± 9.1	39.2 ± 9.8	36.5 ± 9.0	38.5 ± 9.1	38.5 ± 9.2
Emotional function	47.8 ± 13.8	46.2 ± 13.6	48.0 ± 13.7	45.4 ± 14.6	45.9 ± 12.8	48.1 ± 13.5
Social function	19.5 ± 7.3	19.1 ± 7.4	20.1 ± 7.6	18.1 ± 7.3	19.0 ± 6.8	19.5 ± 7.6
Systemic symptom	16.2 ± 5.7	15.8 ± 5.4	16.6 ± 5.5	15.1 ± 5.0	16.1 ± 4.9	15.9 ± 5.3
CSS	39.4 ± 8.4	39.8 ± 7.5	39.6 ± 8.4	42.2 ± 8.0	40.0 ± 7.8	41.2 ± 8.5
SF-36 PCS	38.9 ± 7.6	38.2 ± 7.2	39.1 ± 7.6	37.2 ± 7.0	38.0 ± 7.5	37.7 ± 8.0
SF-36 MCS	40.0 ± 9.7	38.0 ± 10.5	39.1 ± 10.8	37.9 ± 10.8	38.4 ± 10.5	39.7 ± 10.5
EQ-5D-5L VAS	49.2 ± 19.4	50.0 ± 19.2	51.0 ± 18.4	45.6 ± 17.7	48.9 ± 19.5	49.7 ± 21.1
FACIT-F	25.8 ± 11.2	24.1 ± 11.5	25.7 ± 11.1	21.5 ± 10.8	23.5 ± 9.6	23.4 ± 11.3
WPAI-CD						
Work time missed [a] (%)	21.6 ± 30.0	23.7 ± 29.0	25.9 ± 32.7	28.4 ± 32.8	29.7 ± 33.0	24.0 ± 31.7
Impairment while working [a] (%)	50.1 ± 23.9	51.6 ± 24.8	48.6 ± 22.0	52.3 ± 24.7	49.9 ± 22.7	48.7 ± 23.5
Overall work impairment [a] (%)	58.6 ± 26.5	60.9 ± 27.6	59.8 ± 27.4	63.6 ± 27.6	63.1 ± 26.5	58.6 ± 28.4
Activity impairment (%)	59.5 ± 23.0	59.9 ± 24.2	55.8 ± 25.4	62.6 ± 25.4	60.1 ± 23.1	59.4 ± 25.6

[a]Reported only for patients who were employed at baseline. Approximately 57% of patients in ADVANCE and 52% of patients in MOTIVATE were employed at baseline.

CD, Crohn's disease; CDAI, Crohn's disease activity index; CSS, Crohn's symptom severity; EQ-5D-5L, EuroQol 5 Dimension 5 Level quality of life survey; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; IBDQ, Inflammatory Bowel Disease Questionnaire; IV, intravenous; MCS, mental component summary; PBO, placebo; PCS, physical component summary; RZB, risankizumab; SD, standard deviation; SF-36, 36-item Short Form Health Survey; VAS, visual analogue scale, WPAI-CD, Work Productivity and Activity Impairment questionnaire in Crohn's Disease.

FIGURE LEGENDS

Figure 1. Percentage of patients achieving IBDQ response and IBDQ remission at Weeks 4, 12, and 52.

A. IBDQ response was defined as an increase ≥16 points from induction baseline in IBDQ total score.

B. IBDQ remission was defined as IBDQ total score ≥170 points.

*p<0.05, **p≤0.01, ***p<0.001 for PBO vs RZB.

CI confidence interval; IBDQ, inflammatory bowel disease questionnaire; IV, intravenous; PBO, placebo; RZB, risankizumab; SC, subcutaneous.

Figure 2. Percentage of patients who achieved MWPC threshold in CSS and FACIT-F at Weeks 12 and 52.

A. CSS response was defined as an increase ≥9 points from induction baseline in CSS score.

*p<0.05, **p≤0.01, ***p<0.001 for PBO vs RZB.

B. FACIT-F response was defined as an increase ≥9 points from induction baseline in FACIT-F score.

CI, confidence interval; CSS, Crohn's symptom severity; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; IV, intravenous; RZB, risankizumab; SC, subcutaneous; SF-36, 36-item Short Form Health Survey.

Figure 3. Percentage of patients who achieved MWPC threshold in SF-36 PCS, SF-36 MCS and EQ-5D-5L VAS at Weeks 12 and 52

A. SF-36 PCS response was defined as an increase ≥4.1 points from induction baseline in SF-36 PCS score.

B. SF-36 MCS response was defined as an increase ≥3.9 points from induction baseline in SF-36 MCS score.

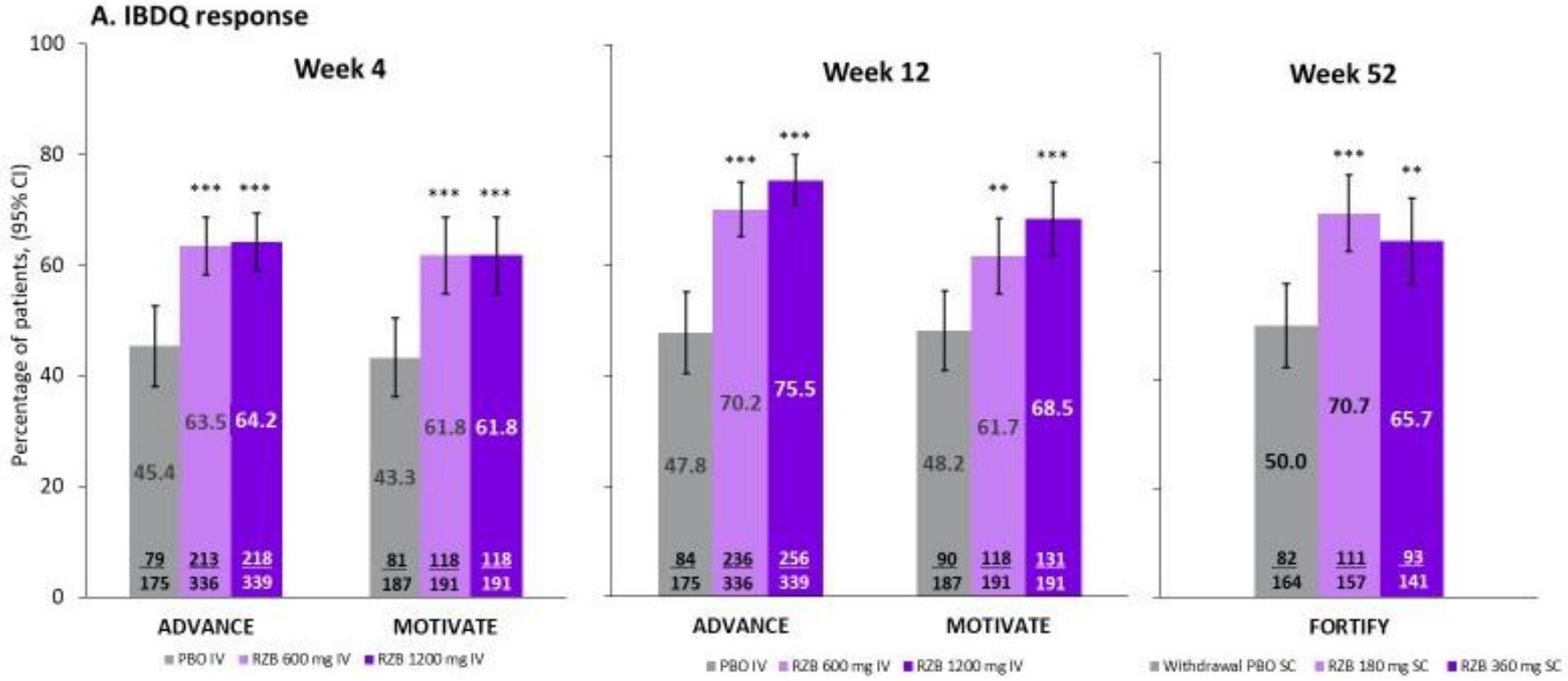
C. EQ-5D-5L response was defined as an increase ≥9.2 points from induction baseline in EQ-5D-5L VAS score.

*p<0.05, **p≤0.01, ***p<0.001 for PBO vs RZB.

CI, confidence interval; EQ-5D-5L, EuroQol 5 Dimension 5 Level quality of life survey; IV, intravenous; MCS, mental component summary; PBO, placebo; PCS, physical component summary; RZB, risankizumab; SC, subcutaneous; SF-36, 36-item Short Form Health Survey.

FIGURES

Figure 1. Percentage of patients achieving IBDQ response and IBDQ remission at Weeks 4, 12, and 52.



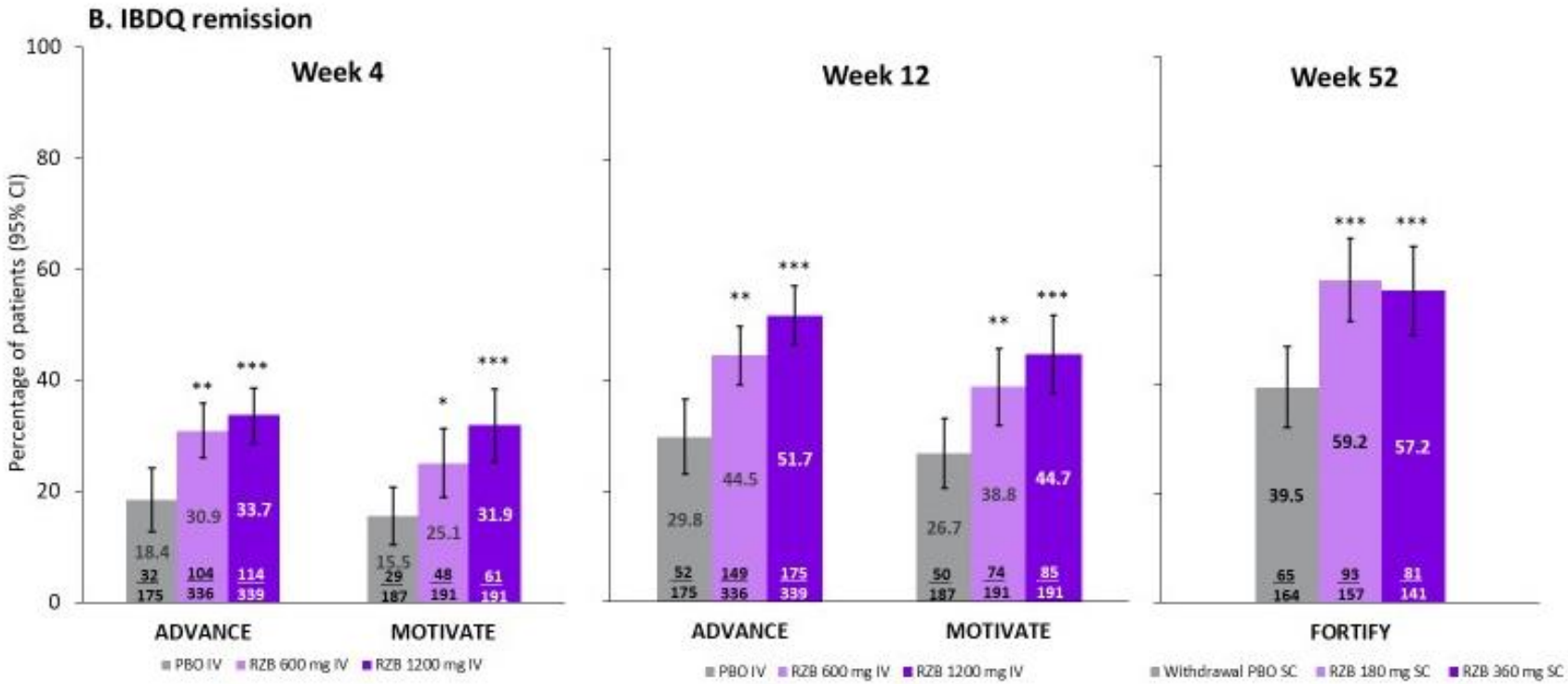

B. IBDQ remission
Week 4
Week 12
Week 52
Percentage of patients (95% CI)
100
80
60
40
20
0
18.4
30.9
33.7
15.5
25.1
31.9
29.8
44.5
51.7
26.7
38.8
44.7
39.5
59.2
57.2
32/175
104/336
114/339
29/187
48/191
61/191
52/175
149/336
175/339
50/187
74/191
85/191
65/164
93/157
81/141
ADVANCE
MOTIVATE
ADVANCE
MOTIVATE
FORTIFY
PBO IV
RZB 600 mg IV
RZB 1200 mg IV
PBO IV
RZB 600 mg IV
RZB 1200 mg IV
Withdrawal PBO SC
RZB 180 mg SC
RZB 360 mg SC

Figure 2. Percentage of patients who achieved MWPC threshold in CSS and FACIT-F at Weeks 12 and 52

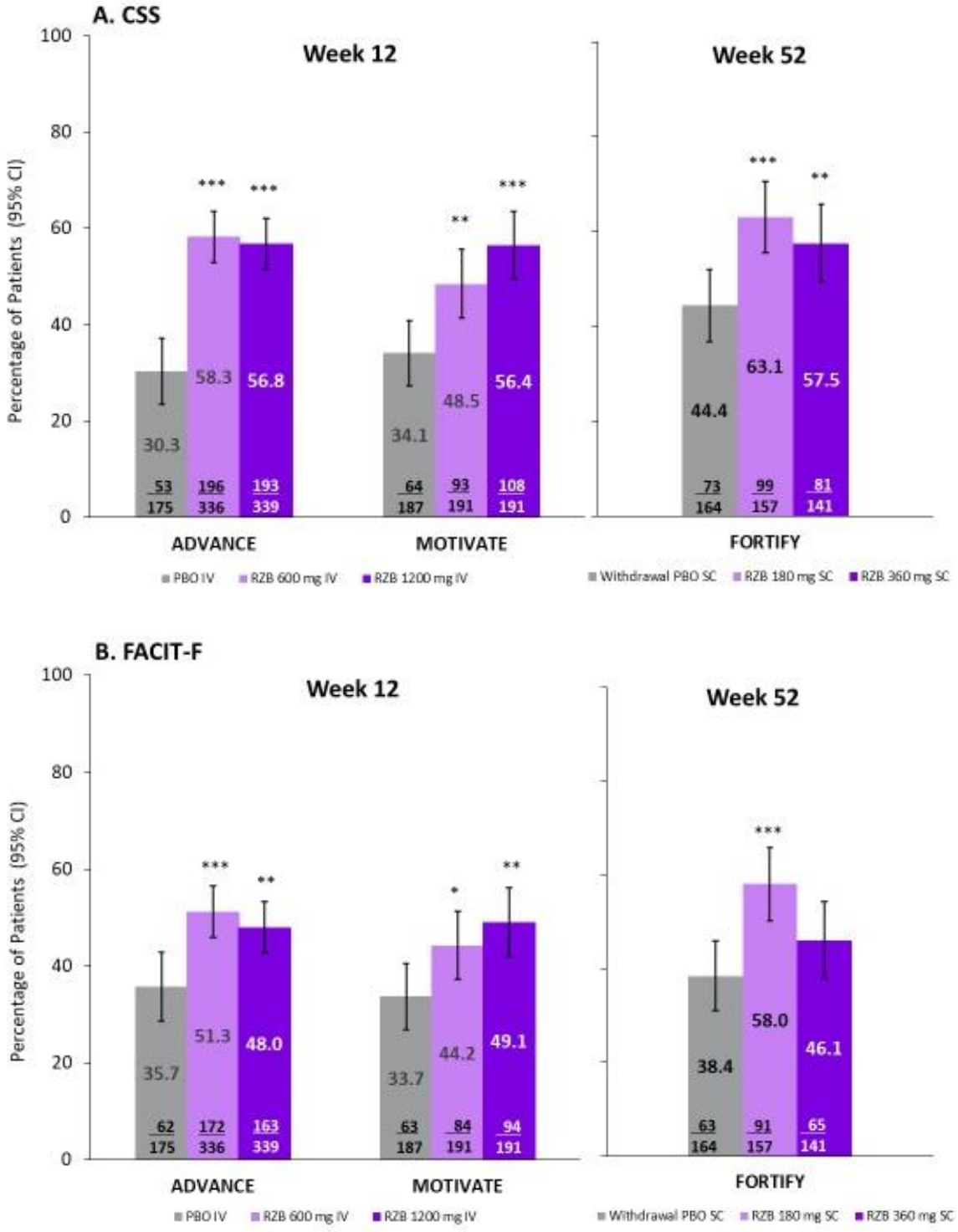
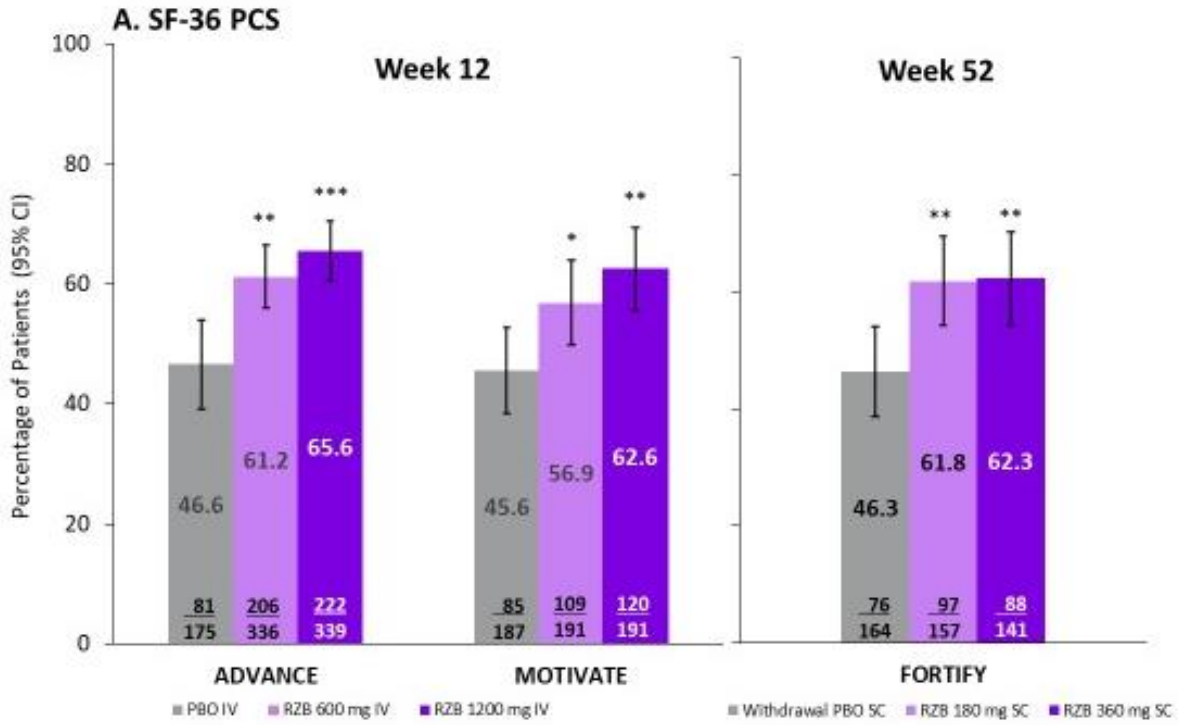
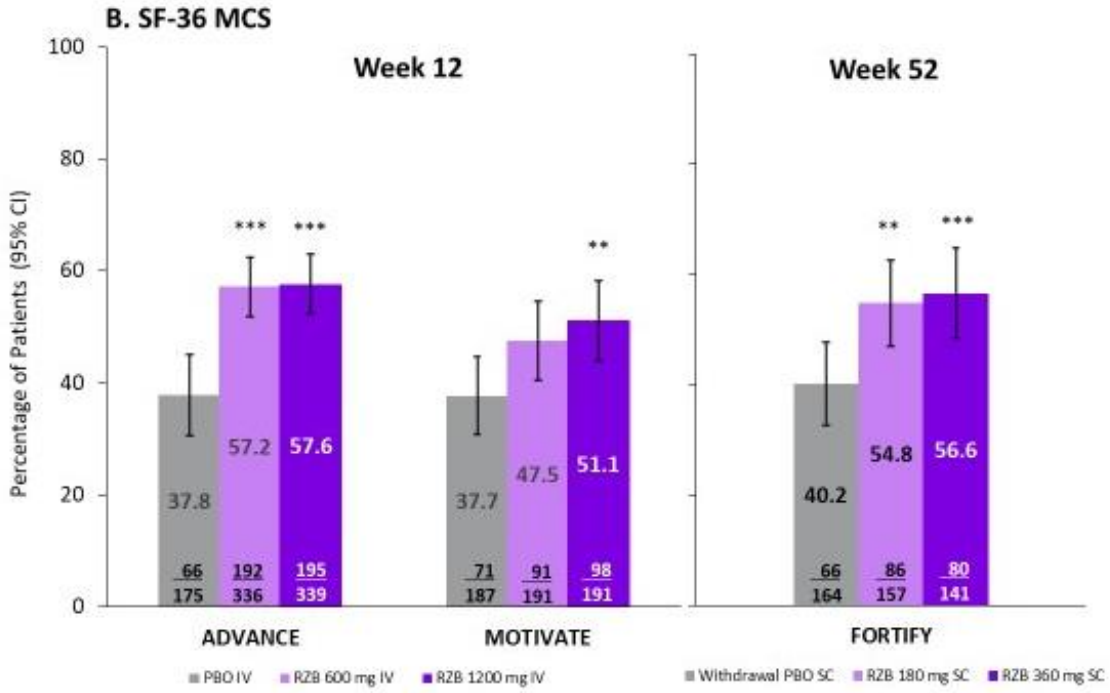
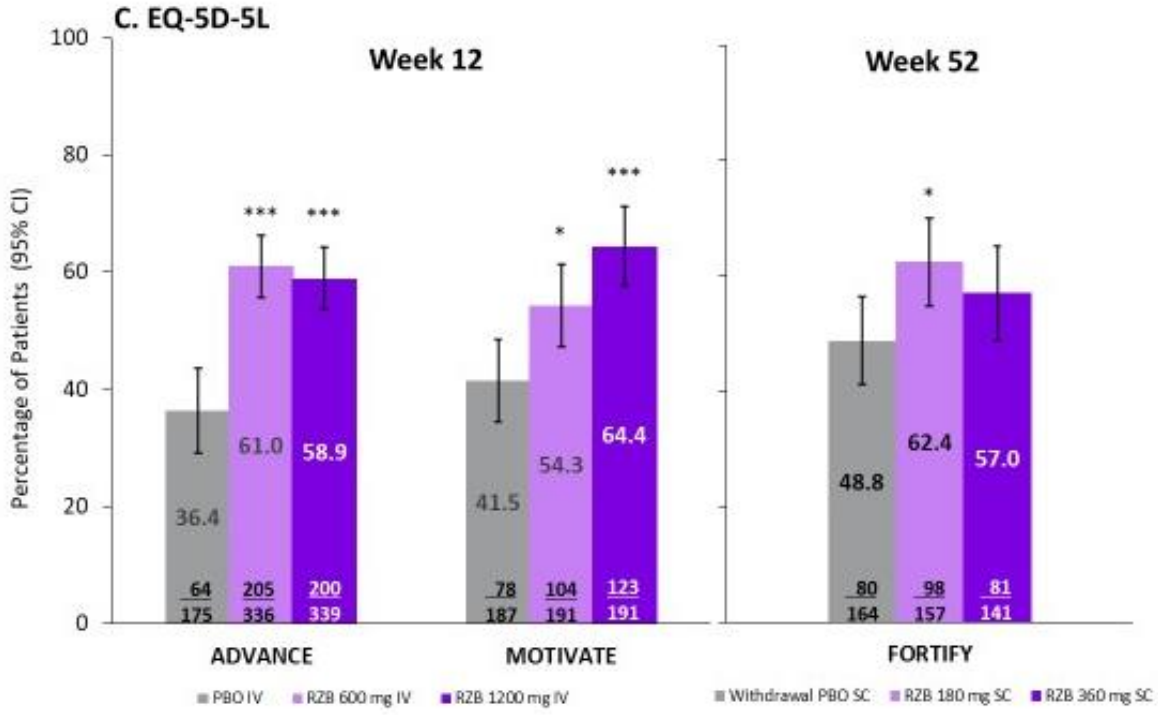


Figure 3. Percentage of patients who achieved MWPC threshold in SF-36 PCS, SF-36 MCS and EQ-5D-5L VAS at Weeks 12 and 52






C. EQ-5D-5L
Week 12
Week 52
Percentage of Patients (95% CI)
100
80
60
40
20
0
***
***
*
***
*
36.4
61.0
58.9
41.5
54.3
64.4
48.8
62.4
57.0
64
205
200
78
104
123
80
98
81
175
336
339
187
191
191
164
157
141
ADVANCE
MOTIVATE
FORTIFY
PBO IV
RZB 600 mg IV
RZB 1200 mg IV
Withdrawal PBO SC
RZB 180 mg SC
RZB 360 mg SC

APPENDIX

FACIT-Fatigue

The Functional Assessment of Chronic Illness Therapy (FACIT) measurement system is a comprehensive compilation of questions that measure health-related quality of life in patients with cancer and chronic diseases. General information, a list of statements in the measure, and the scoring manual for the FACIT subscale used in this study can be found at https://www.facit.org/measures/FACIT-Fatigue.

Anchor-based Methodology

Using data generated from the two induction studies (ADVANCE and MOTIVATE), anchor-based methods were employed to generate results that could be used as a treatment responder definition of the observed within-person change for the FACIT-F total score and the Crohn's symptom severity (CSS) score. In anchor-based approaches, external indicators are used to identify patients who have experienced an improvement, no change, or deterioration on the concept being measured, or the broader condition under evaluation.

For this study, the FACIT-F total score and CSS score were anchored to categories defined by Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC) scores between Baseline and Week 12. A one- to two-point improvement on the seven-level PGIS, and a seven-level PGIC response of 'minimally improved' and 'much improved', were used as the main definitions of improvement for the two anchors. These were used to estimate the meaningful within-person change

for the FACIT-F total score change and the CSS score change from baseline, according to the FDA guidance.[1]

Statistical assumptions for power calculations

Power calculations for ADVANCE determined that, assuming a clinical remission rate of 27.8% for risankizumab and 12% for the placebo, a sample size of 342 patients for each risankizumab group and 171 patients in the placebo group has 97% power to detect a treatment difference between risankizumab and placebo in clinical remission at Week 12 using a Fischer's exact test at alpha of 0.025 (two-sided). Assuming an endoscopic response rate of 25.5% for risankizumab and 8% for placebo, this sample size has 99% power to detect a treatment difference between risankizumab and placebo at Week 12 in endoscopic response rate. Power calculations for the MOTIVATE trial determined that, assuming a clinical remission rate of 23.5% for risankizumab and 10% for placebo, a sample size of 193 patients per treatment group has 89% power to detect a difference between risankizumab and placebo in clinical remission rates at Week 12 using Fischer's exact test at alpha of 0.025 (two-sided). Assuming an endoscopic response rate of 17% for risankizumab and 5% for placebo, this sample size has 93% power to detect a difference between risankizumab and placebo at Week 12 in endoscopic response rates. Power calculations for the FORTIFY trial determined that, assuming a clinical remission rate of 40% for risankizumab and 20% for the withdrawal placebo group, a sample size of 150 patients in each

[1] United States Food and Drug Administration. Patient-focused drug development guidance public workshop. Methods to identify what is important to patients and select, develop, or modify fit-for-purpose clinical outcomes assessments workshop. October 15-16, 2018. https://www.fda.gov/drugs/news-events-human-drugs/patient-focused-drug-development-guidance-methods-identify-what-important-patients-and-select. Accessed March 11, 2022.

treatment group has 92% power to detect a treatment difference between risankizumab and placebo at Week 52 using Fisher's exact test at alpha of 0.05 (two-sided). Assuming an endoscopic response rate of 36% for risankizumab and 10% for withdrawal placebo, this sample size has 99% power to detect a treatment difference between risankizumab and placebo at Week 52 in endoscopic response rates.

Appendix Table 1. Change from induction baseline in patient reported outcomes at Week 12

	ADVANCE					MOTIVATE				
	Change from induction baseline			Adjusted treatment difference		Change from induction baseline			Adjusted treatment difference	
Mean change (95% CI)	**PBO IV N = 175**	**RZB 600 mg IV N = 336**	**RZB 1200 mg IV N = 339**	**RZB 600 mg IV vs PBO IV**	**RZB 1200 mg IV vs PBO IV**	**PBO IV N = 187**	**RZB 600 mg IV N = 191**	**RZB 1200 mg IV N = 191**	**RZB 600 mg IV vs PBO IV**	**RZB 1200 mg IV vs PBO IV**
IBDQ total score	n=134 23.6 (18.2, 28.9)	n=302 44.3 (40.6, 48.0)	n=310 43.0 (39.4, 46.6)	20.7 (14.3, 27.1) ***	19.4 (13.1, 25.8) ***	n=144 27.2 (21.8, 32.6)	n=168 39.6 (34.5, 44.7)	n=172 42.2 (37.1, 47.3)	12.4 (5.0, 19.8) **	15.0 (7.7, 22.4) ***
IBDQ domain scores										
Bowel symptom	n=134 7.9 (6.2, 9.5)	n=302 14.9 (13.7, 16.0)	n=310 14.4 (13.2, 15.5)	7.0 (5.0, 9.0) ***	6.5 (4.5, 8.5) ***	n=144 9.1 (7.4, 10.8)	n=168 13.3 (11.7, 14.8)	n=172 14.6 (13.1, 16.2)	4.1 (1.9, 6.4) ***	5.5 (3.2, 7.8) ***
Emotional function	n=134 7.9 (5.8, 10.0)	n=302 14.9 (13.4, 16.3)	n=310 14.4 (13.0, 15.8)	7.0 (4.5, 9.5) ***	6.5 (4.0, 9.0) ***	n=144 9.4 (7.2, 11.5)	n=168 13.2 (11.2, 15.2)	n=172 13.7 (11.7, 15.7)	3.8 (0.9, 6.7) **	4.3 (1.4, 7.2) **
Social function	n=134 4.0 (2.9, 5.0)	n=302 7.4 (6.7, 8.2)	n=310 7.2 (6.5, 7.9)	3.5 (2.2, 4.8) ***	3.2 (2.0, 4.5) ***	n=144 4.5 (3.5, 5.6)	n=168 7.0 (6.0, 8.0)	n=172 7.2 (6.2, 8.2)	2.4 (1.0, 3.9) **	2.7 (1.2, 4.1) ***
Systemic symptom	n=134 4.1 (3.1, 5.1)	n=302 7.1 (6.4, 7.8)	n=310 7.1 (6.4, 7.8)	2.9 (1.8, 4.1) ***	3.0 (1.8, 4.2) ***	n=144 4.3 (3.3, 5.3)	n=168 6.2 (5.3, 7.1)	n=172 6.8 (5.9, 7.7)	1.9 (0.6, 3.2) **	2.5 (1.2, 3.8) ***
CSS	n=132 –6.0 (–7.4, –4.6)	n=306 –11.5 (–12.4, –10.6)	n=312 –11.2 (–12.1, –10.3)	–5.5 (–7.1, –3.9) ***	–5.2 (–6.8, –3.6) ***	n=145 –7.5 (–8.9, –6.1)	n=167 –11.0 (–12.3, –9.7)	n=172 –11.8 (–13.1, –10.5)	3.5 (–5.4, –1.6) ***	–4.3 (–6.1, –2.4) ***
SF-36 PCS	n=134 5.5 (4.3, 6.7)	n=302 8.4 (7.6, 9.2)	n=309 8.8 (8.0, 9.6)	2.9 (1.5, 4.3) ***	3.3 (1.9, 4.7) ***	n=142 5.2 (4.0, 6.4)	n=167 7.5 (6.3, 8.6)	n=172 8.0 (6.8, 9.1)	2.2 (0.6, 3.9) **	2.7 (1.1, 4.4) **
SF-36 MCS	n=134 3.8 (2.3, 5.3)	n=302 7.6 (6.6, 8.7)	n=309 7.3 (6.2, 8.3)	3.8 (2.0, 5.6) ***	3.5 (1.7, 5.3) ***	n=142 4.9 (3.4, 6.4)	n=167 7.0 (5.6, 8.4)	n=172 6.0 (4.6, 7.5)	2.1 (0.1, 4.2) *	1.2 (–0.9, 3.2) NS

EQ-5D-5L VAS	n=134 9.8 (6.7, 13.0)	n=303 19.1 (17.0, 21.3)	n=310 18.6 (16.5, 20.8)	9.3 (5.6, 13.1) ***	8.8 (5.1, 12.5) ***	n=144 10.7 (7.8, 13.7)	n=168 18.4 (15.6, 21.2)	n=173 20.3 (17.5, 23.0)	7.7 (3.7, 11.7) ***	9.6 (5.6, 13.5) ***
FACIT-F	n=134 6.0 (4.4, 7.7)	n=302 11.2 (10.1, 12.4)	n=310 10.1 (9.0, 11.3)	5.2 (3.2, 7.2) ***	4.1 (2.1, 6.1) ***	n=144 7.7 (6.0, 9.4)	n=168 10.5 (8.9, 12.1)	n=172 10.8 (9.2, 12.4)	2.8 (0.4, 5.1) *	3.0 (0.7, 5.3) **
WPAI-CD										
Work time missed [a] (%)	n=65 3.5 (–2.9, 10.0)	n=156 –3.3 (–7.5, 1.0)	n=162 –6.6 (–10.8, –2.5)	–6.8 (–14.5, 0.8) NS	–10.2 (–17.8, –2.6) **	n=68 –3.3 (–9.6, 3.0)	n=73 –6.8 (–12.9, –0.7)	n=86 –7.7 (–13.2, –2.1)	–3.5 (–12.0, 5.1 NS)	–4.4 (–12.6, 3.9) NS
Impairment while working [a] (%)	n=59 –12.2 (–18.0, –6.5)	n=142 –20.7 (–24.6, –16.9)	n=144 –21.1 (–24.9, –17.3)	–8.5 (–15.4, –1.6) *	–8.9 (–15.7, –2.0) *	n=61 –14.6 (–20.1, –9.0)	n=67 –20.6 (–25.9, –15.3)	n=73 –21.3 (–26.3, –16.2)	–6.0 (–13.5, 1.5) NS	–6.7 (–14.0, 0.6) NS
Overall work impairment [a] (%)	n=65 –8.3 (–15.4, –1.3)	n=156 –17.9 (–22.5, –13.3)	n=162 –20.5 (–25.0, –15.9)	–9.6 (–17.9, –1.3) *	–12.1 (–20.4, –3.9) **	n=68 –12.3 (–18.9, –5.6)	n=73 –19.6 (–26.0, –13.1)	n=86 –21.0 (–26.9, –15.1)	–7.3 (–16.4, 1.8) NS	–8.8 (–17.5, –0.0) *
Activity impairment (%)	n=133 –13.4 (–17.7, –9.1)	n=301 –22.4 (–25.4, –19.5)	n=308 –23.0 (–25.9, –20.1)	–9.1 (–14.1, –4.0) ***	–9.6 (–14.7, –4.5) ***	n=142 –14.0 (–17.9, –10.1)	n=167 –23.8 (–27.4, –20.1)	n=172 –21.5 (–25.2, –17.9)	–9.7 (–15.0, 4.5) ***	–7.5 (–12.8, –2.3) **

*$p \leq 0.05$; **$p \leq 0.01$; ***$p < 0.001$ for RZB versus PBO.

[a]Reported only for patients who were employed.

CI, confidence interval; CSS, Crohn's symptom severity; EQ-5D-5L, EuroQol 5 Dimension 5 Level quality of life survey; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; IBDQ, Inflammatory Bowel Disease Questionnaire; IV, intravenous; LS, least squares; MCS, mental component summary; NS, not statistically significant; PBO, placebo; PCS, physical component summary; RZB, risankizumab; SF-36, 36-item Short Form Health Survey; VAS, visual analogue scale; WPAI-CD, Work Productivity and Activity Impairment questionnaire in Crohn's Disease.

Appendix Table 2. Change from induction baseline in patient-reported outcomes at Week 52 (excluding data points after censoring)

Mean change (95% CI)	FORTIFY				
	Change from induction baseline			Adjusted treatment difference	
	Withdrawal PBO SC N = 164	RZB 180 mg SC N = 157	RZB 360 mg SC N = 141	RZB 180 mg SC vs PBO SC	RZB 360 mg SC vs PBO SC
IBDQ total score	n=93 56.4 (51.3, 61.6)	n=117 60.9 (56.3, 65.5)	n=104 62.2 (57.4, 67.0)	4.5 (–2.3, 11.3) NS	5.8 (–1.2, 12.8) NS
IBDQ domain scores					
Bowel symptom	n=93 18.1 (16.4, 19.8)	n=117 19.7 (18.1, 21.2)	n=104 19.9 (18.3, 21.5)	1.6 (–0.7, 3.8) NS	1.8 (–0.6, 4.1) NS
Emotional function	n=93 18.9 (16.9, 21.0)	n=117 20.3 (18.5, 22.1)	n=104 21.6 (19.7, 23.5)	1.3 (–1.4, 4.0) NS	2.6 (–0.1, 5.4) NS
Social function	n=93 9.8 (8.9, 10.7)	n=117 10.9 (10.1, 11.7)	n=104 10.6 (9.7, 11.4)	1.1 (–0.1, 2.4) NS	0.8 (–0.5, 2.0) NS
Systemic symptom	n=93 9.2 (8.2, 10.2)	n=117 9.7 (8.9, 10.6)	n=104 10.4 (9.4, 11.3)	0.6 (–0.7, 1.8) NS	1.2 (–0.2, 2.5) NS
CSS	n=143 –10.1 (–11.4, –8.7)	n=140 –13.3 (–14.7, –11.9)	n=126 –12.6 (–14.1, –11.1)	3.3 (–5.2, –1.3) **	–2.6 (–4.6, –0.6) *
SF-36 PCS	n=92 11.3 (10.1, 12.6)	n=117 11.9 (10.8, 13.0)	n=103 12.0 (10.8, 13.1)	0.6 (–1.0, 2.2) NS	0.6 (–1.1, 2.3) NS
SF-36 MCS	n=92 9.1 (7.6, 10.7)	n=117 10.8 (9.4, 12.2)	n=103 11.4 (10.0, 12.8)	1.7 (–0.4, 3.7) NS	2.3 (0.2, 4.4) *
EQ-5D-5L VAS	n=93 26.6 (23.6, 29.6)	n=117 28.5 (25.8, 31.3)	n=104 29.2 (26.3, 32.0)	1.9 (–2.1, 6.0) NS	2.6 (–1.6, 6.7) NS
FACIT-F	n=93 15.0 (13.3, 16.6)	n=117 15.5 (13.9, 17.0)	n=104 15.4 (13.8, 17.0)	0.5 (–1.7, 2.7) NS	0.4 (–1.9, 2.7) NS
WPAI-CD					
Work time missed [a] (%)	n=54 –8.1 (–14.2, –2.0)	n=62 –13.9 (–19.8, –8.0)	n=50 –12.4 (–18.8, –5.9)	–5.8 (–14.4, 2.7) NS	–4.3 (–13.2, 4.6) NS
Impairment while working [a] (%)	n=46 –25.0 (–30.5, –19.6)	n=59 –29.9 (–34.9, –25.0)	n=44 –28.1 (–33.8, –22.5)	–4.9 (–12.2, 2.5) NS	–3.1 (–10.9, 4.8) NS

Mean change (95% CI)	FORTIFY				
	Change from induction baseline			Adjusted treatment difference	
	Withdrawal PBO SC N = 164	RZB 180 mg SC N = 157	RZB 360 mg SC N = 141	RZB 180 mg SC vs PBO SC	RZB 360 mg SC vs PBO SC
Overall work impairment [a] (%)	n=54 –27.0 (–34.3, –19.7)	n=62 –33.6 (–40.6, –26.7)	n=50 –29.9 (–37.6, –22.2)	–6.6 (–16.7, 3.4) NS	–2.9 (–13.5, –7.7) NS
Activity impairment (%)	n=92 –31.7 (–36.0, –27.4)	n=117 –35.0 (–38.9, –31.1)	n=102 –33.5 (–37.6, –29.4)	–3.3 (–9.0, 2.4) NS	–1.8 (–7.7, 4.1) NS

*$p \leq 0.05$; **$p \leq 0.01$; ***$p < 0.001$ for RZB versus PBO.

[a]Reported only for patients who were employed.

CI, confidence interval; CSS, Crohn's symptom severity; EQ-5D-5L, EuroQol 5 Dimension 5 Level quality of life survey; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; IBDQ, Inflammatory Bowel Disease Questionnaire; LS, least squares; MCS, mental component summary; NS, not statistically significant; PBO, placebo; PCS, physical component summary; RZB, risankizumab; SC, subcutaneous; SF-36, 36-item Short Form Health Survey; VAS, visual analog scale; WPAI-CD, Work Productivity and Activity Impairment questionnaire in Crohn's Disease.

Appendix Table 3. Change from induction baseline in patient-reported outcomes at Week 52 (including data points after censoring)

Mean change (95% CI)	FORTIFY				
	Change from induction baseline			Adjusted treatment difference	
	Withdrawal PBO SC N = 164	RZB 180 mg SC N = 157	RZB 360 mg SC N = 141	RZB 180 mg SC vs PBO SC	RZB 360 mg SC vs PBO SC
IBDQ total score	n=152 48.9 (44.6, 53.3)	n=148 57.7 (53.3, 62.2)	n=132 56.9 (52.2, 61.6)	8.8 (2.6, 14.9) **	8.0 (1.6, 14.3) *
IBDQ domain scores					
Bowel symptom	n=152 15.9 (14.4, 17.3)	n=148 18.7 (17.2, 20.1)	n=132 18.0 (16.5, 19.5)	2.8 (0.7, 4.8) **	2.1 (–0.0, 4.2) NS
Emotional function	n=152 16.1 (14.4, 17.8)	n=148 19.1 (17.4, 20.9)	n=132 19.7 (17.8, 21.5)	3.1 (0.6, 5.5) *	3.6 (1.1, 6.1) **
Social function	n=152 8.8 (8.0, 9.6)	n=148 10.4 (9.6, 11.3)	n=132 10.0 (9.1, 10.8)	1.6 (0.5, 2.8) **	1.2 (–0.0, 2.4) NS
Systemic symptom	n=152 7.9 (7.1, 8.7)	n=148 9.4 (8.5, 10.2)	n=132 9.4 (8.6, 10.3)	1.4 (0.3, 2.6) *	1.5 (0.3, 2.7) *
CSS	n=155 –13.0 (–14.2, –11.8)	n=152 –14.1 (–15.3, –12.9)	n=133 –13.4 (–14.7, –12.2)	–1.1 (–2.8, 0.5) NS	–0.5 (–2.2, 1.3) NS
SF-36 PCS	n=151 9.9 (8.9, 10.9)	n=148 11.5 (10.5, 12.5)	n=131 11.3 (10.2, 12.4)	1.6 (0.1, 3.0) *	1.4 (–0.1, 2.8) NS
SF-36 MCS	n=151 7.5 (6.3, 8.7)	n=148 9.9 (8.7, 11.1)	n=131 10.2 (8.9, 11.5)	2.4 (0.7, 4.1) **	2.7 (0.9, 4.5) **
EQ-5D-5L VAS	n=152 22.6 (19.9, 25.2)	n=148 25.9 (23.2, 28.6)	n=132 26.1 (23.2, 28.9)	3.3 (–0.4, 7.1) NS	3.5 (–0.4, 7.3) NS
FACIT-F	n=152 13.0 (11.6, 14.4)	n=148 14.8 (13.4, 16.2)	n=132 14.1 (12.6, 15.6)	1.8 (–0.1, 3.7) NS	1.1 (–0.9, 3.1) NS
WPAI-CD					
Work time missed [a] (%)	n=79 –8.7 (–13.7, –3.7)	n=77 –15.6 (–20.7, –10.5)	n=68 –11.4 (–16.7, –6.0)	–6.9 (–14.0, 0.3) NS	–2.7 (–10.0, 4.6) NS
Impairment while working [a] (%)	n=68 –22.1 (–26.7, –17.5)	n=73 –29.5 (–34.1, –25.0)	n=60 –26.9 (–31.8, –21.9)	–7.4 (–13.9, –1.0) *	–4.8 (–11.6, 2.0) NS

Mean change (95% CI)	FORTIFY				
	Change from induction baseline			Adjusted treatment difference	
	Withdrawal PBO SC N = 164	RZB 180 mg SC N = 157	RZB 360 mg SC N = 141	RZB 180 mg SC vs PBO SC	RZB 360 mg SC vs PBO SC
Overall work impairment [a] (%)	n=79 –24.6 (–30.5, –18.6)	n=77 –33.6 (–39.7, –27.5)	n=68 –27.7 (–34.1, –21.3)	–9.0 (–17.5, –0.6) *	–3.1 (–11.8, 5.6) NS
Activity impairment (%)	n=151 –26.1 (–29.6, –22.5)	n=148 –34.1 (–37.7, –30.5)	n=129 –33.2 (–37.0, –29.3)	–8.0 (–13.0, –3.0) **	–7.1 (–12.3, –1.9) **

*$p \leq 0.05$; **$p \leq 0.01$; ***$p < 0.001$ for RZB versus PBO.

[a]Reported only for patients who were employed.

CI, confidence interval; CSS, Crohn's symptom severity; EQ-5D-5L, EuroQol 5 Dimension 5 Level quality of life survey; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; IBDQ, Inflammatory Bowel Disease Questionnaire; LS, least squares; MCS, mental component summary; NS, not statistically significant; PBO, placebo; PCS, physical component summary; RZB, risankizumab; SC, subcutaneous; SF-36, 36-item Short Form Health Survey; VAS, visual analog scale; WPAI-CD, Work Productivity and Activity Impairment questionnaire in Crohn's Disease.

Appendix Table 4. Percentage of patients achieving MWPC in WPAI-CD from induction baseline to Week 12: Combined results from ADVANCE and MOTIVATE

	PBO IV			RZB 600 mg IV			RZB 1200 mg IV		
WPAI-CD domains	**N**	**n (%)**	**95% CI**	**N**	**n (%)**	**95% CI**	**N**	**n (%)**	**95% CI**
Work time missed (≥ 6.5%)	192	55 (28.8)	22.4–35.2	303	113 (37.4)*	31.9–42.0	319	117 (36.7)*	31.4–42.0
Impairment while working (≥ 6.1%)	192	70 (36.4)	29.6–43.2	303	149 (49.1)**	43.4–54.7	319	164 (51.5)**	46.0–57.0
Overall work impairment (≥ 7.3%)	192	72 (37.4)	30.5–44.2	303	151 (49.7)**	44.1–55.4	319	171 (53.6)***	48.2–59.1
Activity impairment (≥ 8.5%)	362	169 (46.7)	41.5–51.9	527	349 (66.2)***	62.2–70.3	530	346 (65.3)***	61.2–69.3

*$p \leq 0.05$; **$p \leq 0.01$; ***$p < 0.001$ for risankizumab versus placebo.

MWPC, meaningful within person change; WPAI-CD, Work Productivity and Activity Impairment questionnaire in Crohn's disease.

Appendix Figure 1. Percentage of patients who achieved MWPC threshold in WPAI-CD at Weeks 12 and 52

A. Work time missed response was defined as a ≥7.3% change from induction baseline in WPAI-CD absenteeism score.

B. Impairment while working response was defined as ≥6.1% change from induction baseline in WPAI-CD presenteeism score.

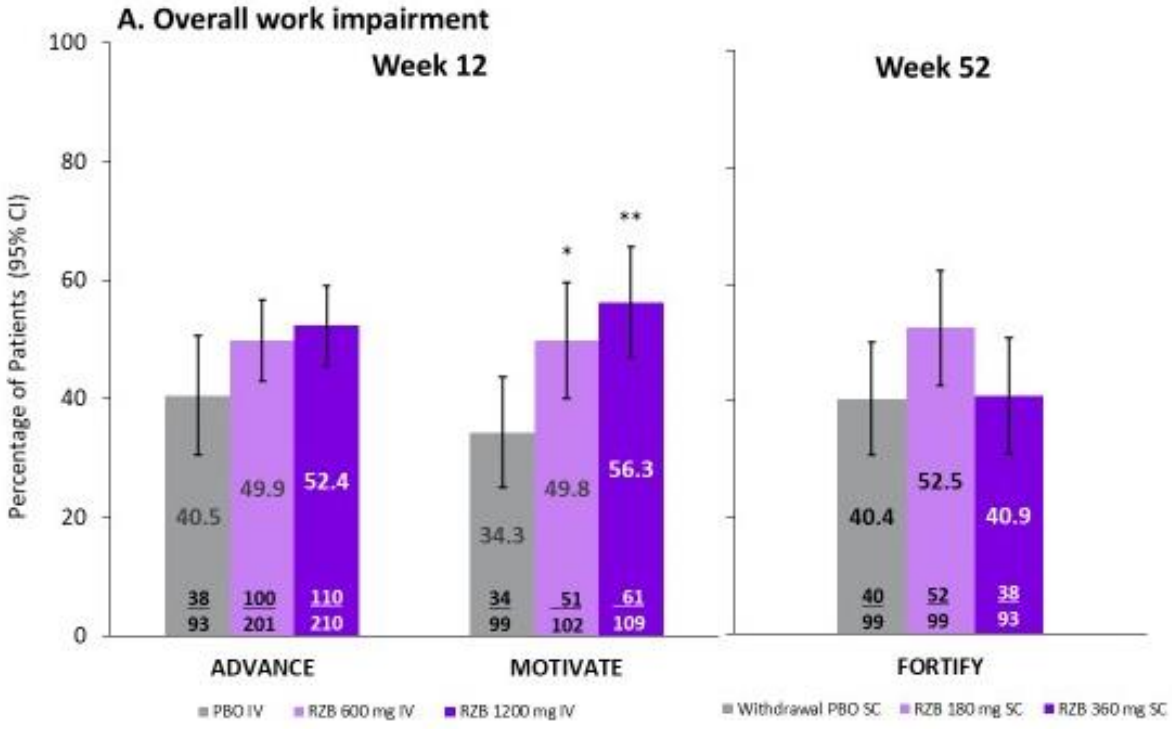
C. Overall work impairment response was defined as ≥7.3% change from induction baseline in WPAI-CD overall work impairment score.

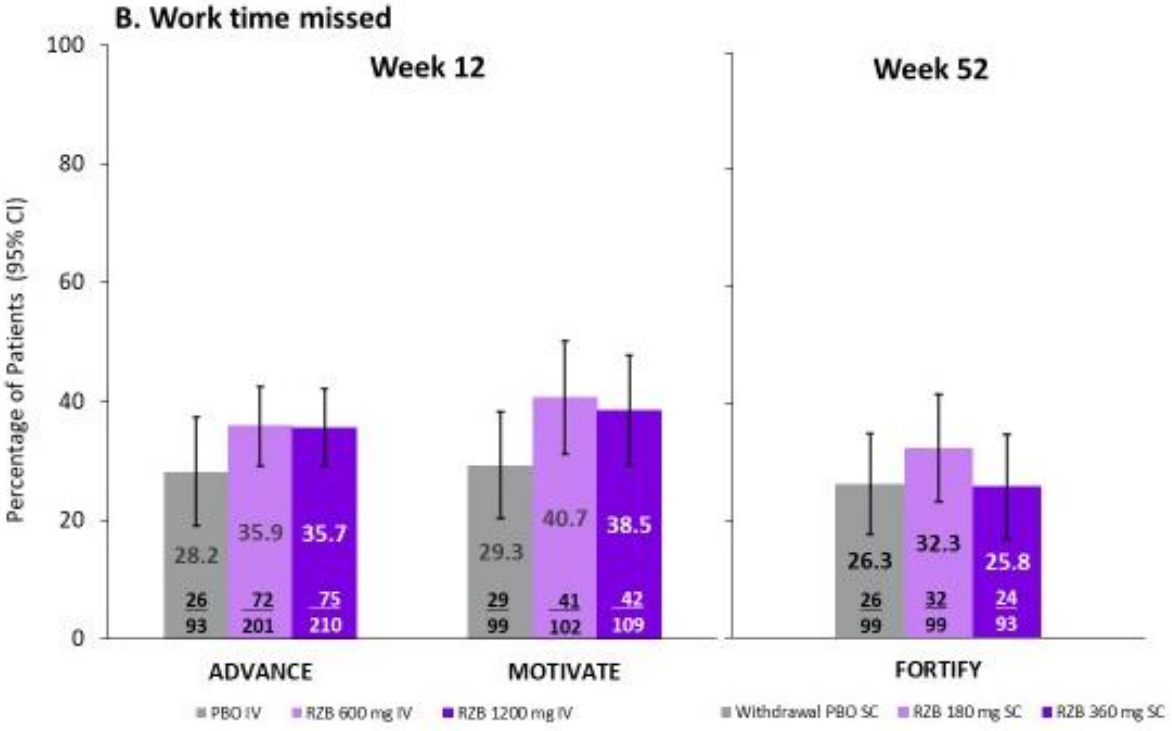
D. Activity impairment response was defined as ≥8.5% change from induction baseline in WPAI-CD activity impairment score.

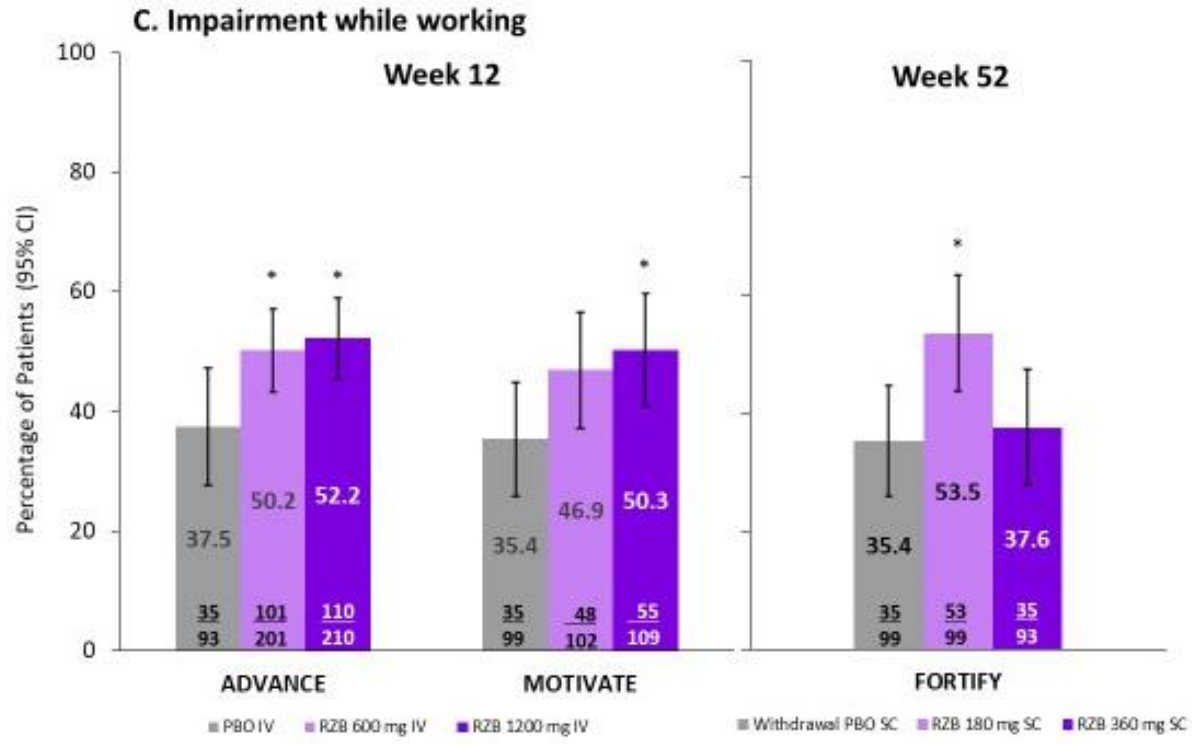
*p<0.05, **p≤0.01, ***P<0.001 for PBO vs RZB.

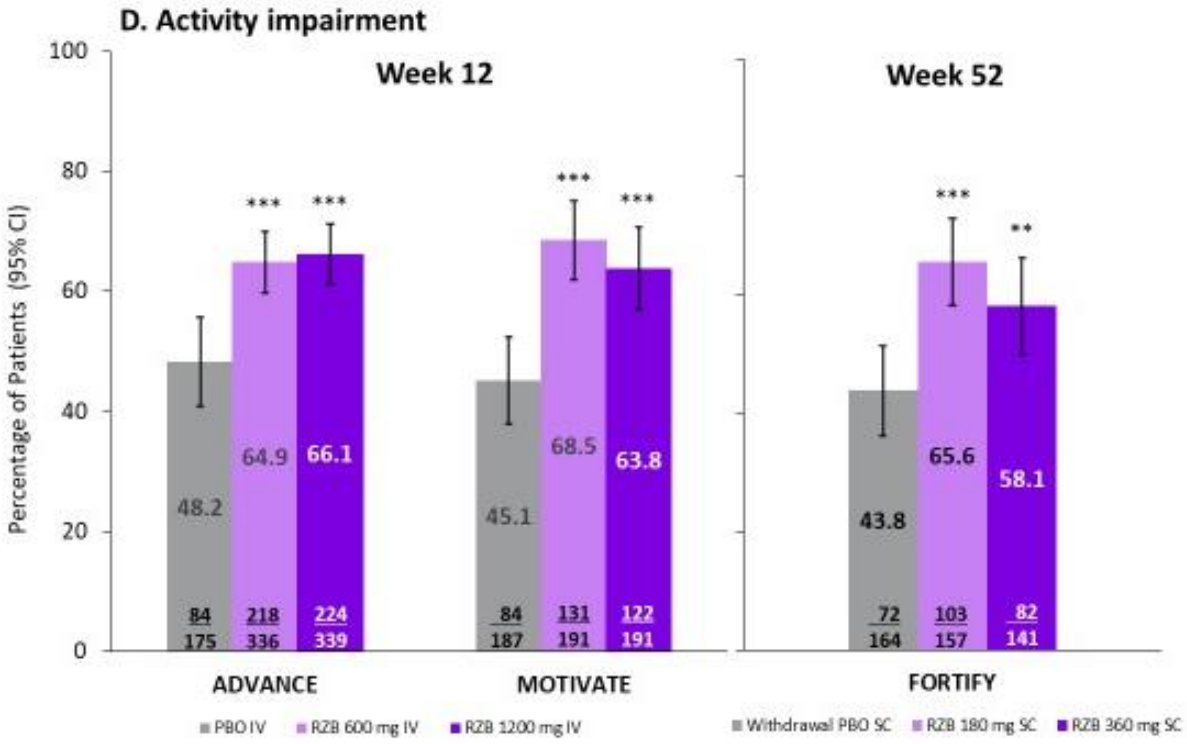
CI, confidence interval; IV, intravenous; PBO, placebo; RZB, risankizumab; SC, subcutaneous; WPAI-CD, Work Productivity and Activity Impairment questionnaire in Crohn's disease.

Appendix Figure 1. Percentage of patients who achieved MWPC threshold in WPAI-CD at Weeks 12 and 52




B. Work time missed
Week 12
Week 52
Percentage of Patients (95% CI)
100
80
60
40
20
0
28.2
35.9
35.7
29.3
40.7
38.5
26.3
32.3
25.8
26/93
72/201
75/210
29/99
41/102
42/109
26/99
32/99
24/93
ADVANCE
MOTIVATE
FORTIFY
PBO IV
RZB 600 mg IV
RZB 1200 mg IV
Withdrawal PBO SC
RZB 180 mg SC
RZB 360 mg SC


C. Impairment while working
Week 12
Week 52
Percentage of Patients (95% CI)
100
80
60
40
20
0
*
*
*
37.5
50.2
52.2
35.4
46.9
50.3
35.4
53.5
37.6
35/93
101/201
110/210
35/99
48/102
55/109
35/99
53/99
35/93
ADVANCE
MOTIVATE
FORTIFY
PBO IV
RZB 600 mg IV
RZB 1200 mg IV
Withdrawal PBO SC
RZB 180 mg SC
RZB 360 mg SC


D. Activity impairment
Week 12
Week 52
Percentage of Patients (95% CI)
100
80
60
40
20
0
***
***
***
***
**
48.2
64.9
66.1
45.1
68.5
63.8
43.8
65.6
58.1
84
175
218
336
224
339
84
187
131
191
122
191
72
164
103
157
82
141
ADVANCE
MOTIVATE
FORTIFY
PBO IV
RZB 600 mg IV
RZB 1200 mg IV
Withdrawal PBO SC
RZB 180 mg SC
RZB 360 mg SC