

## Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

## eMethods 1. Methods and Statistical Analysis for Phase 2b Induction Substudy

### Study Design and Patients:

The phase 2b substudy consisted of a dose-ranging, double-blind, placebo-controlled, multicenter 12-week induction substudy, an open-label period, and an extension period for patients that failed to achieve clinical response per Adapted Mayo score at week 12 (**eFigure 1**). The phase 2b induction substudy included a screening period of up to 35 days and an induction period of 12 weeks, with a 140-day follow-up period from the last dose of the study drug. The phase 2b/3 induction studies were operationally seamless, where patients could continue to enroll into an open-label risankizumab 1800 mg intravenous (IV) induction group during the analysis of the phase 2b dose-ranging study (**eFigure 1**).

Patients aged between 18 and 80 years of age, with moderately to severely active ulcerative colitis, defined by an Adapted Mayo score of 5 to 9 points, endoscopic subscore of 2 or 3 (confirmed by central review), and a confirmed diagnosis of ulcerative colitis for at least 3 months prior to baseline, were eligible for the study. For the phase 2b dose-ranging substudy, all patients were required to have previous intolerance or inadequate response to 1 or more prior approved advanced therapies for ulcerative colitis (including infliximab, adalimumab, golimumab, vedolizumab). Patients with prior exposure to p40 inhibitors (eg, ustekinumab) or p19 inhibitors (eg, risankizumab, mirikizumab, guselkumab) were excluded. Patients who achieved a clinical response to IV risankizumab (defined as a decrease from baseline in the Adapted Mayo score  $\geq 2$  points and  $\geq 30\%$  from baseline, in addition to a decrease in rectal bleeding score [RBS]  $\geq 1$  or an absolute RBS  $\leq 1$ ) at week 12 or 24 of induction were eligible for randomization into the risankizumab phase 3 maintenance study (**Figure 1**). A full list of inclusion and exclusion criteria is included in **eMethods 2**.

### **Randomization and Masking:**

In the dose-ranging, phase 2b induction substudy, patients were randomized 1:1:1:1 via web-based Interactive Response Technologies (IRT) to receive a single dose of IV risankizumab (600 mg [n = 61], 1200 mg [n = 61], 1800 mg [n = 58]) or placebo (n = 60) at weeks 0, 4, and 8. Randomization was stratified by baseline corticosteroid use (yes, no) and baseline Adapted Mayo score ( $\leq 7$ ,  $> 7$ ).

Additional patients were enrolled in the phase 2b study after enrollment completion of the dose-ranging substudy and received open-label risankizumab 1800 mg IV (n = 340). The randomization at baseline was stratified by baseline corticosteroid use (yes, no) and baseline Adapted Mayo score ( $\leq 7$  vs.  $> 7$ ). A  $\pm 7$ -day window was permitted around all study visits. Nonresponding patients to risankizumab phase 2b induction therapy entered an extended treatment period for an additional 12 weeks of treatment and were randomized 1:1:1 to receive either risankizumab 1800 mg IV (every 4 weeks), 180 mg subcutaneous (SC), or 360 mg SC ([every 8 weeks], not shown). Patients who achieved clinical response to risankizumab IV or SC were enrolled in maintenance to risankizumab 180 mg, risankizumab 360 mg, or placebo SC (risankizumab withdrawal group), every 8 weeks.

### **Endpoints:**

The primary endpoint was clinical remission per Adapted Mayo score at week 12. Secondary endpoints were assessed at week 12 unless noted and included clinical response per Adapted Mayo score, clinical response per Partial Adapted Mayo (week 4), histologic endoscopic mucosal remission (HEMR), endoscopic improvement, and endoscopic remission.

### **Sample Size Calculation:**

For the phase 2b substudy, assuming a clinical remission rate of 7% in the placebo group and a maximum of 25% in at least one of the risankizumab treatment groups at week 12, a sample size of 60 patients per treatment group was sufficient to test for the presence of a dose-

response signal with an average power of approximately 87% at 5% level of significance (one-sided), via modeling using the multiple comparison procedure – modeling (MCP-Mod) approach.

### **Statistical Analysis:**

Efficacy and safety analyses were performed on all randomized patients who received at least 1 dose of study drug during the induction phase 2b substudy. For the primary endpoint, the dose-response relationships among the 3 risankizumab dose groups (600 mg, 1200 mg, and 1800 mg IV) and placebo group were characterized at week 12 using the MCP-Mod approach based on the intention to treat (ITT) population.<sup>1,2</sup> For categorical efficacy endpoints, pairwise comparisons between each risankizumab treatment group and placebo were performed using the 2-sided Cochran-Mantel-Haenszel test and stratified by baseline corticosteroid use (yes, no) and baseline Adapted Mayo score ( $\leq 7$ ,  $> 7$ ). Nonresponder imputation (NRI) was used as the primary imputation method, which categorized any patient who did not have an evaluation during a prespecified visit window (either due to missing assessment or due to early placebo (withdrawal) from the study) as a nonresponder for the visit. Continuous secondary efficacy endpoints were analyzed using a mixed-effect model repeated measures (MMRM) model which includes the categorical fixed effects of treatment, visit, and treatment-by-visit interaction, stratification factors at randomization, and the continuous fixed covariates of baseline measurement.

**eMethods 2. Full Patient Eligibility Criteria in the Final Protocol Amendment of the Phase 2b and Phase 3 INSPIRE Induction Study**

1. Males or females  $\geq$  18 and  $\leq$  80 years of age, or minimum age of adult consent according to local regulations at the baseline visit.
  - Phase 3 induction substudy only: Where locally permissible, subjects 16 to < 18 years of age who meet the definition of Tanner Stage 5 for development at the baseline visit.
2. Confirmed diagnosis of ulcerative colitis for at least 3 months prior to baseline. Appropriate documentation of biopsy results consistent with the diagnosis of ulcerative colitis or in the assessment of the investigator, must be available.
3. Active ulcerative colitis with an Adapted Mayo score of 5 to 9 points and endoscopic subscore of 2 to 3 (confirmed by central review).
4. Demonstrated intolerance or inadequate response to one or more of the following categories of drugs: aminosalicylates, oral locally acting steroids, systemic steroids (prednisone or equivalent), immunosuppressants, and/or biologic therapies.
  - Demonstration of intolerance requires no minimum dose or duration of use.
  - Inadequate response is defined as outlined below:
    - Oral aminosalicylates (eg, mesalamine, sulfasalazine, olsalazine, balsalazide):
      - Signs and symptoms of persistently active disease, in the opinion of the investigator, during a current or prior course of at least 4 weeks of treatment with 2.4 g/day mesalamine (2 g/day if controlled release), 4 g/day sulfasalazine, 1 g/day olsalazine, or 6.75 g/day balsalazide.
    - Oral locally acting steroids (eg, budesonide, beclomethasone):
      - Signs and symptoms of persistently active disease in the opinion of the investigator, during or after a course of at least 4 weeks of treatment with 9 mg/day budesonide or 5 mg/day beclomethasone, or
      - Inability to taper oral budesonide to at or below 6 mg/day without recurrent active disease,
    - IV or oral systemic steroids (prednisone or equivalent):

- Signs and symptoms of persistently active disease in the opinion of the investigator, during or after tapering of at least one regimen consisting of a dose equivalent to prednisone  $\geq$  40 mg/day orally for 3 weeks or IV for 1 week, or
- Inability to taper oral systemic steroids at or below a dose equivalent to prednisone 10 mg/day without recurrent active disease,
- Immunosuppressants:
  - Signs and symptoms of persistently active disease in the opinion of the investigator, during a current or prior course of at least 90 days of treatment with one or more of the following:
    - Azathioprine (AZA):  $\geq$  2.0 mg/kg/day rounded to the nearest available tablet or half tablet formulation ( $\geq$  1 mg/kg/day for subjects in Japan, Korea, Taiwan, Singapore, or China) (or a documented 6-TGN level of  $\geq$  230 pmol/ $8 \times 10^8$  RBC)
    - 6-mercaptopurine (6-MP):  $\geq$  1 mg/kg/day rounded to the nearest available tablet or half tablet formulation ( $\geq$  0.6 mg/kg/day for subjects in Japan, Korea, Taiwan, Singapore, or China) (or a 6 TGN level of  $\geq$  230 pmol/ $8 \times 10^8$  RBC)
    - Methotrexate (MTX):  $\geq$  15 mg/week subcutaneous (SC) or intramuscular (IM)
      - *Note:* Oral MTX use is allowed during the study, however prior or current use of oral MTX is not sufficient for inclusion into the study
    - Tacrolimus: (for Japan, Taiwan and other countries in Asia with local treatment guidelines that include tacrolimus) documented trough level 5 - 10 ng/mL
  - Biologic therapies and tofacitinib for ulcerative colitis
  - Signs and symptoms of persistently active disease despite a history of one or more of the following:
    - At least one 6-week induction regimen of infliximab ( $\geq$  5 mg/kg IV at weeks 0, 2, and 6),

- At least one 4-week induction regimen of adalimumab (one 160 mg SC dose at week 0, followed by one 80 mg SC dose at week 2 [or one 80 mg SC dose at week 0, followed by one 40 mg SC dose at week 2, in countries where this dosing regimen is approved]),
  - At least one 4-week induction regimen of golimumab (200 mg SC at week 0 and 100 mg SC at week 2),
  - At least one 6-week induction regimen of vedolizumab (300 mg IV at weeks 0, 2, and 6),
  - At least one 8-week induction regimen of tofacitinib (10 mg per os [PO] twice daily).
- Recurrence of symptoms during scheduled maintenance dosing following prior clinical benefit of the above biologics
    - Note: Subjects who discontinued biologics or tofacitinib for reasons other than inadequate response as defined above or intolerance (eg, change of insurance) must meet the criteria for intolerance or inadequate response to aminosalicylates, oral locally acting steroids, systemic steroids (prednisone or equivalent), and/or immunosuppressants as defined above.
5. If female, subject must meet the criteria as stated in this protocol
- *Contraception Recommendations.* Females of childbearing potential must have a negative serum pregnancy test result during screening, and a negative urine pregnancy at baseline. Females of nonchildbearing potential (either postmenopausal or permanently surgically sterile) during screening do not require pregnancy testing at baseline.
- Note: Subjects with borderline serum pregnancy test at screening must have a serum pregnancy test  $\geq$  3 days later to document continued lack of a positive result.
6. Subject must be able and willing to give written informed consent and to comply with the requirements of this study protocol. In Japan, if the subject is under the legal age of adulthood, a subject's parent or legal guardian must be willing to give written informed consent.

## **Exclusion Criteria**

1. Subject with a current diagnosis of Crohn's disease (CD) or IBD-unclassified (IBD-U) or a history of radiation colitis or ischemic colitis.

## Concomitant Medications and Treatments

2. Subject on oral ulcerative colitis-related antibiotics who have not been on stable doses for greater than, or discontinued within, 14 days prior to baseline.
3. Subject on oral aminosalicylates who have not been on stable doses for greater than, or discontinued within, at least 14 days prior to baseline.
4. Subject taking oral corticosteroids:
  - Budesonide > 9 mg/day
  - Beclomethasone > 5 mg/day
  - Prednisone or equivalent > 20 mg/day
  - Or has not been on the current course for  $\geq$  14 days prior to baseline and on a stable dose for  $\geq$  7 days prior to baseline
5. Subject on immunosuppressants (AZA, 6-MP, MTX) who:
  - Has not been on the course for  $\geq$  42 days prior to baseline, and
  - Has not been on a stable dose for  $\geq$  35 days prior to baseline

## Medications and Treatments During the Screening Period

6. Subject who received IV anti-infectives within 35 days prior to baseline visit or oral anti-infectives (nonulcerative colitis-related) within 14 days prior to the baseline visit. This does not apply to TB prophylaxis.
7. Subject who received any parenteral nutrition within 35 days prior to baseline.

8. Subject who received any live bacterial or viral vaccination within 35 days (8 weeks for Japan) prior to baseline.
9. Subject who received cyclosporine, tacrolimus, or mycophenolate mofetil within 35 days prior to baseline.
10. Subject who received fecal microbial transplantation within 35 days prior to baseline.

Prior Medications and Treatments

11. Subject who received any:
  - Approved biologic agent (eg, infliximab, adalimumab, golimumab, vedolizumab) within 8 weeks prior to baseline,
  - Tofacitinib within 35 days prior to baseline,
  - Any investigational agent or procedure within 35 days or 5 half-lives prior to the baseline, whichever is longer, or
  - Subject who is currently enrolled in another interventional clinical study.
12. Subject with prior exposure to p40 inhibitors (eg, ustekinumab) or p19 inhibitors (eg, risankizumab).
13. Subject has been taking combination of 2 or more of the following oral budesonides, oral beclomethasone, and/or oral prednisone (or equivalent) simultaneously, with the exception of inhalers, within 14 days prior to screening or during the screening period.
14. Subject who received IV/intramuscular corticosteroids within 14 days prior to screening or during the screening period.
15. Subject who received therapeutic enema or suppository (ie, rectal aminosalicylates/corticosteroids), other than required for endoscopy, within 14 days prior to screening or during the screening period.
16. Subject who received apheresis (eg Adacolumn apheresis) ≤ 60 days prior to screening or during the screening period.
17. Subject who has concomitant cannabis use either for recreational or medical reasons within 14 days prior to baseline or any history of clinically significant drug, or alcohol abuse in the last 12 months.

Ulcerative colitis-related

18. Extent of inflammatory disease limited to the rectum as assessed by screening endoscopy.
19. Subject with currently known complications of ulcerative colitis such as:
  - Fulminant colitis,
  - Toxic megacolon,
  - Previous colectomy (total or subtotal),
  - Or any other manifestation that might require surgery while enrolled in the study.
20. Subject with ostomy or ileoanal pouch.

Safety

21. Subject who has a known hypersensitivity to risankizumab or the excipients of any of the study drugs or the ingredients of Chinese hamster ovary (CHO).
22. Subjects with the following chronic or active infections:
  - Active, chronic, or recurrent infection that based on the investigator's clinical assessment makes the subject an unsuitable candidate for the study,
  - Infection with *C. difficile* toxin as identified during screening,
  - Known infection with an intestinal pathogen,
  - Are infected with human immunodeficiency virus (HIV),
  - Have active hepatitis B or hepatitis C defined as:

- HBV: hepatitis B surface antigen (HBs Ag) positive (+), or detected sensitivity on the HBV deoxyribonucleic acid (DNA) polymerase chain reaction (PCR) qualitative test for hepatitis B core antibody (HBc Ab) positive subjects;
  - Hepatitis C Virus (HCV): HCV ribonucleic acid (RNA) detectable in any subject with anti-HCV antibody (HCV Ab).
- Note: QuantiFERON®-TB test or Purified Protein Derivative (PPD) skin test, or both, according to local guidelines, will be performed during screening. QuantiFERON®-TB test is preferred for subjects who received BCG vaccination or were exposed to other Mycobacteria species. Subjects with a positive test result (or indeterminate results that have been repeated) may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the subject has no evidence of active tuberculosis. Subjects with a history of active TB who have documented completion of a full course of anti-TB therapy may be allowed to enter the study after consultation with the AbbVie TA MD. *If latent TB is established, TB prophylaxis/treatment should be initiated and maintained according to local country guidelines.*
23. Subject with a previous history of dysplasia of the gastrointestinal tract or found to have dysplasia, other than completely removed low-grade dysplastic lesions, in any biopsy performed during the screening endoscopy.
  24. Subject with a known history of lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy and/or splenomegaly.
  25. Subject with history of malignancy other than a successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma or localized carcinoma in situ of the cervix.
  26. Subject who has severe, progressive, or uncontrolled renal, hepatic, hematological, endocrine, disorder or symptoms thereof.
  27. Female subjects who are pregnant, breastfeeding, or is considering becoming pregnant during the study or for approximately 140 days after the last dose of study drug.

28. Subject who has any condition, including any physical, psychological, or psychiatric condition, which in the opinion of the investigator, would compromise the safety of the subject or the quality of the data and renders the subject an unsuitable candidate for the study.
29. Screening laboratory and other analyses show any of the following abnormal results:
  - Aspartate transaminase (AST), alanine transaminase (ALT)  $> 2 \times$  upper limit of the reference range;
  - White blood cell (WBC) count  $< 3.0 \times 10^9/L$ ;
  - Total bilirubin  $\geq 2$  mg/dL; except for subjects with isolated elevation of indirect bilirubin relating to Gilbert's syndrome;
  - Estimated glomerular filtration rate by simplified 4-variable Modification of Diet in Renal Disease (MDRD) formula  $< 30$  mL/min/1.73 m<sup>2</sup>;
  - Hemoglobin  $< 8$  g/dL;
  - Platelets  $< 100,000/\mu L$ ;
  - Positive serum pregnancy test at the screening visit or positive urine pregnancy test at the baseline visit;
  - Laboratory values can be re-tested once during the screening period. If the retested lab value(s) remain(s) exclusionary, the subject will be considered a screen failure. Redrawing samples if previous samples were unable to be analyzed would not count as a retest since the previous result was never obtained.
30. No known active COVID-19 infection. If a subject has signs/symptoms suggestive of COVID-19, they should undergo molecular (ie, PCR) testing to rule out SARS-CoV-2 infection.

Subjects who do not meet COVID-19 eligibility criteria must be screen failed and may only rescreen after they meet the following COVID-19 criteria:

- Symptomatic subjects: At least 14 days have passed since recovery, defined as resolution of fever without use of antipyretics and improvement in symptoms

- Asymptomatic subjects: At least 14 days have passed since the first positive molecular (ie, PCR) test result

### eMethods 3. Supplementary Methods for the Phase 3 Induction and Maintenance Studies

#### Concomitant Therapy

Patients taking conventional therapies, such as aminosalicylates, immunosuppressants, and/or ulcerative colitis-related antibiotics at baseline continued their concomitant treatment for the duration of the phase 3 induction study.

Decreasing doses were prohibited during the study, except in the event of moderately to severely active treatment-related toxicities.

Patients taking corticosteroids at baseline were required to continue their concomitant treatment at the baseline dose for the duration of induction.

Patients who entered the 12-week blinded extended treatment period of induction were permitted to taper corticosteroids at the discretion of the investigator. While stopping the taper was permitted, dose increases above the baseline dose was prohibited.

At week 0 of maintenance, patients on corticosteroid therapy were required to taper their dose to completion by maintenance week 8, with the recommended tapering schedule provided on the next page. All efficacy measurements at or after initiating and/or increasing doses of any corticosteroids were excluded. Starting at week 16, patients who demonstrated inadequate response (based upon increased symptom activity and/or endoscopic confirmation of inflammation) could receive open-label risankizumab rescue therapy (ie, one single dose of risankizumab 1200 mg followed by 360 mg SC maintenance regimen, which was delivered as 4 injections [90 mg SC] every 8 weeks thereafter). Patients could receive up to 2 rescue doses. Patients taking corticosteroids at week 0 who had a loss of satisfactory clinical response per the investigator's judgment after the steroid taper had been initiated could have their corticosteroid dose increased up to the dose used at baseline of maintenance per the investigator's discretion. Patients taking oral budesonide multi-matrix system formulation or oral beclomethasone were required to discontinue medication without a taper.

## Recommended Tapering Schedule for the Maintenance Study

	Dose	Rate
Prednisone (or equivalent)	> 10 mg/day	5 mg/day per week
	≤ 10 mg/day	2.5 mg/day per week
Budesonide	≤ 9 mg/day	3 mg/day per week

## Endpoint Definitions for Primary and Secondary Outcomes for Phase 3 Induction and Maintenance

### Clinical Endpoints

- **Adapted Mayo score (score range 0-9):** RBS, 0-3; stool frequency score (SFS, 0-3); endoscopy score (0-3). Higher scores indicate more severe disease.
- **Partial Adapted Mayo score (score range 0-6):** RBS (0-3); SFS (0-3). Higher scores indicate more severe disease.

### Patient-Reported Outcomes

- **Abdominal pain score:** Abdominal pain was assessed using a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) to evaluate symptom frequency and severity over time. The mean of the scores from the most recent 3 days, and up to 10 days, prior to each study visit was calculated.
- **Bowel urgency, nocturnal bowel movements, or tenesmus:** Each of these symptoms were scored independently as categorical (dichotomous) variables with 2 response options, where the response option “Yes” meant the respondent did experience the symptom within the past 24 hours and the response option “No” meant the respondent did not experience the symptom within the past 24 hours. For computing affected days with symptom, daily responses of “No” were coded as 0 and “Yes” were coded as 1. Scores were determined by

calculating the sum of the numeric values over the 3 days, and up to 10 days, prior to each study visit. If scores for fewer than 3 days in the 10 days prior to the study visit were available, then score was set to missing for that visit.

- **Sleep interruption:** Sleep interruption scoring quantified the number of nights with sleep interruption due to ulcerative colitis symptoms in the most recent week (i.e., 7 days) prior to each study visit. If patients answered “Yes” and “due to ulcerative colitis symptoms”, they received a score of 1 for that day; otherwise, patients received a score of 0. Scores were determined by calculating the mean of the numeric values (0 for no sleep interruption due to ulcerative colitis symptoms, and 1 for sleep interruption due to ulcerative colitis symptoms) over the most recent week (i.e., 7 days) and then multiplying the result by 7; therefore, scores ranged between 0 and 7 for each study visit.
- **Fecal incontinence:** Fecal incontinence scoring quantified the number of weekly episodes of accidental bowel leakage (e.g. accidental soiling of underwear) prior to each study visit. Scores were determined by calculating the mean of the number of fecal incontinence episodes over the most recent week (i.e., 7 days) prior to a study visit and then multiplying by 7.

#### **Definitions for Study Endpoints in Both Induction and Maintenance**

- **Clinical remission per Adapted Mayo score:** SFS  $\leq 1$ , and not greater than baseline, RBS of 0, and endoscopic subscore  $\leq 1$ .
- **Clinical response per Adapted Mayo score:** Decrease from baseline  $\geq 2$  points and  $\geq 30\%$ , in addition to a decrease in RBS  $\geq 1$  or an absolute RBS  $\leq 1$ .
- **Clinical response per Partial Adapted Mayo score:** Decrease from baseline  $\geq 1$  point and  $\geq 30\%$ , in addition to a decrease in RBS  $\geq 1$  or an absolute RBS  $\leq 1$ .
- **Endoscopic improvement:** Endoscopic subscore  $\leq 1$  without the evidence of friability.
- **Endoscopic remission:** Endoscopic subscore of 0.

- **Histological endoscopic mucosal improvement (HEMI):** Endoscopic subscore of 0 or 1 without evidence of friability and Geboes score  $\leq 3.1$ .
- **HEMR:** Endoscopic subscore of 0 and Geboes score  $< 2.0$ .
- **Histologic remission:** Geboes score of  $< 2.0$ .
- **No bowel urgency:** A mean score of 0 denoting the absence of symptoms for the 3 most recent days prior to each study visit.
- **No abdominal pain:** A mean score of 0 denoting the absence of symptoms for the 3 most recent days prior to each study visit.
- **No nocturnal bowel movements:** A mean score of 0 denoting the absence of symptoms for the 3 most recent days prior to each study visit.
- **No tenesmus:** A mean score of 0 denoting the absence of symptoms for the 3 most recent days prior to each study visit.
  - For all patient-reported outcomes (no bowel urgency, no abdominal pain, no nocturnal bowel movements, no tenesmus), the 3 most recent days should not include the day prior to endoscopy, the day the subject underwent endoscopy, and 2 days following the endoscopy. Earlier diary entries will be used accordingly in order to provide the most recent data for 3 days prior to the respective study visit.

#### Health-Related Quality of Life (HRQOL) Endpoints

- **Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F):** A 13-item assessment of fatigue associated with disease and how it impacts daily activities and function. Lower scores indicate greater fatigue.
- **Inflammatory Bowel Disease Questionnaire (IBDQ):** This questionnaire consists of 32 questions divided into 4 dimensions: bowel symptoms, systemic symptoms, emotional function, and social function. The total score ranges from 32 to 224, with higher scores representing better quality of life.

## **Definitions for Study Endpoints in Maintenance Only**

- **Corticosteroid-free clinical remission:** Clinical remission per Adapted Mayo score at week 52 in patients who abstained from corticosteroid use for 90 days.
- **Maintenance of clinical remission:** Achievement of clinical remission per Adapted Mayo score at week 52 in patients with clinical remission at baseline of maintenance.
- **Maintenance of endoscopic improvement:** Achievement of endoscopic improvement at week 52 in patients with endoscopic improvement at baseline of maintenance.

## **Statistical Analysis for IL-22**

An MMRM analysis was conducted on the log<sub>2</sub> transformed biomarker values. In the mixed model, the outcome variable was the change from baseline of the log<sub>2</sub> transformed values. Baseline biomarker values were adjusted by including log<sub>2</sub> (baseline) as a covariate. Treatment, time, and treatment by time were fixed effects; and patient was a random effect. Least square mean estimates for treatment by time combinations from the mixed model were used for reporting and comparisons. The least-square means of the change in the log scale were back-transformed to the original scale, which gave a percent change from the baseline. Change from baseline comparisons within the treatment group were made at weeks 4, 12, and 52, and Bonferroni adjusted *P* values were calculated.

## **Pharmacokinetics and Immunogenicity Assessments**

Risankizumab serum levels were measured every 4 weeks, from week 4 through week 12 during induction, and for maintenance every 16 weeks through week 48, with a final measurement 4 weeks later at week 52; serum anti-drug antibodies including neutralizing antibodies were measured according to the same schedule as risankizumab but also included induction baseline prior to risankizumab treatment. Assay methods have been previously described.<sup>3</sup>

## **Safety Outcomes**

Adverse events were coded with the Medical Dictionary for Regulatory Activities (MedDRA), version 25.1. The severity of adverse events and laboratory abnormalities was graded with the Common Terminology Criteria for Adverse Events, version 4.03. Major adverse cardiovascular events (MACE) and anaphylactic reactions were adjudicated by external independent adjudication committees. An external data monitoring committee (DMC), independent of the sponsor and with relevant expertise in their field, reviewed unblinded safety data from the studies according to the DMC Charter.

## **Additional Statistical Analysis For Induction and Maintenance**

### *Overall Type I Error Control*

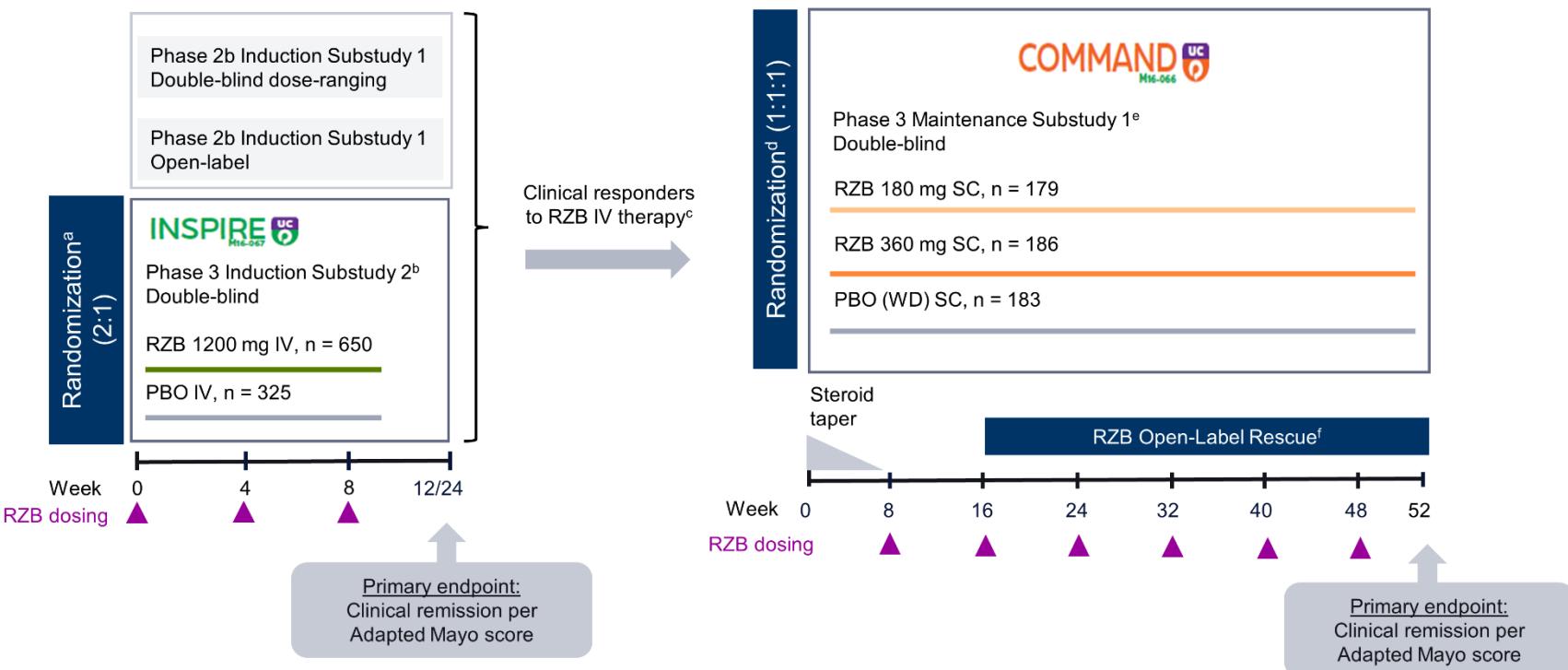
The overall type I error rate for the primary and secondary endpoints for the double-blind, phase 3 induction period was controlled using a graphical multiple-testing procedure (**eFigure 4**). The primary endpoint was tested at the prespecified significance level of 0.05 (2-sided). The secondary efficacy endpoints were divided into 2 groups (**eFigure 4**). The first group included the first 10 secondary endpoints. The second group included all the remaining 5 secondary endpoints which were tested using the Holm procedure. If the primary endpoint achieved statistical significance, continued testing followed a prespecified weight of  $\alpha$  allocation (**eFigure 4**). In the graph, the arrows specify the weight of  $\alpha$  allocation between nodes. Once a hypothesis was rejected (ie, deemed the endpoint is significant) at its assigned significance level, its significance level was allocated to the subsequent node. If more than one arrow originates from a node, the significance level was split between multiple subsequent nodes following the prespecified weight. The numbers on the arrows denote the weights. For example, weight 1 denotes 100% transfer of significance level to the next node, and the weight  $\epsilon$  denotes 0.02% of the overall significance level (corresponding to  $\alpha$  of  $0.02\% \times 0.05 = 0.00001$ ) to be transferred.

For maintenance, the graphical testing procedure was similar to that performed for induction, with testing for the primary endpoint beginning at the prespecified significance level of 0.025 (2-sided) for each risankizumab dose group compared with placebo. If the primary endpoint achieved statistical significance, testing was continued following a prespecified weight of  $\alpha$  allocation.

In **eFigure 5**, the arrows specify weight of  $\alpha$  allocation between nodes. Once a hypothesis was rejected (ie, deemed the endpoint significant) at its assigned significance level, the significance was allocated to the subsequent node. If more than one arrow originates from a node, the significance level will be split between multiple subsequent nodes following the prespecified weight. The numbers on the arrows denote the weights. For example, weight 1 denotes 100% transfer of significance level to the next node, and the weight  $\varepsilon$  denotes 0.04% of the overall significance level each dose starts with (corresponding to  $\alpha$  of  $0.04\% \times 0.025=0.00001$ ) to be transferred.

No type I error control was applied to the additional nonranked efficacy endpoints. The analysis for additional efficacy endpoints was performed at the nominal  $\alpha$  level of 0.05 (two-sided) for each dose.

**eFigure 1.** Key Study Design Features and Trial Profile of Induction and Maintenance Studies



The phase 3 induction and maintenance studies lasted up to 81 weeks and included a screening period that lasted up to 5 weeks, a 12-week double-blind induction period (substudy 2), and a 52-week maintenance period.

<sup>a</sup>Randomization for induction was stratified by the presence of baseline corticosteroid use (yes, no), baseline Adapted Mayo score ( $\leq 7$ ,  $> 7$ ), and number of prior failed advanced therapies (0, 1,  $> 1$ ).

<sup>b</sup>The primary efficacy analysis population for phase 3 induction substudy 2 included all randomized patients who received at least one dose of study drug during the first 12-week, double-blind induction period.

<sup>c</sup>Clinical responders after 12 weeks of risankizumab IV were randomized to the primary efficacy population of maintenance. Patients who did not achieve a clinical response could receive an additional 12 weeks of risankizumab therapy during the induction extended treatment period (not shown). Patients who were placebo nonresponders after 12 weeks who then received and responded to risankizumab 1200 mg or 1800 mg at 24 weeks were included in the rerandomization into maintenance (not shown).

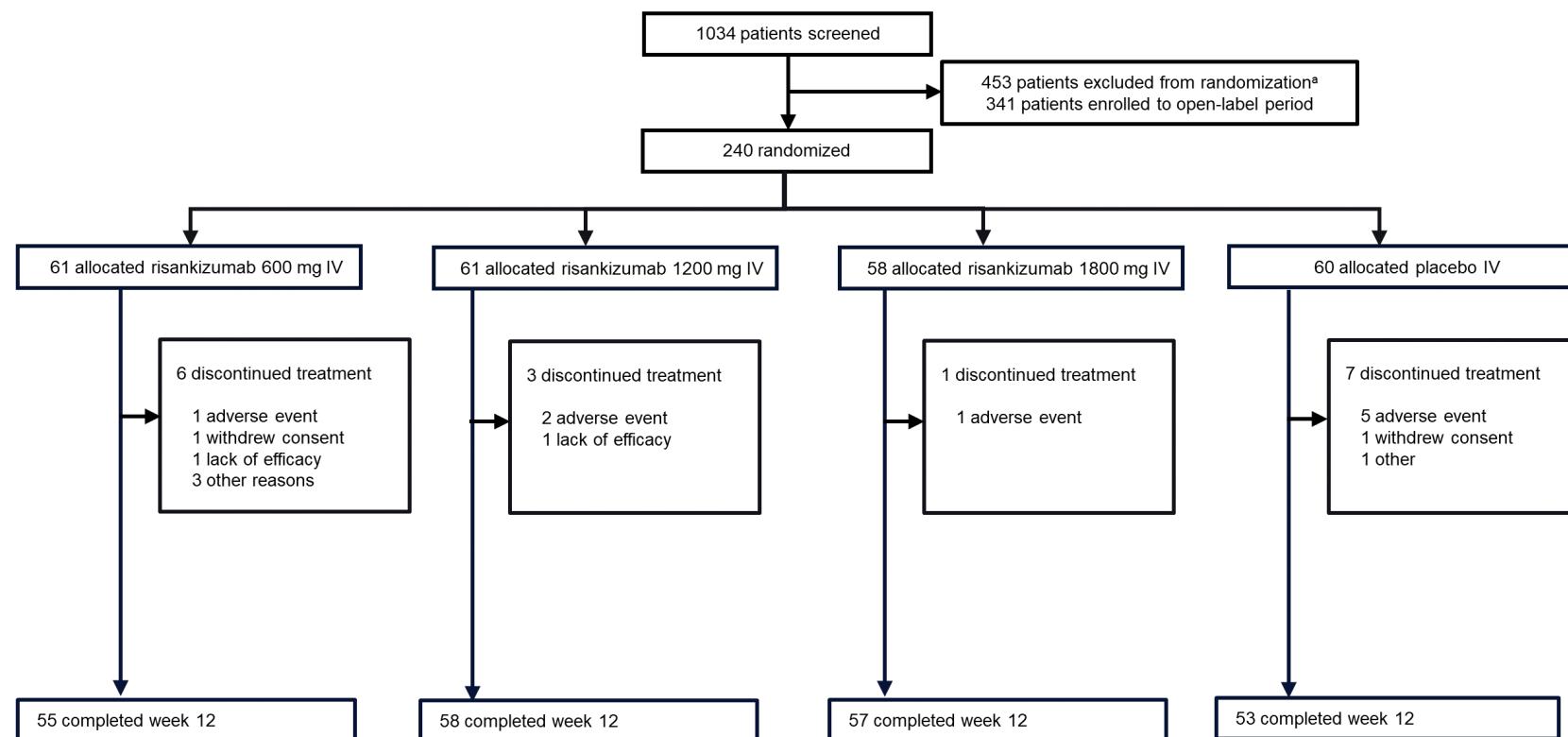
<sup>d</sup>Randomization was stratified by history of advanced therapy failure (yes, no), last risankizumab induction dose (600 mg, 1200 mg, 1800 mg), and clinical remission status (per local evaluation) at the last visit of induction (yes, no).

<sup>e</sup>The primary efficacy analysis population for maintenance included patients who achieved a clinical response per Adapted Mayo score after 12 weeks of risankizumab IV during the phase 2b dose-ranging substudy (600 mg, 1200 mg, 1800 mg), phase 2b open-label period (1800 mg), or phase 3 induction (1200 mg).

<sup>f</sup>Patients who experienced inadequate response were eligible for risankizumab rescue therapy starting at week 16 of maintenance (one dose of 1200 mg or 1800 mg followed by 360 mg every 8 weeks). Loss of response or inadequate response was based on clinical and endoscopic symptoms (RBS at least 1 point greater than the week 0 value or endoscopic subscore of 2 or 3).

IV, intravenous; PBO, placebo; RBS, rectal bleeding score; RZB, risankizumab; SC, subcutaneous; WD, placebo (withdrawal)

**eFigure 2.** Trial Profile of the Dose-Ranging Phase 2b Substudy



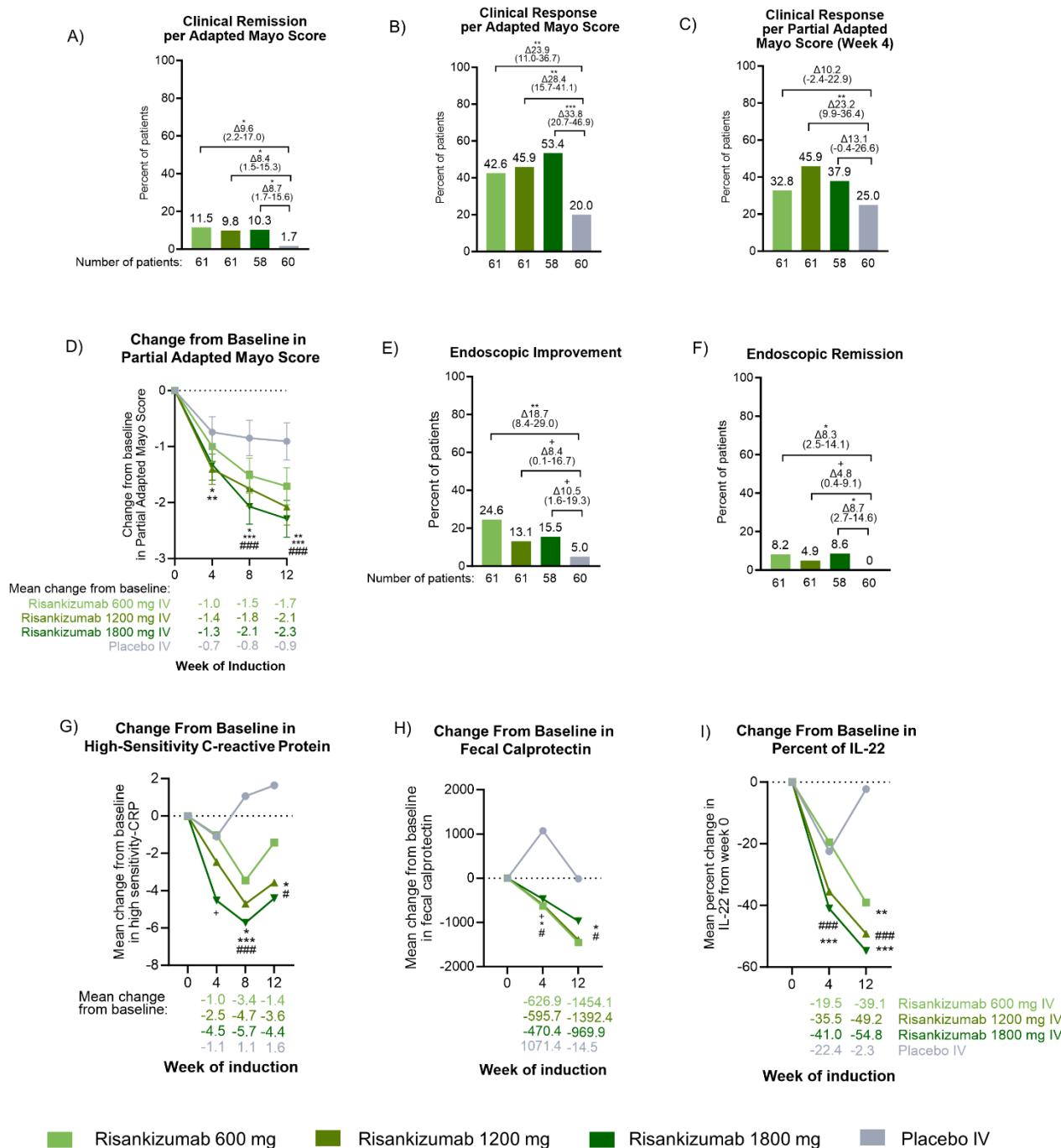
The primary analysis populations for the phase 2b substudy included all randomized patients who received at least one dose of study drug during the 12-week, double-blind, dose-ranging substudy.

Patients who attained a clinical response at week 12 of phase 2b open-label induction treatment were randomized into the maintenance study, and patients with clinical response to 12-week risankizumab IV therapy were included in the primary efficacy analysis.

<sup>a</sup>Failed to meet inclusion criteria or met exclusion criteria.

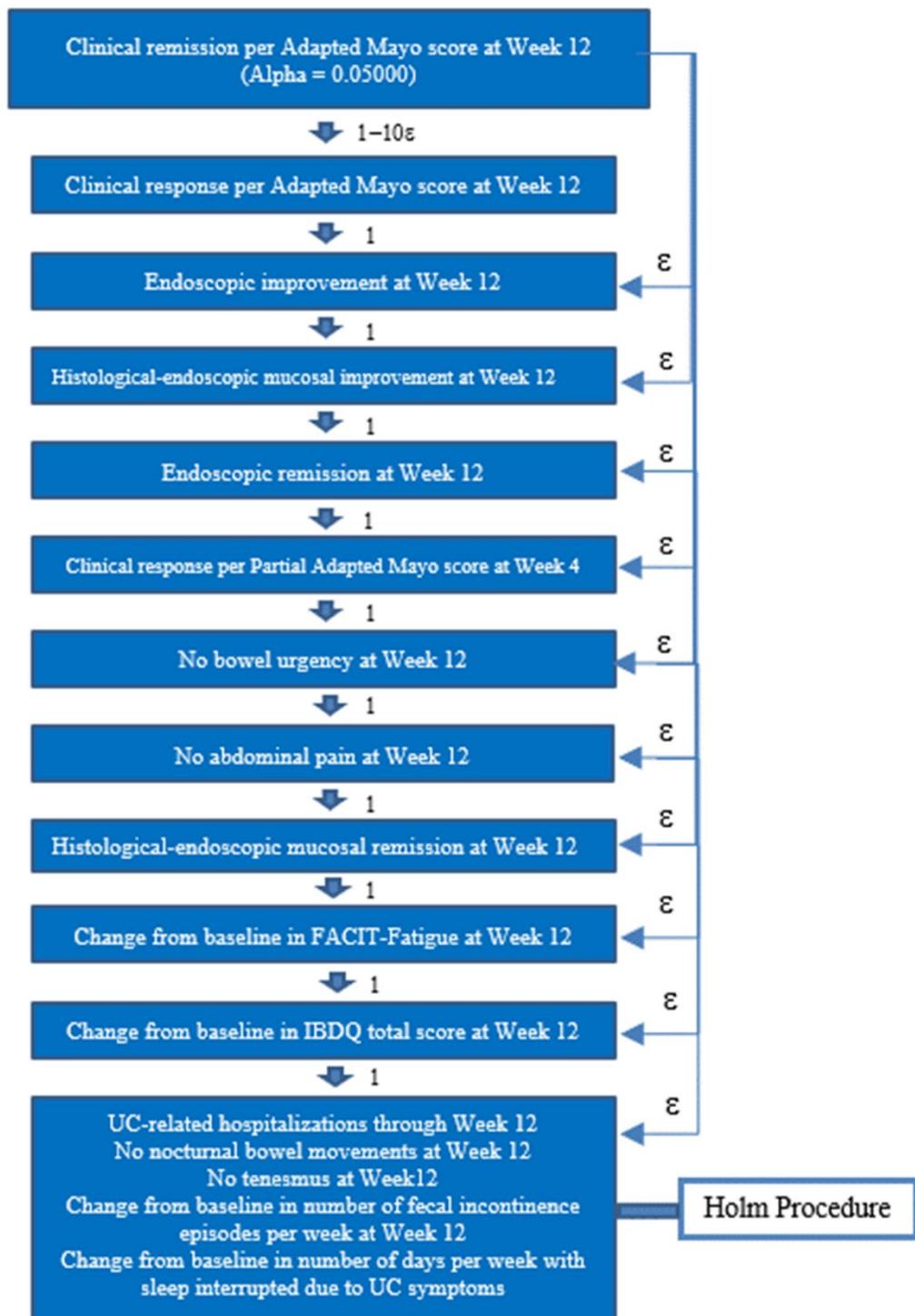
IV, intravenous.

**eFigure 3. Key Clinical and Endoscopic Endpoints and Inflammatory Biomarkers for the Dose-Ranging Phase 2b Substudy**



For eFigure 3A-C and E-F, all data shown is at week 12 of induction, with adjusted treatment differences versus placebo (90% CI) denoted by the deltas shown above treatment groups. For eFigures 3G and 3H, data shown is LS mean change from baseline. Analysis was based on the CMH test stratified by baseline corticosteroid use (yes, no) and baseline Adapted Mayo score ( $\leq 7$ ,  $> 7$ ). Significance was determined using Chi-square test or Fisher's exact test if  $\geq 20\%$  of the cells have expected cell count  $< 5$ . 90% confidence intervals for risk difference were calculated based on normal approximation using PROC FREQ. +  $P \leq .1$ ; \*  $P \leq .05$ ; \*\*  $P \leq .01$ ; \*\*\*  $P \leq .001$  versus placebo. For eFigure 3D, \*  $P \leq .05$  RZB 1800 mg vs. PBO at week 4; \*\*  $P \leq .01$  RZB 1200 mg vs. PBO at week 4; \*\*\*  $P \leq .001$  RZB 1200 mg vs. PBO at week 8; ###  $P \leq .001$  RZB 1800 mg vs. PBO at week 8; \*\*  $P \leq .01$  RZB 600 mg vs. PBO at week 12; \*\*\*  $P \leq .001$  RZB 1200 mg vs. PBO at week 12; ###  $P \leq .001$  RZB 1800 mg vs. PBO at week 12; eFigure 3G, +  $P \leq .1$  RZB 1800 mg vs. PBO at week 4; \*  $P \leq .05$  RZB 600 mg vs. PBO at week 8; \*\*\*  $P \leq .001$  RZB 1200 mg vs. PBO at week 8; ###  $P \leq .001$  RZB 1200 mg vs. PBO at week 8; #  $P \leq .05$  RZB 1200 mg vs. PBO at week 12; \*  $P \leq .05$  RZB 1800 mg vs. PBO at week 12; eFigure 3H, +  $P \leq .1$  RZB 1800 mg vs. PBO at week 4; #  $P \leq .1$  RZB 1800 mg vs. PBO at week 4; \*  $P \leq .05$  RZB 600 mg vs. PBO at week 4; \*  $P \leq .05$  RZB 600 mg vs. PBO at week 4; \*  $P \leq .1$  RZB 1200 mg vs. PBO at week 4; \*  $P \leq .1$  RZB 1800 mg vs. PBO at week 4; \*  $P \leq .05$  RZB 600 mg vs. PBO at week 12; eFigure 3I, \*\*\*  $P \leq .001$  RZB 1200 mg vs. baseline at week 4; ###  $P \leq .001$  RZB 1800 mg vs. baseline at week 4; \*\*  $P \leq .05$  RZB 600 mg vs. baseline at week 12; \*\*\*  $P \leq .001$  RZB 1200 mg vs. baseline at week 12; ###  $P \leq .001$  RZB 1800 mg vs. baseline at week 12. CI, confidence intervals; CMH, Cochran-Mantel-Haenszel; IV, intravenous. LS, least-square.

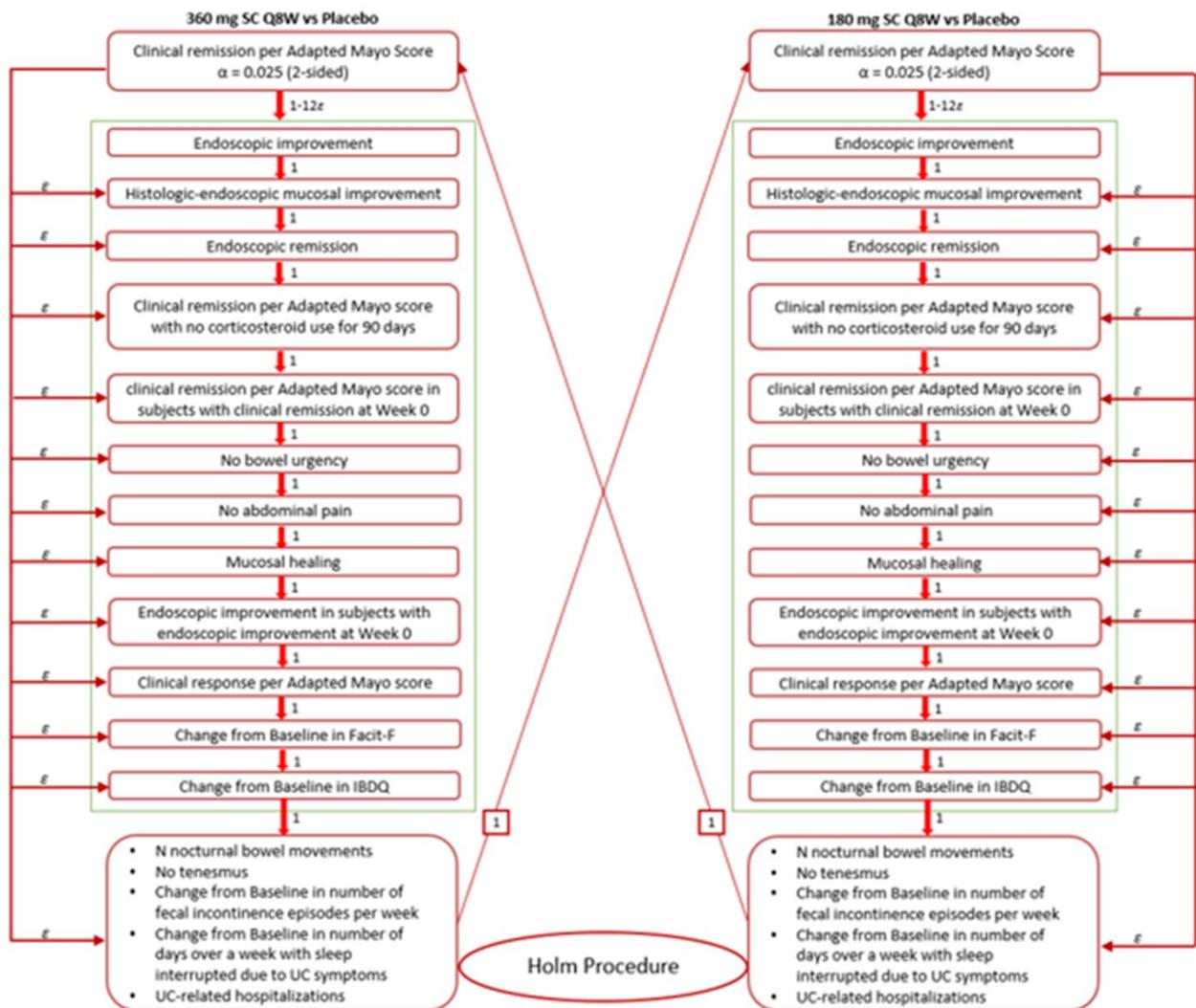
**eFigure 4.** Graphical Multiple-Testing Procedure for the Phase 3 Induction Study



Weight  $\epsilon$  denotes 0.02% of the overall significance level (corresponding to  $\alpha$  of  $0.02\% * 0.05 = 0.00001$ ).

FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; IBDQ, Inflammatory Bowel Disease Questionnaire; IV, intravenous; Q8, every 8 weeks; SC, subcutaneous; UC, ulcerative colitis

**eFigure 5.** Graphical Multiple-Testing Procedure For the Phase 3 Maintenance Study



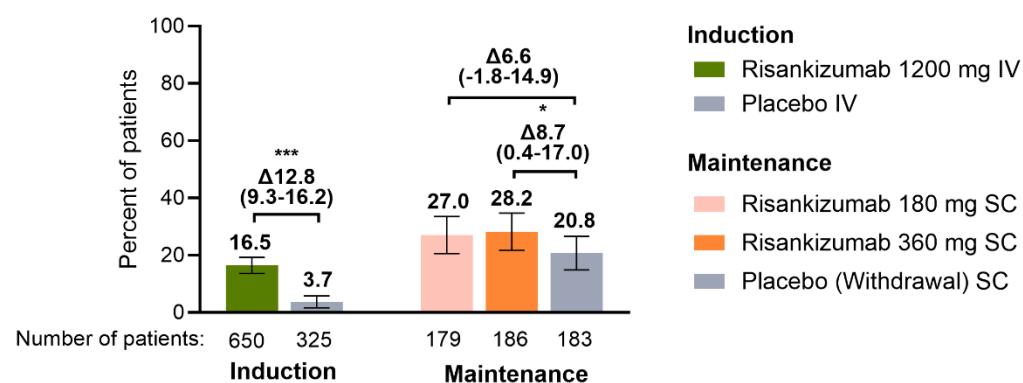
Weight  $\epsilon$  denotes 0.04% of the overall significance level that each dose starts with (corresponding to  $\alpha$  of  $0.04\% * 0.025 = 0.00001$ ).

FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; IBDQ, Inflammatory Bowel Disease Questionnaire; IV, intravenous; Q8, every 8 weeks; SC, subcutaneous; UC, ulcerative colitis

For each study, the subgroup analyses were conducted for prespecified subgroups for the primary efficacy endpoint. No post hoc subgroups are shown. Point estimate and 95% CI for treatment difference between each risankizumab group and placebo group were calculated using normal approximation to the binomial distribution. 95% CI for difference were calculated using normal approximation to the binomial distribution. The calculations were based on NRI incorporating multiple imputation to handle missing data due to logistic restrictions (COVID-19 or the geopolitical conflict in Ukraine and surrounding impacted regions) or NRI only if there were no missing data due to logistic restrictions (COVID-19 or the geopolitical conflict in Ukraine and surrounding impacted regions). If any of the resulting subgroups except for age, sex and race had fewer than 10% of the planned study size, the subgroup analyses for that category were not presented. Type I error was not controlled in this analysis. CI, confidence interval; COVID-19, coronavirus disease 2019.

IV, intravenous; IR, inadequate response, TNF, tumor necrosis factor; SC, subcutaneous; UC, ulcerative colitis; hs-CRP, high sensitivity C-reactive protein.

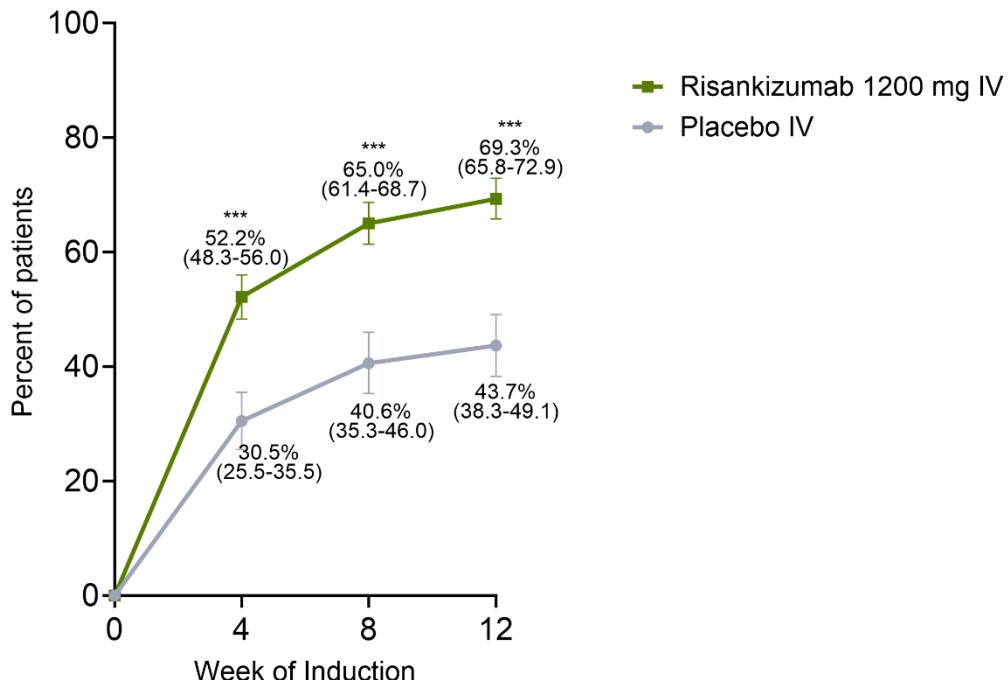
**eFigure 7.** Percent of Patients Who Achieved Histologic Remission at Week 12 of Induction and Week 52 of Maintenance



Histologic remission was defined as Geboes score of < 2.0. 95% CIs for the response rates were the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there were missing data due to logistic restrictions (COVID-19 or geopolitical restrictions) or is based on the normal approximation to the binomial distribution. Significance was calculated according to the CMH test adjusted for strata for the comparison of treatment groups. Adjusted risk difference and 95% CI for adjusted difference were calculated based on Mantel-Haenszel common rate difference. 95% CIs for difference were calculated using normal approximation to the binomial distribution. \*  $P \leq .05$ ; \*\*\*  $P \leq .001$  versus placebo IV or versus placebo (withdrawal) SC.

CMH, Cochran-Mantel-Haenszel; CI, confidence interval; COVID-19, coronavirus disease 2019; IV, intravenous; SC, subcutaneous.

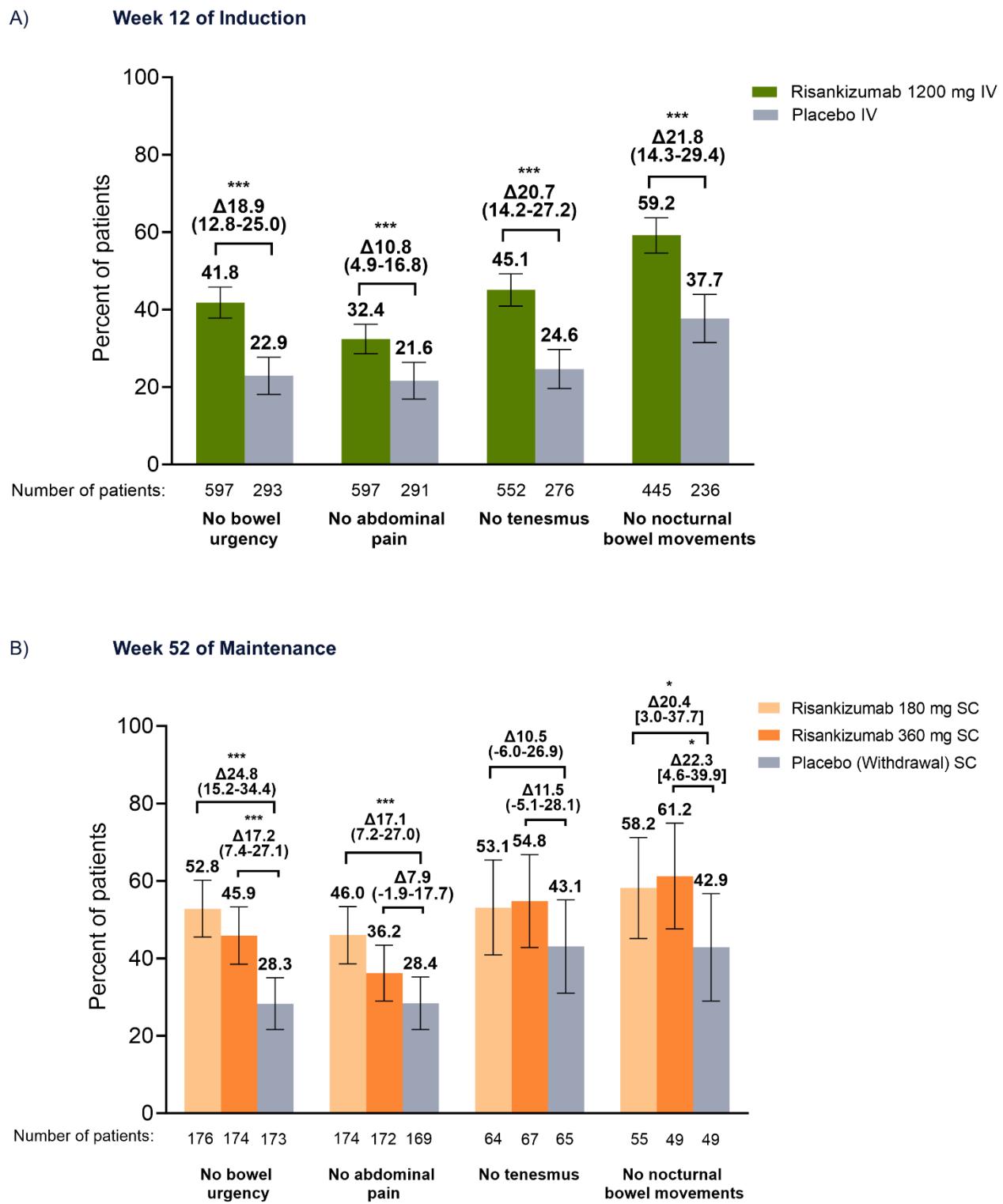
**eFigure 8.** Percent of Patients that Achieved Clinical Response per Partial Adapted Mayo Score Through Week 12 of INSPIRE



95% CIs for response rates were the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there were missing data due to logistic restrictions (COVID-19 or geopolitical restrictions).  $P$  value was calculated according to the CMH test adjusted for strata. Within each stratum, 95% CI for difference were calculated using normal approximation to the binomial distribution. The calculations were based on nonresponder imputation incorporating multiple imputation to handle missing data due to logistic restrictions. \*\*\*  $P \leq .001$  versus placebo IV.

CMH, Cochran-Mantel-Haenszel; COVID-19, coronavirus disease 2019; IV, intravenous.

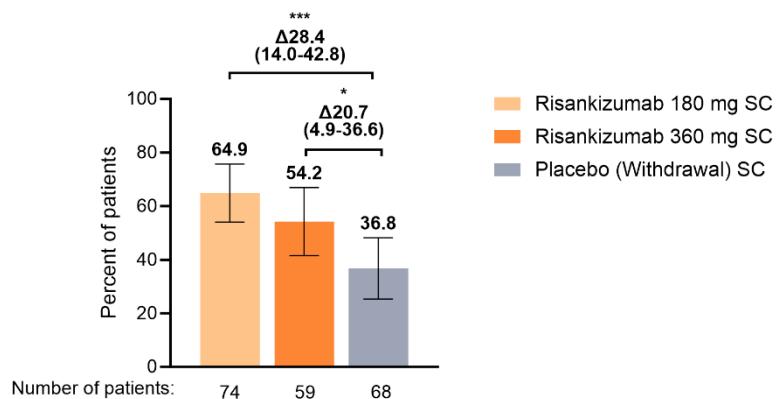
**eFigure 9.** Patient-Reported Outcomes Among Patients Who Reported Having Symptoms at Baseline of Phase 3 Induction



95% CIs for response rate were the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there were missing data due to logistic restrictions (COVID-19 or the geopolitical conflict in Ukraine and surrounding impacted regions), with all calculations performed among patients that reported having bowel urgency, abdominal pain, tenesmus, or nocturnal bowel movements at baseline of phase 3 induction (for baseline values for these endpoints, see **eTable 3**). Across the strata, statistical significance was calculated according to the Cochran-Mantel-Haenszel test. Adjusted risk difference and 95% CI were calculated based on Mantel-Haenszel common rate difference. The calculations were based on nonresponder imputation incorporating multiple imputation to handle missing data due to logistic restrictions (COVID-19 or the geopolitical conflict in Ukraine and surrounding impacted regions). \*  $P \leq .05$ ; \*\*  $P \leq .01$ ; \*\*\*  $P \leq .001$  versus placebo or placebo (withdrawal).

CMH, Cochran-Mantel-Haenszel; COVID-19, coronavirus disease 2019; CI, confidence interval; IV, intravenous; MMRM, mixed-effect model repeated measures; SC, subcutaneous.

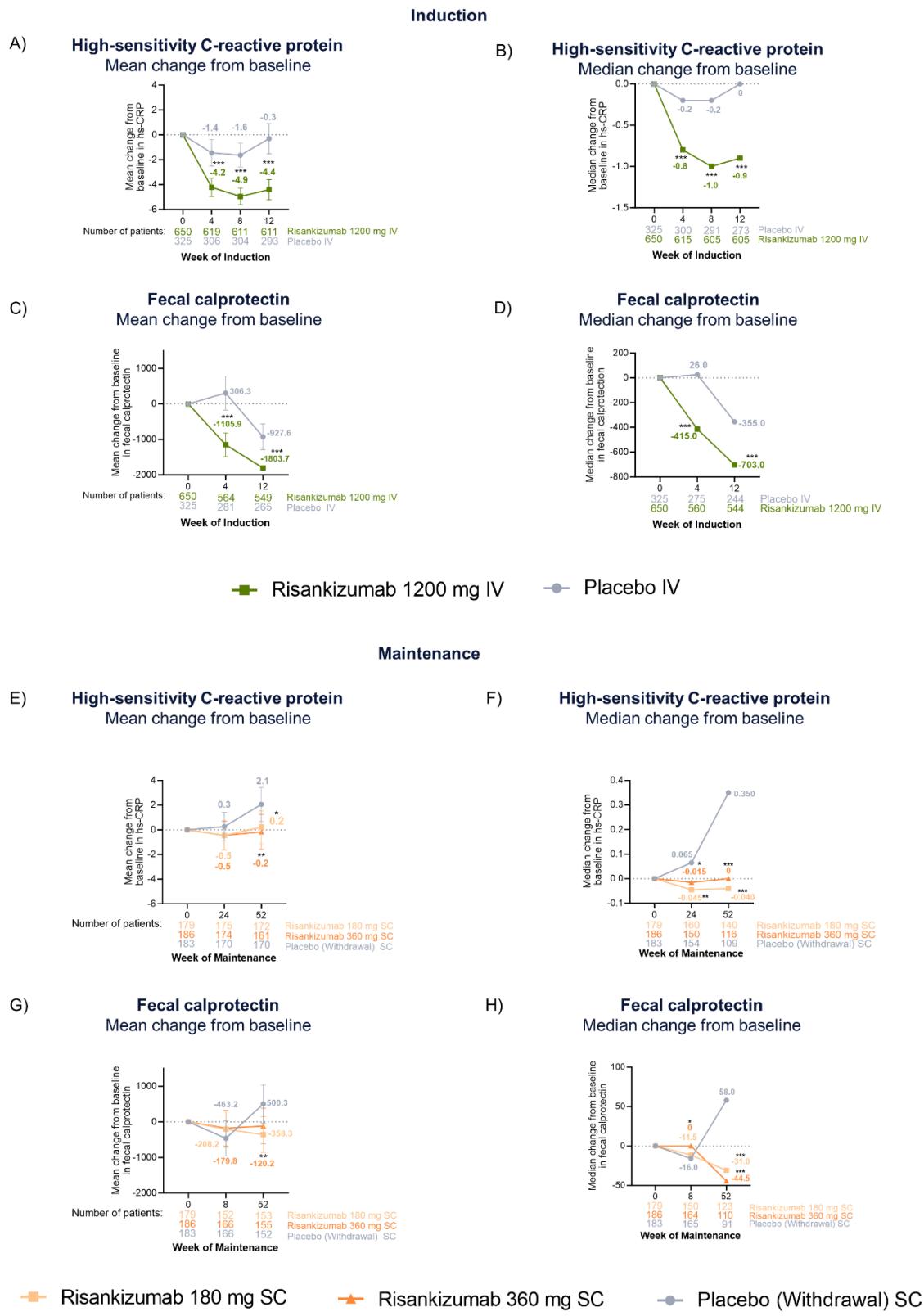
**eFigure 10.** Discontinuation of Corticosteroids at Week 52 of Maintenance Among Patients Taking Corticosteroids at Baseline of Induction



Shown is the achievement of the discontinuation of corticosteroids at week 52 for the entire 52-week maintenance period in patients taking corticosteroids at baseline of the induction study. Baseline refers to week 0 of maintenance (week 12 or 24 of induction). 95% CIs for the response rates were based on the normal approximation to the binomial distribution. Significance was calculated according to the CMH test adjusted for stratification factors. Adjusted risk difference and 95% CIs were calculated based on Mantel-Haenszel common rate difference. \*  $P \leq .05$ ; \*\*\*  $P \leq .001$  versus placebo (withdrawal).

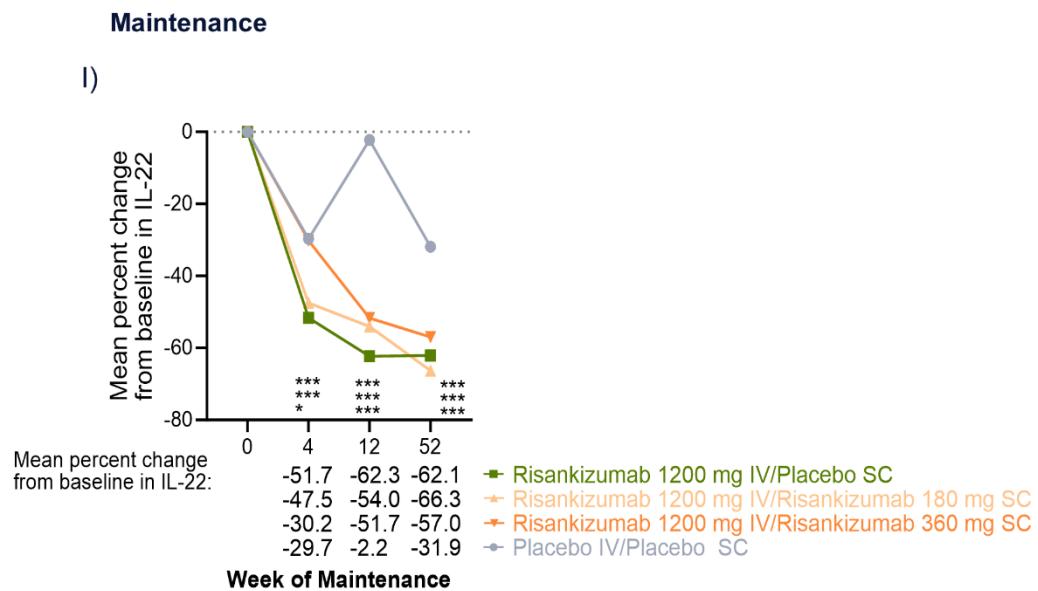
CMH, Cochran-Mantel-Haenszel; CI, confidence interval; SC, subcutaneous.

**eFigure 11.** Change From Baseline in Biomarkers During the Phase 3 Induction and Maintenance Studies



**eFigure 11.** Change From Baseline in Biomarkers During Phase 3 Induction and Maintenance Studies

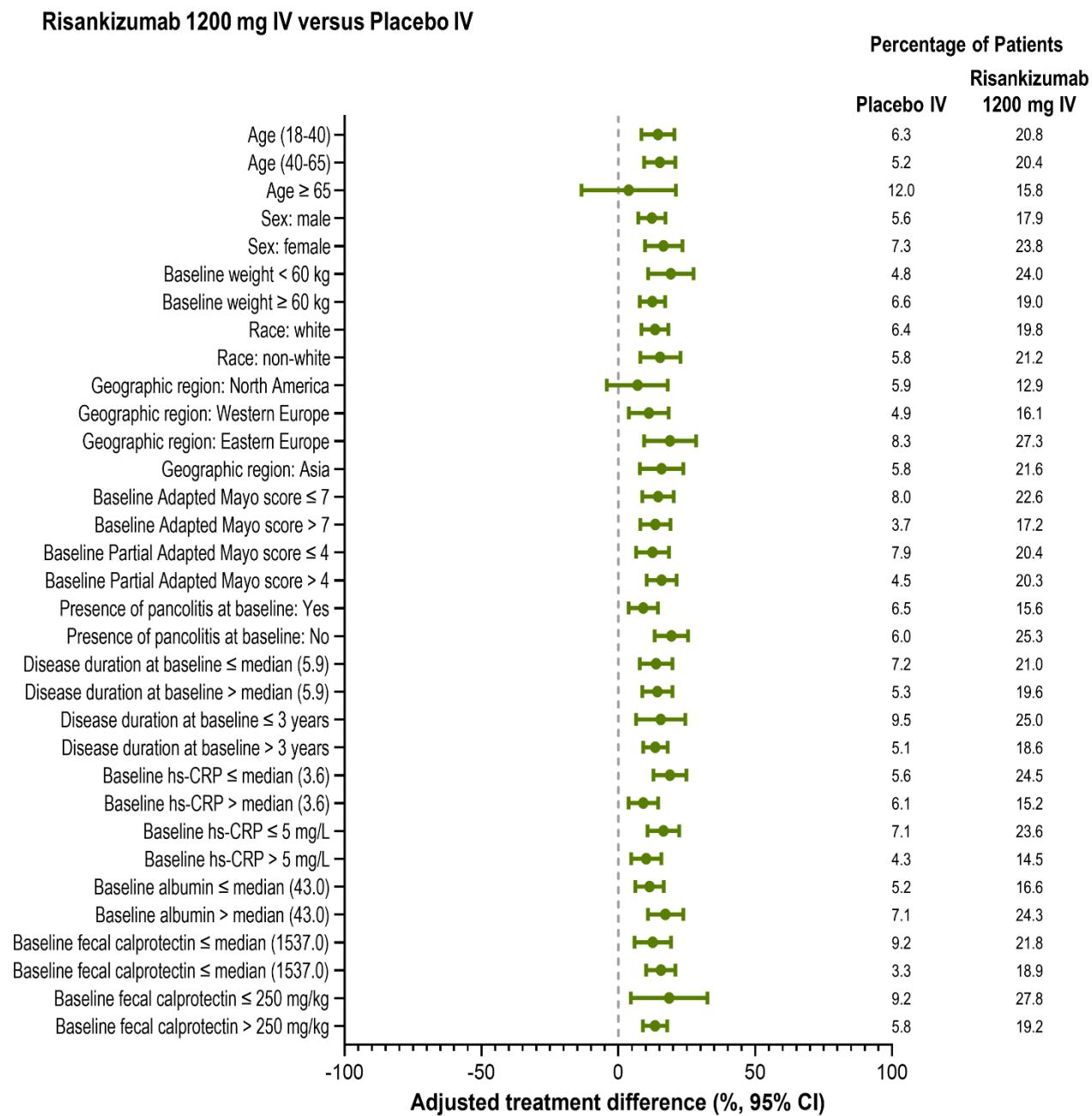
(continued)



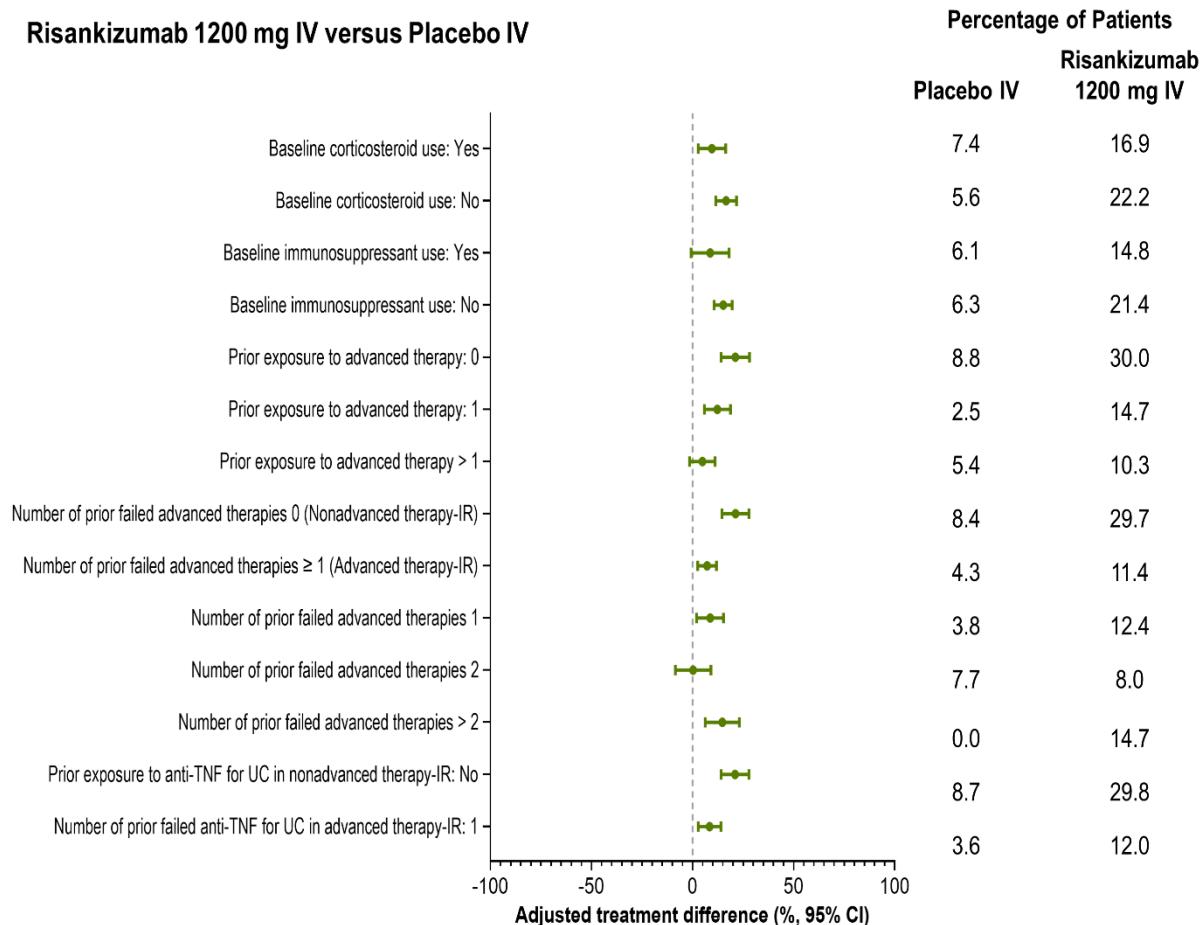
The LS mean and 95% CIs for the synthetic results were based on MMRM, with week 0, treatment, visit, treatment-by-visit interaction, and stratification factors. Median change from baseline and 95% CI were based on nonparametric analysis. Nonparametric analysis was performed, with *P* values for the treatment comparisons of each risankizumab dose versus placebo provided based on the Wilcoxon Rank Sum test. C-reactive protein and fecal calprotectin values were considered as observed before censoring. Week 0 was the last nonmissing measurement before the first dose of study drug in maintenance. Patients with only nonmissing change from week 0 values were included in this analysis. For eFigures 11A-D, \*\*\* *P* ≤ .001 RZB 1200 mg vs. PBO; eFigure 11E, \* *P* ≤ .05 RZB 180 mg vs. PBO (withdrawal) at week 52; \*\* *P* ≤ .01 RZB 180 mg or 360 mg vs. PBO (WD) at week 52; eFigure 11F, \*\* *P* ≤ .01 RZB 180 mg vs. PBO (WD) at week 24; \* *P* ≤ .05 RZB 360 mg vs. PBO (WD) at week 24; \*\*\* *P* ≤ .001 RZB 180 or 360 mg vs. PBO (WD) at week 52; eFigure 11G, \*\* *P* ≤ .01 RZB 360 mg vs. baseline at week 52; figure H, \* *P* ≤ .05 RZB 180 mg vs. PBO (withdrawal) at week 8; \*\*\* *P* ≤ .001 RZB 180 mg or 360 mg vs. PBO (WD) at week 52; eFigure 11I, \*\*\* *P* ≤ .001 vs. baseline for all groups except PBO IV/PBO SC. \* *P* ≤ .05 RZB 360 mg vs. baseline at week 4. CI, confidence interval; IL-22, interleukin-22; IV, intravenous; least square; MMRM, mixed-effect model repeated measures; RTB-MI; return-to-baseline multiple imputation; RZB, risankizumab; SC, subcutaneous.

**eFigure 6.** Clinical Remission per Adapted Mayo Score by Subgroup Analysis at Week 12 of Induction and Week 52 of Maintenance

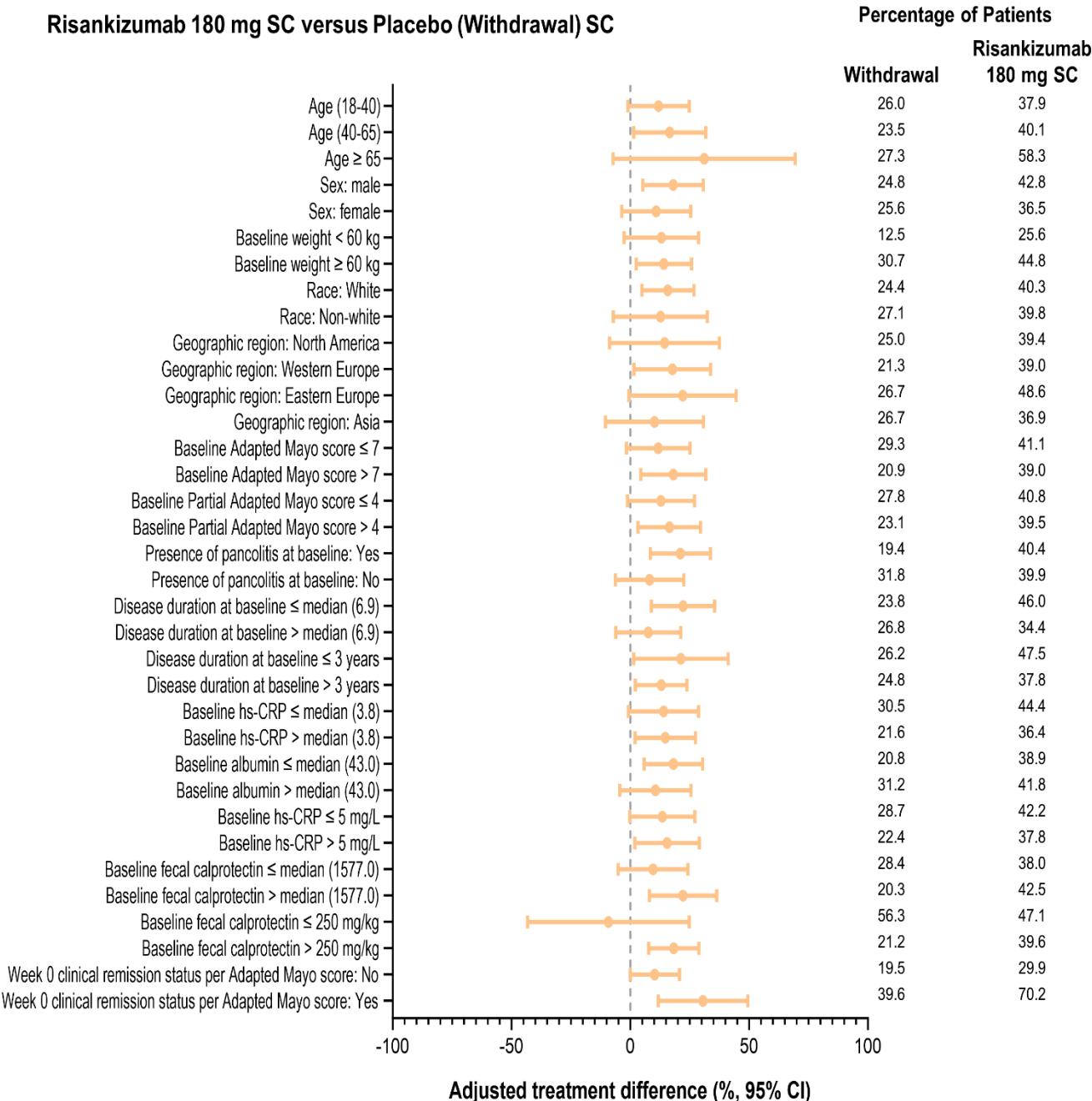
**A) Clinical Remission per Adapted Mayo Score at Week 12 of INSPIRE**



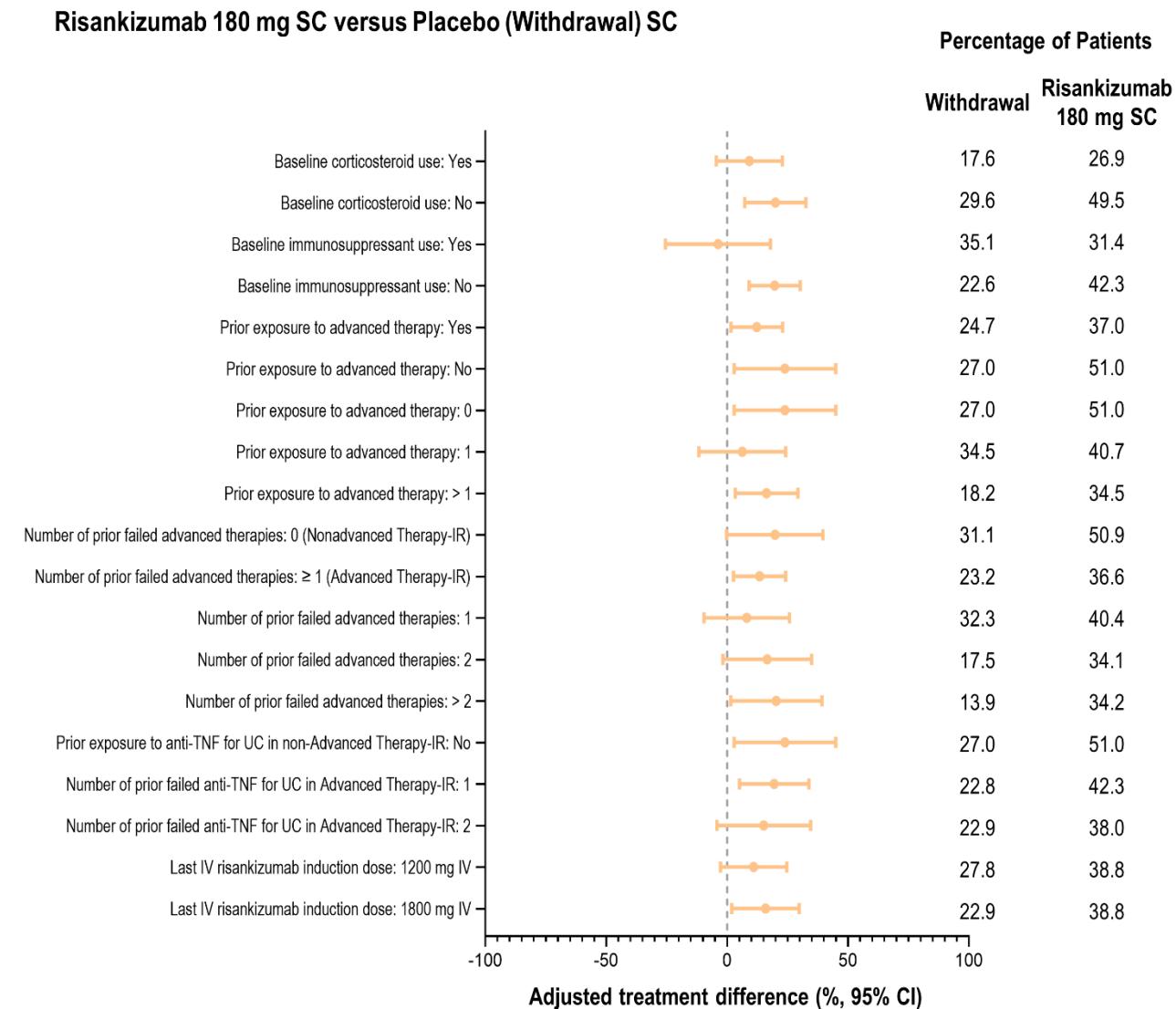
**A) Clinical Remission per Adapted Mayo Score at Week 12 of INSPIRE (continued)**



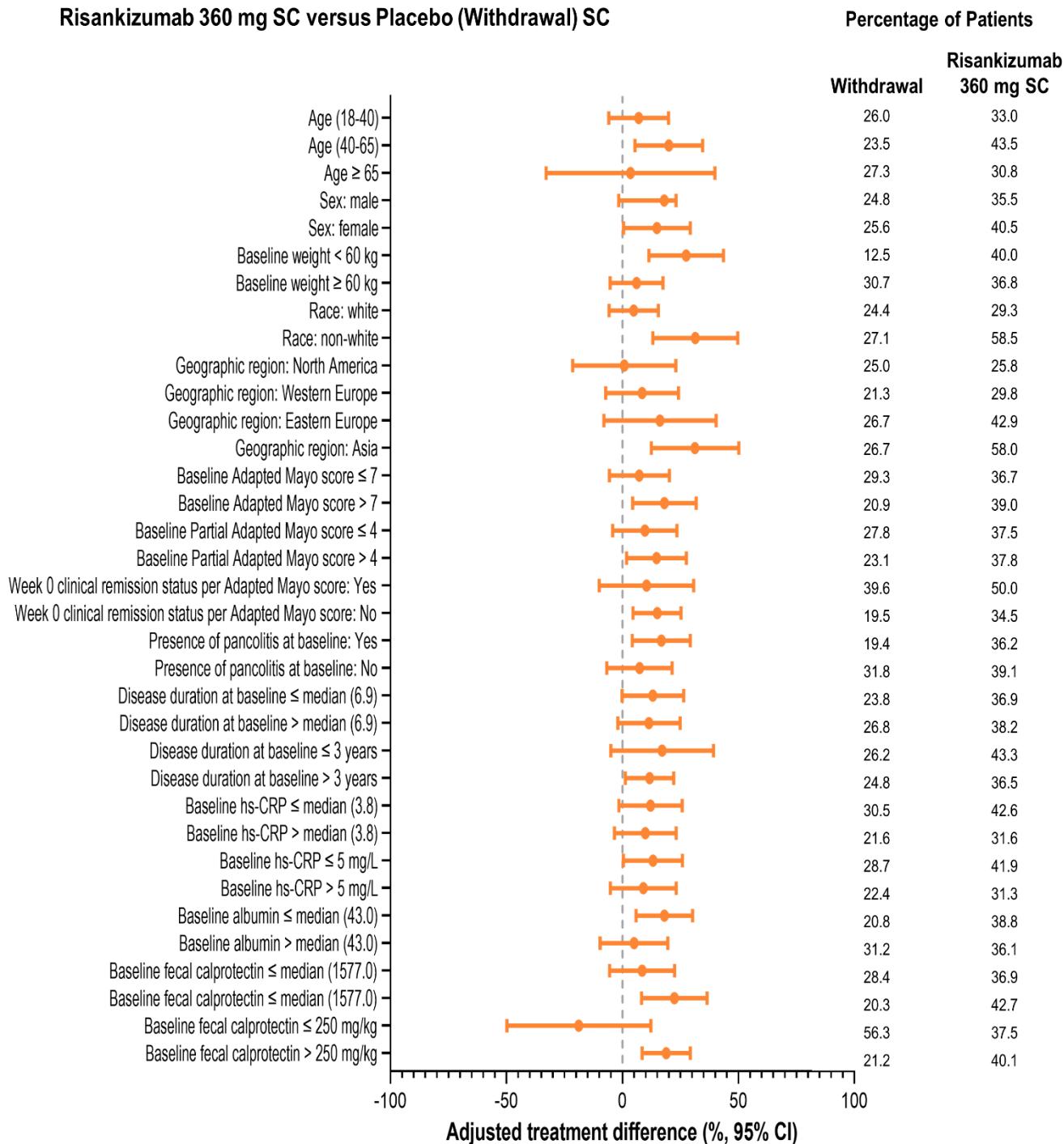
## B) Clinical Remission per Adapted Mayo Score at Week 52 of COMMAND



**B) Clinical Remission per Adapted Mayo Score at Week 52 of COMMAND (continued)**

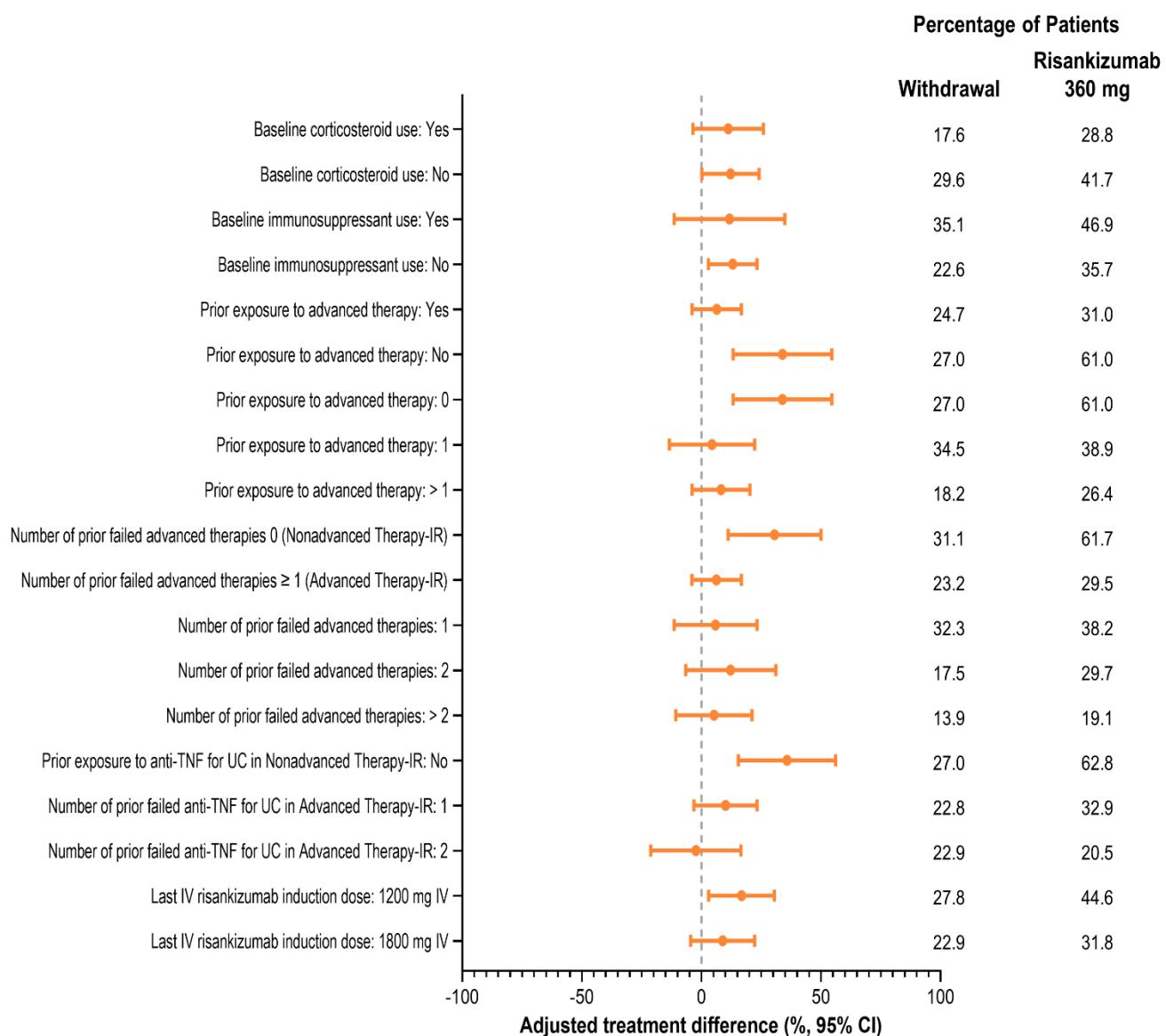


### C) Clinical Remission per Adapted Mayo Score at Week 52 of COMMAND



### C) Clinical Remission per Adapted Mayo Score at Week 52 of COMMAND (continued)

#### Risankizumab 360 mg SC versus Placebo (Withdrawal) SC



**eTable 1.** Baseline Characteristics for the Dose-Ranging Phase 2b Induction Substudy

Variable	Risankizumab			
	600 mg IV n = 61	1200 mg IV n = 61	1800 mg IV n = 58	Placebo IV n = 60
Sex				
Females	21 (34.4)	26 (42.6)	27 (46.6)	24 (40.0)
Males	40 (65.6)	35 (57.4)	31 (53.4)	36 (60.0)
Age, years, mean (SD)	43.0 (14.9)	41.8 (13.8)	40.9 (13.7)	44.4 (14.1)
Race				
White	49 (80.3)	45 (73.8)	45 (77.6)	44 (73.3)
Other <sup>a</sup>	12 (19.6)	16 (26.2)	13 (22.4)	16 (26.6)
Body mass index, kg/m <sup>2</sup> , mean (SD)	n = 60 24.2 (5.0)	n = 61 25.6 (6.3)	n = 58 24.0 (5.5)	n = 60 24.9 (5.1)
Disease duration, years, mean (SD)	10.0 (6.9)	9.8 (8.3)	8.5 (5.5)	10.4 (6.8)
Disease extent				
Left-sided colitis	29 (47.5)	22 (36.1)	23 (39.7)	30 (50.0)
Extensive colitis/pancolitis	32 (52.5)	39 (63.9)	35 (60.3)	30 (50.0)
Adapted Mayo score, mean (SD)	6.9 (1.2)	7.0 (1.1)	7.2 (1.4)	7.0 (1.2)
Endoscopy score, mean (SD)	2.7 (0.5)	2.7 (0.5)	2.8 (0.4)	2.8 (0.4)
High sensitivity-CRP (mg/L), median (range)	n = 57 3.3 (0.2, 112.0)	n = 60 6.4 (0.2, 46.7)	n = 58 4.7 (0.2, 167.0)	n = 59 3.4 (0.2, 57.8)
Fecal calprotectin, mg/kg, median (range)	n = 53 1792 (40, 19 839)	n = 50 1436 (30, 17 820)	n = 52 1467 (75, 24 505)	n = 53 1750 (30, 28800)
Medications at baseline				
Corticosteroids	27 (44.3)	30 (49.2)	25 (43.1)	25 (41.7)
Immunosuppressants	14 (23.0)	15 (24.6)	11 (19.0)	10 (16.7)
Aminosalicylates	33 (54.1)	40 (65.6)	42 (72.4)	38 (63.3)
Prior exposure to advanced therapies				
1	15 (24.6)	18 (29.5)	24 (41.4)	20 (33.3)
2	26 (42.6)	16 (26.2)	16 (27.6)	18 (30.0)
>2	20 (32.8)	27 (44.3)	18 (31.0)	22 (36.7)
Prior exposure to Anti-TNF	58 (95.1)	58 (95.1)	56 (96.6)	55 (91.7)
Patients who failed to respond to advanced therapies				
Any biologic	60 (98.4)	61 (100)	55 (94.8)	59 (98.3)
Anti-integrin inhibitor	35 (57.4)	33 (54.1)	27 (46.6)	34 (56.7)
Janus kinase inhibitors	10 (16.4)	16 (26.2)	8 (13.8)	12 (20.0)

<sup>a</sup> For race, the Other category included patients who were Asian or Black/African American. No identified as being American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander, or multiple races.

CRP, C-reactive protein; IV, intravenous; SD, standard deviation; TNF, tumor necrosis factor.

**eTable 2.** Treatment-Emergent Adverse Events From the Dose-Ranging Phase 2b Induction Substudy

AE, n (%)	Risankizumab			
	600 mg IV n = 64	1200 mg IV n = 61	1800 mg IV n = 56	Placebo IV n = 59
<b>Overview of Treatment-Emergent Adverse Events</b>				
Any AE	37 (57.8)	27 (44.3)	27 (48.2)	37 (62.7)
AE possibly related to study drug <sup>a</sup>	10 (15.6)	9 (14.8)	10 (17.9)	13 (22.0)
Severe AE	3 (4.7)	3 (4.9)	3 (5.4)	6 (10.2)
Serious AE	6 (9.4)	4 (6.6)	3 (5.4)	6 (10.2)
AE leading to discontinuation of study drug	2 (3.1)	2 (3.3)	1 (1.8)	5 (8.5)
All deaths	0	0	0	0
<b>Most Frequently Occurring Adverse Events (≥ 5% in any treatment group)</b>				
Nasopharyngitis	5 (7.8)	3 (4.9)	5 (8.9)	4 (6.8)
Headache	2 (3.1)	3 (4.9)	4 (7.1)	3 (5.1)
Colitis ulcerative	2 (3.1)	3 (4.9)	1 (1.8)	7 (11.9)
Anemia	0	4 (6.6)	1 (1.8)	2 (3.4)
Bronchitis	4 (6.3)	1 (1.6)	0	0
<b>Treatment-Emergent Adverse of Special Interest<sup>b</sup></b>				
Serious infections	2 (3.1)	1 (1.6)	2 (3.6)	0
Opportunistic infection excluding tuberculosis and herpes zoster	1 (1.6)	0	0	0
Malignancies	0	0	0	1 (1.7)
Malignancies excluding nonmelanoma skin cancer	0	0	0	1 (1.7)
Serious hypersensitivity	0	0	0	1 (1.7)

<sup>a</sup> As assessed by study investigator.

<sup>b</sup> No active tuberculosis, serious anaphylactic reactions, adjudicated anaphylactic reactions, or adjudicated MACE were reported in any treatment group.

AE, adverse event; IV, intravenous; MACE, major adverse cardiovascular event; NMSC, nonmelanoma skin cancer.

**eTable 3.** Additional Baseline Characteristics and Demographics

Endpoint, n/N (%)	Induction – 12 weeks		Maintenance – 52 weeks		
	Risankizumab 1200 mg IV	Placebo IV	Risankizumab 180 mg SC n = 179	Risankizumab 360 mg SC n = 186	Placebo (Withdrawal) SC n = 183
<b>Additional Baseline Characteristics and Demographics for Phase 3 Induction and Maintenance Studies</b>					
Baseline of Induction (Week 0) <sup>a</sup>					
No bowel urgency	47/650 (7.3)	30/325 (9.3)	97/176 (55.1)	83/174 (47.7)	79/173 (45.7)
No abdominal pain	47/650 (7.3)	32/325 (9.9)	87/174 (50.0)	77/172 (44.8)	74/169 (43.8)
No tenesmus	84/650 (13.2)	42/325 (13.2)	37/64 (57.8)	40/67 (59.7)	42/65 (64.6)
No nocturnal bowel movements	191/650 (30.0)	82/325 (25.8)	43/55 (78.2)	36/49 (73.5)	41/49 (83.7)
Baseline of Maintenance (Week 0)					
Endpoint, n (%)	Induction – 12 weeks		Maintenance – 52 weeks		
	Risankizumab 1200 mg IV	Placebo IV	Risankizumab 180 mg SC n = 179	Risankizumab 360 mg SC n = 186	Placebo (Withdrawal) SC n = 183
Adapted Mayo score, mean (SD)	--	--	n = 177 3.1 (1.6)	n = 185 3.1 (1.5)	n = 180 3.0 (1.6)
Endoscopy score, mean (SD)	--	--	n = 177 1.9 (1.0)	n = 185 1.9 (1.0)	n = 180 1.7 (1.1)
Clinical remission status, yes	--	--	44 (24.7)	40 (21.6)	53 (29.3)
Endoscopic improvement status, yes	--	--	61 (34.1)	68 (36.6)	78 (42.6)
C-reactive protein (mg/L), median (range)	--	--	2.3 (0.2, 40.4)	1.2 (0.2, 41.0)	1.4 (0.2, 66.7)
Fecal calprotectin (µg/g), median (range)	--	--	366 (30, 8466)	279 (30, 16182)	324 (30, 24505)
Corticosteroid use, yes	--	--	67 (37.4)	52 (28.0)	61 (33.3)

**eTable 3.** Additional Baseline Characteristics and Demographics (continued)

Characteristic	Patients Who Received Risankizumab 1200 mg IV During Induction			
	Risankizumab 1200 mg/ Placebo IV n = 90	Risankizumab 1200 mg IV/ Risankizumab 180 mg SC n = 90	Risankizumab 1200 mg/ Risankizumab 360 mg n = 92	Placebo IV/ Placebo SC n = 70
Sex				
Females	36 (40.0)	37 (41.1)	39 (42.4)	24 (34.3)
Males	54 (60.0)	53 (58.9)	53 (57.6)	46 (65.7)
Age, years, mean (SD)	40.7 (14.7)	42.9 (14.3)	42.3 (13.4)	45.4 (14.4)
Body mass index, <sup>b</sup> kg/m <sup>2</sup> , mean (SD)	n = 90 24.9 (5.9)	n = 89 25.2 (5.1)	n = 92 23.8 (5.2)	n = 70 24.9 (4.6)
Race <sup>c</sup>				
American Indian or Alaska Native	0	0	0	0
Asian	31 (34.4)	24 (26.7)	33 (35.9)	27 (38.6)
Black or African American	0	2 (2.2)	0	3 (4.3)
Native Hawaiian or Other Pacific Islander	0	0	0	0
Multiple	0	0	1 (1.1)	2 (2.9)
White	59 (65.6)	64 (71.1)	58 (63.0)	38 (54.3)
Ethnicity				
Hispanic/Latino	2 (2.2)	11 (12.2)	6 (6.5)	3 (4.3)
Not Hispanic/Latino	88 (97.8)	79 (87.8)	86 (93.5)	67 (95.7)
Disease duration, years, mean (SD)	8.3 (7.9)	7.8 (6.7)	8.4 (7.3)	8.0 (6.5)
Disease extent				
Left-sided	48 (53.3)	49 (54.4)	45 (48.9)	37 (52.9)
Extensive or pancolitis	42 (46.7)	41 (45.6)	47 (51.1)	33 (47.1)
Limited to rectum	0	0	0	0
Adapted Mayo score <sup>d</sup>				
≤ 7	50 (55.6)	58 (64.4)	52 (56.5)	34 (48.6)
> 7	40 (44.4)	32 (35.6)	40 (43.5)	36 (51.4)
Mean (SD)	7.1 (1.2)	7.1 (1.2)	7.0 (1.3)	7.2 (1.3)
Endoscopic subscore <sup>e</sup>				
2	28 (31.1)	28 (31.1)	35 (38.0)	18 (25.7)
3	62 (68.9)	62 (68.9)	57 (62.0)	52 (74.3)
Mean (SD)	2.7 (0.5)	2.7 (0.5)	2.6 (0.5)	2.7 (0.4)
C-reactive protein (mg/L), <sup>f</sup> median (range)	n = 86 3.5 (0.2, 40.8)	n = 90 4.5 (0.2, 82.2)	n = 92 2.0 (0.2, 113.0)	n = 68 2.9 (0.2, 59.3)
Fecal calprotectin (μg/g), <sup>g</sup> median (range)	n = 83 1508 (30, 20,202)	n = 82 1533 (30, 28,800)	n = 84 1381 (30, 28,800)	n = 67 1495 (30, 28,800)
Immunosuppressants	16 (17.8)	14 (15.6)	13 (14.1)	15 (21.4)
Aminosalicylates	65 (72.2)	65 (72.2)	75 (81.5)	48 (68.6)
Corticosteroids	29 (32.2)	38 (42.2)	26 (28.3)	20 (28.6)
Advanced therapy – Inadequate response <sup>h</sup>				
Advanced therapy – inadequate response	48 (53.3)	48 (53.3)	43 (52.2)	36 (51.4)
Non-advanced therapy – inadequate response	42 (46.7)	42 (46.7)	44 (47.8)	34 (48.6)
Nonresponse to advanced therapies				
0	42 (46.7)	42 (46.7)	44 (47.8)	34 (48.6)
1	26 (28.9)	20 (22.2)	20 (21.7)	21 (30.0)
2	11 (12.2)	18 (20.0)	11 (12.0)	8 (11.4)
>2	11 (12.2)	10 (11.1)	17 (18.5)	7 (10.0)
Nonresponse to anti-TNF therapy for advanced therapy – inadequate response patients				
0	4 (8.3)	7 (14.6)	5 (10.4)	7 (19.4)
1	34 (70.8)	26 (54.2)	29 (60.4)	18 (50.0)
2	8 (16.7)	15 (31.3)	13 (27.1)	9 (25.0)
>2	2 (4.2)	0	1 (2.1)	2 (5.6)

Data are presented are reported on nonmissing data and reported as n (%) unless stated otherwise. Reported here are baseline demographics and disease characteristics at week 0 of induction and maintenance for the primary efficacy populations of each study, which included all randomized patients who received at least one dose of study drug during the 12-week induction or 52-week maintenance studies after receiving risankizumab IV for one period of 12 weeks in the induction study. Additional baseline demographics and disease characteristics are presented in Table 1.

Also included are baseline characteristics and disease demographics for all patients who received risankizumab 1200 mg or placebo IV during induction and were randomized to maintenance. Treatment groups were named according to treatments received during induction/maintenance.

<sup>a</sup>For the patient-reported outcomes, the baseline disease characteristics were assessed in patients with disease symptoms at baseline of induction.

<sup>b</sup>The body mass index is the weight in kilograms divided by the square of the height in meters.

<sup>c</sup>The multiple race category includes participants who responded to 2 or more categories. For reporting race, patients were asked to respond to closed category questions, with the option of multiple selection.

<sup>d</sup>Adapted Mayo score (score range 0-9): RBS, 0-3; SFS, 0-3; endoscopy score (0-3).

<sup>e</sup>Endoscopy score was evaluated for each observed segment of the colon (rectum, sigmoid, descending colon, transverse colon, ascending colon/cecum) using a 4-point scale, with a higher score indicating more severe disease.

<sup>f</sup>The reference range for C-reactive protein is 0 to 10 mg per liter.

<sup>g</sup>The reference value for fecal calprotectin is less than 50 µg per gram.

<sup>h</sup>Advanced therapies included infliximab, adalimumab, golimumab, vedolizumab, tofacitinib, filgotinib, upadacitinib, and/or ozanimod. Inadequate response was defined as an inability to respond or unacceptable side effects to therapy.

IV, intravenous; SC, subcutaneous; SD, standard deviation; TNF, tumor necrosis factor.

**eTable 4.** Primary and Secondary Endpoints at Week 52 of Maintenance for All Patients Who Responded to 12-Week Risankizumab 1200 mg Induction Therapy and Were Randomized to Maintenance

Endpoint, % (95% CI) <sup>a</sup> unless otherwise specified	Risankizumab 1200 mg IV/ Placebo SC n = 90	Risankizumab 1200 mg IV/ Risankizumab 180 mg SC n = 90	Adjusted Treatment Difference	Risankizumab 1200 mg IV/ Risankizumab 360 mg SC n = 92	Adjusted Treatment Difference	Placebo IV/Placebo SC n = 70
Clinical remission per Adapted Mayo score	27.8 (18.5, 37.0)	38.8 (28.7, 48.9)	12.3 (-0.4, 25.0)	44.6 (34.4, 54.7)	18.3 (5.3, 31.3)**	17.1 (8.3, 26.0)
Clinical response per Adapted Mayo score	58.9 (48.7, 69.1)	72.2 (63.0, 81.5)	13.3 (0.0, 26.7)*	68.5 (59.0, 78.0)	9.2 (-4.4, 22.8)	38.6 (27.2, 50.0)
Endoscopic improvement	36.7 (26.7, 46.6)	52.1 (41.8, 62.5)	16.6 (2.9, 30.2)*	57.5 (47.4, 67.7)	21.8 (8.2, 35.3)**	18.6 (9.5, 27.7)
Histologic-endoscopic mucosal improvement	27.8 (18.5, 37.0)	47.6 (37.2, 57.9)	20.9 (7.7, 34.1)**	53.0 (42.8, 63.3)	26.7 (13.6, 39.8)***	12.9 (5.0, 20.7)
Endoscopic remission	15.6 (8.1, 23.0)	25.9 (16.8, 35.0)	11.5 (0.5, 22.5)*	35.3 (25.5, 45.1)	19.6 (8.0, 31.2)***	5.7 (0.3, 11.2)
No bowel urgency	38.9 (28.8, 49.0)	55.6 (45.3, 65.8)	17.0 (3.0, 30.9)*	52.0 (41.7, 62.2)	13.0 (-1.0, 27.1)	37.1 (25.8, 48.5)
No abdominal pain	35.6 (25.7, 45.4)	51.1 (40.8, 61.4)	15.6 (1.5, 29.7)*	43.6 (33.5, 53.8)	7.9 (-6.3, 22.1)	31.4 (20.6, 42.3)
Histologic endoscopic mucosal remission	11.1 (4.6, 17.6)	18.0 (10.0, 25.9)	7.6 (-2.3, 17.4)	20.9 (12.5, 29.2)	10.2 (0.2, 20.2)*	2.9 (0.0, 6.8)
Change from induction baseline in FACIT-F total score	n = 84 (6.0) (3.3, 8.6)	n = 82 (9.4) (7.1, 11.6)	3.4 (-0.03, 6.9)	n = 86 (8.4) (5.9, 10.8)	2.4 (-1.1, 5.8)	n = 62 (8.5) (4.8, 12.3)
Change from induction baseline in IBDQ total score	n = 84 37.2 (28.4, 46.0)	n = 82 52.5 (44.0, 61.0)	15.3 (3.2, 27.4)*	n = 88 46.8 (38.1, 55.5)	9.6 (-2.8, 22.0)	n = 62 36.9 (23.6, 50.2)
Occurrence of UC-related hospitalizations, n/100 PYs	3.6	0	-3.6 (-7.6, 0.5)	0	-3.6 (-7.6, 0.5)	3.7
No nocturnal bowel movements	46.7 (36.4, 57.0)	54.4 (44.2, 64.7)	8.1 (-5.2, 21.4)	57.4 (47.3, 67.6)	10.8 (-2.8, 24.5)	35.7 (24.5, 46.9)
No tenesmus	37.8 (27.8, 47.8)	48.9 (38.6, 59.2)	11.2 (-2.4, 24.8)	49.7 (39.4, 59.9)	12.0 (-2.2, 26.1)	27.1 (16.7, 37.6)
Change from baseline in number of fecal incontinence episodes per week	n = 69 -2.8 (-4.3, -1.4)	n = 66 -3.4 (-4.7, -2.2)	-0.6 (-2.4, 1.3)	n = 70 -2.9 (-4.2, -1.5)	-0.02 (-2.0, 1.9)	n = 48 -1.8 (-3.6, 0.0)
Change from baseline in number of days per week with sleep interrupted due to UC symptoms	n = 69 -1.8 (-2.3, -1.2)	n = 66 -2.6 (-3.1, -2.0)	-0.8 (-1.6, -0.01)*	n = 70 -2.5 (-3.0, -1.9)	-0.7 (-1.5, 0.1)	-2.0 (-2.9, -1.0)
Maintenance of clinical remission	n = 30 40.0 (22.5, 57.5)	n = 26 72.8 (55.6, 90.0)	32.3 (7.7, 56.8)**	n = 21 61.9 (41.1, 82.7)	21.6 (-5.2, 48.5)	n = 13 38.5 (12.0, 64.9)
Corticosteroid-free clinical remission	27.8 (18.5, 37.0)	37.7 (27.7, 47.7)	11.3 (-1.3, 23.9)	43.5 (33.3, 53.6)	17.3 (4.3, 30.3)**	17.1 (8.3, 26.0)
Maintenance of endoscopic improvement	n = 43 51.2 (36.2, 66.1)	n = 36 74.8 (60.6, 89.1)	21.4 (1.6, 41.3)*	n = 42 59.4 (44.5, 74.3)	6.4 (-14.4, 27.2)	n = 19 26.3 (6.5, 46.1)

Reported here are maintenance efficacy outcomes at week 52 for all patients who received risankizumab 1200 mg or placebo during induction and were randomized to maintenance. Treatment groups were named according to treatments received during induction/maintenance. Analyses for placebo IV/placebo SC were not adjusted for multiplicity. Results for categorical endpoints (except occurrence of ulcerative colitis-related hospitalization) were based on nonresponder imputation incorporating multiple imputation to handle missing data due to logistic restrictions (COVID-19 or the geopolitical conflict in Ukraine and surrounding impacted regions) (NRI-MI). Results for continuous endpoints were based on RTB-MI. Between-group difference and 95% CIs were calculated using Mantel-Haenszel common rate difference with NRI-MI for categorical endpoints (Normal approximation to binomial distribution for occurrence of hospitalization) and ANCOVA/MMRM with RTB-MI for continuous endpoints.\*  $P \leq .05$ ; \*\*  $P \leq .01$ ; \*\*\*  $P \leq .001$  versus risankizumab 1200 mg IV/placebo SC.

<sup>a</sup>Adjusted treatment differences refer to the difference between risankizumab 1200 mg IV/risankizumab 180 mg or risankizumab 360 mg vs. risankizumab 1200 mg IV/placebo SC.

ANCOVA, analysis of covariance; CI, confidence interval; COVID-19, coronavirus disease 2019; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; LS, least-square; IBDQ, Inflammatory Bowel Disease Questionnaire; IV, intravenous; MMRM, mixed-effect model repeated measures; NRI-MI, nonresponder multiple imputation; PY, patient-years; RTB-MI, return-to-baseline multiple imputation; SC, subcutaneous; UC, ulcerative colitis.

**eTable 5.** Prespecified Primary and Secondary Endpoints in Non-Advanced and Advanced Therapy-Inadequate Response Patients in the Phase 3 Induction and Maintenance Studies

Induction, Week 12						
Endpoint, % (95% CI)	Non-Advanced Therapy Inadequate Response Patients			Advanced Therapy-Inadequate Response Patients		
	Risankizumab 1200 mg IV n = 317	Placebo IV n = 155	Adjusted treatment difference versus placebo	Risankizumab 1200 mg IV n = 333	Placebo IV n = 170	Adjusted treatment difference versus placebo
Primary Outcome						
Clinical remission per Adapted Mayo Score	29.7 (24.6, 34.7)	8.4 (4.0, 12.8)	21.3 (14.6, 27.9)	11.4 (8.0, 14.8)	4.3 (1.2, 7.3)	7.2 (2.6, 11.8)
Secondary Outcomes						
Clinical response per Adapted Mayo score	73.8 (69.0, 78.7)	40.6 (32.9, 48.4)	33.2 (24.0, 42.3)	55.2 (49.8, 60.5)	31.2 (24.2, 38.1)	24.0 (15.2, 32.8)
Endoscopic improvement	47.6 (42.1, 53.1)	14.2 (8.7, 19.7)	33.4 (25.7, 41.2)	25.9 (21.2, 30.6)	10.1 (5.6, 14.7)	15.8 (9.2, 22.3)
Histologic-endoscopic mucosal improvement	33.4 (28.2, 38.6)	8.4 (4.0, 12.8)	25.1 (18.3, 31.8)	16.0 (12.0, 19.9)	7.1 (3.2, 11.0)	8.9 (3.3, 14.4)
Endoscopic remission	16.7 (12.6, 20.8)	3.9 (0.8, 6.9)	12.8 (7.7, 18.0)	4.8 (2.5, 7.1)	3.0 (0.4, 5.5)	1.8 (-1.6, 5.3)
Clinical response per Partial Adapted Mayo score at week 4	57.7 (52.3, 63.2)	32.3 (24.9, 39.6)	25.5 (16.3, 34.6)	46.9 (41.5, 52.3)	28.9 (22.1, 35.8)	18.0 (9.3, 26.7)
No bowel urgency	53.0 (47.5, 58.5)	29.7 (22.5, 36.9)	23.3 (14.3, 32.4)	35.6 (30.4, 40.8)	25.9 (19.3, 32.5)	9.7 (1.4, 18.1)
No abdominal pain	39.4 (34.1, 44.8)	25.2 (18.3, 32.0)	14.3 (5.6, 23.0)	32.3 (27.2, 37.3)	27.6 (20.9, 34.4)	4.6 (-3.8, 13.0)
Histologic-endoscopic mucosal remission	10.7 (7.3, 14.1)	0	10.7 (7.3, 14.1)	2.1 (0.6, 3.6)	1.2 (0.0, 2.8)	0.9 (-1.3, 3.2)
Change from baseline in mean FACIT-F	n = 302 8.7 (7.5, 9.9)	n = 147 4.1 (2.4, 5.8)	n = 312 4.6 (2.6, 6.5)	n = 312 6.9 (5.8, 8.1)	n = 161 2.4 (0.7, 4.1)	4.6 (2.5, 6.6)
Change from baseline in mean IBDQ total score	n = 305 48.5 (44.3, 52.6)	n = 148 28.3 (22.5, 34.2)	n = 314 20.1 (13.3, 27.0)	n = 314 36.8 (32.6, 41.0)	n = 162 19.9 (14.0, 25.8)	16.9 (9.7, 24.1)
UC-related hospitalizations through week 12	0.9 (0.0, 2.0)	3.2 (0.4, 6.0)	-2.3 (-5.3, 0.7)	0.6 (0.0, 1.4)	7.6 (3.7, 11.6)	-7.0 (-11.1, -3.0)
No nocturnal bowel movements	73.5 (68.6, 78.4)	49.0 (41.2, 56.9)	24.5 (15.2, 33.7)	61.4 (56.1, 66.6)	37.6 (30.4, 44.9)	23.7 (14.7, 32.7)
No tenesmus	55.8 (50.4, 61.3)	27.1 (20.1, 34.1)	28.7 (19.9, 37.6)	42.0 (36.6, 47.3)	32.9 (25.9, 40.0)	9.0 (0.2, 17.9)
Change from baseline in number of fecal incontinence episodes per week	n = 303 -3.9 (-4.5, -3.4)	n = 136 -2.2 (-3.1, -1.3)	n = 299 -1.7 (-2.8, -0.7)	n = 299 -3.7 (-4.3, -3.1)	n = 152 -2.1 (-3.1, -1.2)	-1.5 (-2.7, -0.4)
Change from baseline to induction week 12 number of days per week with sleep interrupted due to UC symptoms	n = 303 -2.5 (-2.8, -2.2)	n = 136 -1.6 (-2.0, -1.2)	n = 299 -0.9 (-1.4, -0.4)	n = 299 -2.4 (-2.7, -2.1)	n = 152 -1.4 (-1.8, -0.9)	-1.1 (-1.6, -0.6)

**eTable 5.** Prespecified Primary and Secondary Endpoints in Non-Advanced and Advanced Therapy-Inadequate Response Patients in the Phase 3 Induction and Maintenance Studies (continued)

Nonadvanced Therapy-Inadequate Response Patients, Week 52 of Maintenance					
Endpoint, % (95% CI) unless otherwise specified	Risankizumab 180 mg SC n = 45	Adjusted treatment difference versus placebo (withdrawal)	Risankizumab 360 mg SC n = 47	Adjusted treatment difference versus placebo (withdrawal)	Placebo (Withdrawal) SC n = 45
Primary Outcome					
Clinical remission per Adapted Mayo Score	50.9 (36.2, 65.6)	19.8 (-0.2, 39.7)	61.7 (47.8, 75.6)	30.6 (11.2, 50.0)	31.1 (17.6, 44.6)
Secondary Outcomes					
Clinical response per Adapted Mayo score	82.2 (71.1, 93.4)	11.1 (-6.2, 28.4)	78.7 (66.9, 90.4)	7.5 (-10.2, 25.2)	71.1 (57.9, 84.4)
Endoscopic improvement	59.8 (45.4, 74.2)	24.2 (4.2, 44.3)	76.2 (63.9, 88.5)	40.6 (22.0, 59.2)	35.6 (21.6, 49.5)
Histologic-endoscopic mucosal improvement	54.8 (40.1, 69.5)	25.9 (6.1, 45.7)	69.3 (55.9, 82.6)	40.4 (21.6, 59.2)	28.9 (15.6, 42.1)
Endoscopic remission	36.6 (22.3, 50.8)	16.6 (-1.8, 35.0)	51.6 (37.2, 66.0)	31.6 (13.1, 50.2)	20.0 (8.3, 31.7)
No bowel urgency	66.7 (52.9, 80.4)	24.4 (4.5, 44.4)	67.8 (54.4, 81.2)	25.6 (5.9, 45.3)	42.2 (27.8, 56.7)
No abdominal pain	55.6 (41.0, 70.1)	22.2 (2.2, 42.2)	49.5 (35.1, 63.9)	16.2 (-3.8, 36.1)	33.3 (19.6, 47.1)
Histologic-endoscopic mucosal remission	27.0 (14.0, 40.1)	9.3 (-7.9, 26.5)	32.1 (18.7, 45.5)	14.3 (-3.1, 31.8)	17.8 (6.6, 28.9)
Change from baseline of induction in FACIT-F	n = 43 8.7 (4.0, 13.4)	3.4 (-1.0, 7.7)	n = 44 7.9 (2.9, 12.9)	2.6 (-1.8, 6.9)	n = 44 5.3 (0.2, 10.5)
Change from baseline of induction in IBDQ total score	n = 43 54.9 (37.8, 72.1)	18.0 (2.7, 33.3)	n = 45 47.9 (29.4, 66.5)	11.0 (-3.8, 25.7)	n = 44 37.0 (17.9, 56.0)
Exposure-adjusted occurrence of UC-related hospitalizations from week 0 through week 52 of maintenance (n/100 PYs)	0	0	0	0	0
No nocturnal bowel movements	77.8 (65.6, 89.9)	15.6 (-3.1, 34.2)	74.4 (61.9, 86.9)	12.2 (-6.7, 31.1)	62.2 (48.1, 76.4)
No tenesmus	68.9 (55.4, 82.4)	24.4 (4.6, 44.3)	59.0 (44.8, 73.2)	14.6 (-5.7, 34.9)	44.4 (29.9, 59.0)
Change from baseline of the induction in the number of fecal incontinence episodes per week	n = 37 -3.9 (-5.0, -2.9)	-1.4 (-3.2, 0.4)	n = 41 -3.3 (-4.6, -2.1)	-0.8 (-2.8, 1.2)	n = 38 -2.6 (-4.1, -1.0)
Change from baseline of the induction number of days per week with sleep interrupted due to UC symptoms	n = 37 -2.9 (-3.4, -2.4)	-1.0 (-1.7, -0.2)	n = 41 -2.7 (-3.3, -2.2)	-0.8 (-1.5, 0.0)	n = 38 -2.0 (-2.5, -1.4)
Maintenance of clinical remission	n = 18 77.2 (57.6, 96.9)	32.8 (2.6, 63.0)	n = 15 60.0 (35.2, 84.8)	15.6 (-18.2, 49.3)	n = 18 44.4 (21.5, 67.4)
Corticosteroid-free clinical remission	50.9 (36.2, 65.6)	19.8 (-0.2, 39.7)	59.6 (45.5, 73.6)	28.5 (9.0, 48.0)	31.1 (17.6, 44.6)
Maintenance of endoscopic improvement	n = 21 85.2 (69.8, 100.0)	30.7 (4.8, 56.6)	n = 27 65.9 (47.8, 84.0)	11.4 (-16.2, 39.0)	n = 22 54.5 (33.7, 75.4)

**eTable 5.** Prespecified Primary and Secondary Endpoints in Non-Advanced and Advanced Therapy-Inadequate Response Patients in the Phase 3 Induction and Maintenance Studies (continued)

Advanced Therapy-Inadequate Response Patients, Week 52 of Maintenance					
Endpoint, % (95% CI) unless otherwise specified	Risankizumab 180 mg SC n = 134	Adjusted treatment difference versus placebo (withdrawal)	Risankizumab 360 mg SC n = 139	Adjusted treatment difference versus placebo (withdrawal)	Placebo (Withdrawal) SC n = 138
<b>Primary Outcome</b>					
Clinical remission per Adapted Mayo Score	36.6 (28.4, 44.7)	13.4 (2.6, 24.2)	29.5 (21.9, 37.1)	6.3 (-4.0, 16.7)	23.2 (16.1, 30.2)
<b>Secondary Outcomes</b>					
Clinical response per Adapted Mayo score	63.4 (55.3, 71.6)	17.8 (6.1, 29.4)	56.8 (48.6, 65.1)	11.2 (-0.5, 22.9)	45.7 (37.3, 54.0)
Endoscopic improvement	47.8 (39.3, 56.2)	17.3 (5.9, 28.7)	38.8 (30.7, 47.0)	8.4 (-2.7, 19.6)	30.4 (22.8, 38.1)
Histologic-endoscopic mucosal improvement	38.8 (30.6, 47.1)	17.1 (6.3, 27.8)	33.1 (25.3, 40.9)	11.4 (0.9, 21.8)	21.7 (14.9, 28.6)
Endoscopic remission	18.7 (12.1, 25.3)	5.6 (-3.1, 14.3)	15.1 (9.2, 21.1)	2.1 (-6.1, 10.3)	13.0 (7.4, 18.7)
No bowel urgency	49.3 (40.8, 57.7)	21.7 (10.4, 33.0)	43.2 (34.9, 51.4)	15.6 (4.5, 26.7)	27.5 (20.1, 35.0)
No abdominal pain	44.0 (35.6, 52.4)	15.8 (4.5, 27.0)	33.8 (25.9, 41.7)	5.6 (-5.3, 16.4)	28.3 (20.7, 35.8)
Histologic-endoscopic mucosal remission	8.2 (3.6, 12.9)	1.0 (-5.4, 7.3)	10.1 (5.1, 15.1)	2.8 (-3.8, 9.4)	7.2 (2.9, 11.6)
Change from baseline of induction in FACIT-F	n = 123 10.4 (7.8, 13.0)	4.1 (0.8, 7.4)	n = 119 9.8 (7.3, 12.4)	3.5 (0.3, 6.8)	n = 127 6.3 (3.8, 8.8)
Change from baseline of induction in IBDQ total score	n = 125 47.9 (38.8, 57.0)	17.5 (6.0, 29.1)	n = 123 47.3 (37.8, 56.8)	16.9 (4.1, 29.7)	n = 128 30.4 (21.2, 39.6)
Exposure-adjusted occurrence of UC-related hospitalizations from week 0 through week 52 of maintenance (n/100 PYs)	0.8	-3.4 (-7.4, 0.6)	1.7	-2.5 (-6.9, 1.8)	4.2
No nocturnal bowel movements	29.9 (22.1, 37.6)	10.3 (0.1, 20.5)	33.0 (25.2, 40.9)	13.5 (3.2, 23.7)	19.6 (12.9, 26.2)
No tenesmus	26.1 (18.7, 33.6)	9.5 (-0.2, 19.1)	29.3 (21.7, 36.9)	12.6 (2.8, 22.4)	16.7 (10.4, 22.9)
Change from baseline of the induction in the number of fecal incontinence episodes per week	n = 29 -2.9 (-5.5, -0.4)	0.1 (-3.4, 3.6)	n = 29 -2.3 (-5.1, 0.6)	0.8 (-3.0, 4.6)	n = 31 -3.0 (-5.4, -0.6)
Change from baseline of the induction number of days per week with sleep interrupted due to UC symptoms	n = 29 -2.3 (-3.4, -1.2) n = 26	-0.7 (-2.1, 0.8)	n = 29 -2.2 (-3.3, -1.1) n = 25	-0.6 (-2.0, 0.9)	n = 31 -1.7 (-2.7, -0.7) n = 35
Maintenance of clinical remission	65.4 (47.1, 83.7)	28.2 (3.9, 52.5)	44.0 (24.5, 63.5)	6.9 (-18.3, 32.1)	37.1 (21.1, 53.2)
Corticosteroid-free clinical remission	35.8 (27.7, 43.9)	12.6 (1.9, 23.4)	29.5 (21.9, 37.1)	6.3 (-4.0, 16.7)	23.2 (16.1, 30.2)
Maintenance of endoscopic improvement	n = 40 67.5 (53.0, 82.0)	22.9 (3.4, 42.4)	n = 41 46.3 (31.1, 61.6)	1.7 (-18.4, 21.8)	n = 56 44.6 (31.6, 57.7)

For induction, the patient population included all randomized patients who received at least one dose of study drug during the first 12-week study period. For maintenance, the patient population included all randomized patients who received at least one dose of study drug after receiving IV risankizumab (either 600 mg, 1200 mg, or 1800 mg) for 12 weeks in the phase 2b/3 induction studies, including those that went through the extended treatment period. Results for categorical endpoints were based on NRI-MI to handle missing data due to logistic restrictions (COVID-19 or the geopolitical conflict in Ukraine and surrounding impacted regions), apart from UC-related hospitalizations. Results for continuous endpoints were based on RTB-MI. Point estimate and 95% CI for treatment differences were based on normal approximation to binomial distribution with NRI-MI for categorical endpoints (normal approximation to Poisson distribution for UC-related hospitalization) and ANCOVA/MMRM with RTB-MI for continuous endpoints. Type I error was not controlled for in this analysis.

ANCOVA, analysis of covariance; CI, confidence interval; COVID-19, coronavirus 2019; MMRM, mixed-effect model repeated measures; NRI-MI, nonresponder multiple imputation; RTB-MI, return-to-baseline-multiple imputation; UC, ulcerative colitis.

**eTable 6.** Sensitivity Analysis for the Primary Endpoint Clinical Remission per Adapted Mayo Score for the Phase 3 Induction and Maintenance Studies

<b>Week 12 of Induction</b>					
Clinical remission per Adapted Mayo score, NRI-MI analysis, % (n/N) (95% CI)	Risankizumab 1200 mg IV	Placebo IV		Adjusted Treatment Difference	
	17.4 (113/650) (14.5, 20.3)	5.0 (16/325) (2.6, 7.4)		12.3 (8.6, 16.0)***	
Clinical remission per Adapted Mayo score, as observed analysis, % (n/N) (95% CI)	20.8 (132/635) (17.6, 23.9)	6.5 (20/307) (3.8, 9.3)		14.4 (10.3, 18.6)***	

<b>Week 52 of Maintenance</b>					
Clinical remission per Adapted Mayo score, NRI-MI analysis, % (n/N) (95% CI)	Risankizumab 180 mg SC	Adjusted Treatment Difference	Risankizumab 360 mg SC	Adjusted Treatment Difference	Placebo (Withdrawal) SC
	34.1 (61/179) (27.1, 41.0)	13.5 (4.7, 22.2)**	34.4 (64/186) (27.6, 41.2)	14.5 (6.0, 23.0)***	21.3 (39/183) (15.4, 27.2)
Clinical remission per Adapted Mayo score, as observed analysis, % (n/N) (95% CI)	48.4 (78/161) (40.7, 56.2)	14.3 (4.5, 24.1)**	51.6 (83/161) (43.8, 59.3)	16.6 (6.5, 26.8)**	36.9 (59/160) (29.4, 44.4)

Clinical remission per Adapted Mayo score was defined as SFS ≤ 1, and not greater than baseline, RBS = 0, and endoscopic subscore ≤ 1 without the evidence of friability.

95% CIs for response rates were the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there was missing data due to logistic restrictions (COVID-19 or the geopolitical conflict in Ukraine and surrounding impacted regions) or is based on the normal approximation to the binomial distribution if there was no missing data due to logistic restrictions. Across the strata, *P* values were calculated according to the Cochran-Mantel-Haenszel test adjusted for strata. 95% CIs for response rates were on the normal approximation to the binomial distribution. \*\* *P* ≤ .01; \*\*\* *P* ≤ .001 versus placebo IV or placebo (withdrawal) SC.

CI, confidence interval; COVID-19, coronavirus disease 2019; IV, intravenous; NRI-MI, nonresponder multiple imputation; RBS, rectal bleeding score; SC, subcutaneous.

**eTable 7.** Exposure-Adjusted Event Rates for Treatment-Emergent Adverse Events Through Week 12 of Induction and Week 52 of Maintenance

Adverse Event	Induction – E (E/100 PY) at 12 Weeks		Maintenance – E (E/100 PY) at 52 Weeks		
	Risankizumab 1200 mg IV n = 651; PY = 157.8 <sup>a</sup>	Placebo IV n = 324; PY = 82.7 <sup>a</sup>	Risankizumab 180 mg SC n = 193; PY = 185.4	Risankizumab 360 mg SC n = 195; PY = 173.5	Placebo (Withdrawal) SC n = 196; PY = 174.9
<b>Treatment-Emergent Adverse Events</b>					
Any AE	523 (331.4)	351 (424.2)	399 (215.2)	406 (234.0)	399 (228.1)
AE possibly related to study drug <sup>b</sup>	98 (62.1)	32 (38.7)	85 (45.9)	61 (35.2)	75 (42.9)
AE leading to discontinuation of study drug	4 (2.5)	14 (16.9)	5 (2.7)	5 (2.9)	4 (2.3)
AE related to COVID-19	36 (22.8)	20 (24.2)	21 (11.3)	29 (16.7)	28 (16.0)
Severe AE <sup>c</sup>	22 (13.9)	40 (48.3)	3 (1.6)	7 (4.0)	14 (8.0)
Serious AE <sup>c</sup>	18 (11.4)	39 (47.1)	11 (5.9)	11 (6.3)	20 (11.4)
All deaths	1 (0.6)	0	0	1 (0.6)	0
<b>Most Frequent Adverse Events (≥ 10 E/100 PY in any risankizumab group)<sup>d</sup></b>					
Colitis ulcerative	11 (7.0)	36 (43.5)	27 (14.6)	30 (17.3)	32 (18.3)
COVID-19	32 (20.3)	19 (23.0)	18 (9.7)	28 (16.1)	23 (13.2)
Headache	25 (15.8)	8 (9.7)	9 (4.9)	15 (8.6)	18 (10.3)
Anemia	23 (14.6)	24 (29.0)	1 (0.5)	1 (0.6)	2 (1.1)
Arthralgia	20 (12.7)	5 (6.0)	12 (6.5)	20 (11.5)	10 (5.7)
Nasopharyngitis	18 (11.4)	9 (10.9)	25 (13.5)	12 (6.9)	24 (13.7)
<b>Treatment-Emergent Adverse Events of Special Interest<sup>d</sup></b>					
Hypersensitivity <sup>e</sup>	27 (17.1)	6 (7.3)	23 (12.4)	15 (8.6)	10 (5.7)
Hepatic events <sup>f</sup>	14 (8.9)	16 (19.3)	3 (1.6)	19 (10.9)	3 (1.7)
Serious infection	4 (2.5)	5 (6.0)	2 (1.1)	1 (0.6)	4 (2.3)
Injection site reactions	4 (2.5)	5 (6.0)	14 (7.6)	10 (5.8)	3 (1.7)
Herpes zoster	2 (1.3)	0	2 (1.1)	1 (0.6)	3 (1.7)
Opportunistic infection (excluding tuberculosis and herpes zoster)	0	0	0	1 (0.6)	0
Active tuberculosis	0	0	0	0	0
Serious hypersensitivity	0	0	0	0	0
Adjudicated anaphylactic reactions	0	0	0	0	0
Adjudicated major cardiovascular events	0	0	0	0	0
Malignancies (all types)	0	2 (2.4)	0	2 (1.2)	1 (0.6)
Nonmelanoma skin cancer	0	0	0	0	1 (0.6)

<sup>a</sup>One patient was randomized to risankizumab 1200 mg and treated with placebo. Patients are reported here according to the treatment they received.

<sup>b</sup>As assessed by study investigator.

<sup>c</sup>Serious AEs were defined as an AE that met any of the following criteria: death of patient, life-threatening, hospitalization or prolongation of hospitalization, congenital anomaly, persistent or significant disability/incapacity, important medical event requiring medical or surgical intervention to prevent serious outcome. Severe AEs were classified as an AE of Grade 3 or above based on CTCAE V 4.03 guidelines.

<sup>d</sup>The most frequent adverse events were ordered by decreasing frequency in the risankizumab 1200 mg group.

<sup>e</sup>Events identified with Hypersensitivity SMQ, a broader medical concept than injection and infusion site reactions, includes injection and infusion site-related terms, ie, injection site rash, which overlap with the term injection site reaction CMQ. Hypersensitivity includes both nonserious and serious hypersensitivity reaction events.

<sup>f</sup>Hepatic events were identified with search criteria covering the standardized MedDRA Queries of hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions, hepatitis, noninfectious, cholestasis and jaundice of hepatic origin, liver-related investigations, signs and symptoms, and liver-related coagulation and bleeding disturbances.

CMQ, customized MedDRA Queries; COVID-19, coronavirus 2019; customized MedDRA Queries; IV, intravenous; SMQ, standardized MedDRA Queries; TEAE, treatment-emergent adverse event.

**eTable 8.** Patients Meeting Criteria for Liver-Related Elevations During Induction and Maintenance

Endpoint, n/N_Obs (%)	Risankizumab 1200 mg IV n = 651	Placebo IV n = 324
ALT ≥ 3 x ULN	3/646 (0.5)	7/319 (2.2)
ALT ≥ 5 x ULN	1/646 (0.2)	0/319
ALT ≥ 10 x ULN	1/646 (0.2)	0/319
ALT ≥ 20 x ULN	0/646	0/319
AST ≥ 3 x ULN	4/648 (0.6)	3/319 (0.9)
AST ≥ 5 x ULN	1/648 (0.2)	0/319
AST ≥ 10 x ULN	1/648 (0.2)	0/319
AST ≥ 20 x ULN	0/648	0/319
TBL ≥ 2 x ULN	6/648 (0.9)	1/320 (0.3)

Endpoint, n/N_Obs (%)	Risankizumab 180 mg SC n = 193	Risankizumab 360 mg SC n = 195	Placebo (Withdrawal) SC n = 196
ALT ≥ 3 x ULN	1/174 (0.6)	4/159 (2.5)	1/177 (0.6)
ALT ≥ 5 x ULN	0/174	1/159 (0.6)	1/177 (0.6)
ALT ≥ 10 x ULN	0/174	1/159 (0.6)	0/177
ALT ≥ 20 x ULN	0/174	0/159	0/177
ULN < AST < 3 x ULN	12/175 (6.9)	16/159 (10.1)	6/178 (3.4)
AST ≥ 3 x ULN	2/175 (1.1)	5/159 (3.1)	1/178 (0.6)
AST ≥ 5 x ULN	0/175	2/159 (1.3)	0/178
AST ≥ 10 x ULN	0/175	0/159	0/178
AST ≥ 20 x ULN	0/175	0/159	0/178

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBL, total bilirubin; ULN, upper limit of normal.

**eTable 9.** Summary of Mean Change From Baseline in Key Chemistry Values During Induction and Maintenance

**Induction Study, Week 12 of Induction**

Endpoint, Week 12	Risankizumab 1200 mg IV	Placebo IV	Between Group Difference LS Mean (95% CI)
Alanine Aminotransferase (U/L)			
Number of patients	n = 593	n = 279	
LS Mean (95% CI)	1.6 (0.3, 3.0)	0.5 (-1.4, 2.5)	1.1 (-1.2, 3.5)
Aspartate aminotransferase (U/L)			
Number of patients	n = 599	n = 277	
LS Mean (95% CI)	2.1 (1.0, 3.2)	1.6 (0.0, 3.1)	0.6 (-1.4, 2.5)
Gamma-glutamyl transferase (U/L)			
Number of patients	n = 607	n = 287	
LS Mean (95% CI)	-0.2 (-4.4, 4.0)	2.7 (-3.4, 8.8)	-2.9 (-10.3, 4.5)
Total cholesterol (mmol/L)			
Number of patients	n = 608	n = 288	
LS Mean (95% CI)	0.2 (0.2, 0.3)	0.05 (0.0, 0.1)	0.2 (0.1, 0.3)

**Maintenance Study, Week 52 of Maintenance**

Endpoint, Week 52	Risankizumab 180 mg SC	Between Group Difference LS mean (95% CI)	Risankizumab 360 mg SC	Between Group Difference LS mean (95% CI)	Placebo (Withdrawal) SC
Alanine Aminotransferase (U/L)					
Number of patients	n = 148		n = 128		n = 110
LS mean (95 % CI)	5.3 (2.7, 7.9)	1.1 (-2.9, 5.1)	6.5 (3.6, 9.3)	2.3 (-1.9, 6.4)	4.2 (1.1, 7.2)
Aspartate Aminotransferase (U/L)					
Number of patients	n = 147		n = 129		n = 110
LS mean (95 % CI)	5.0 (2.9, 7.1)	0.4 (-2.8, 3.6)	6.0 (3.8, 8.2)	1.4 (-1.9, 4.7)	4.6 (2.2, 7.0)
Gamma Glutamyl Transferase (U/L)					
Number of patients	n = 150		n = 131		n = 112
LS mean (95 % CI)	1.7 (-2.3, 5.7)	-1.0 (-7.1, 5.1)	5.5 (1.3, 9.8)	2.9 (-3.4, 9.1)	2.7 (-1.9, 7.3)
Total Cholesterol (U/L)					
Number of patients	n = 147		n = 129		n = 112
LS mean (95 % CI)	0.5 (0.3, 0.6)	0.3 (0.1, 0.5)	0.3 (0.1, 0.4)	0.1 (-0.1, 0.3)	0.2 (0.0, 0.4)

CI, confidence interval; IV, intravenous; LS, least squares; Obs, observed.

**eTable 10.** Summary of Treatment-Emergent Adverse Events Through Week 52 of Maintenance for All Patients Who Responded to 12-Week Risankizumab 1200 mg Intravenous Induction Therapy and Were Randomized to Maintenance

AE, n (%)	Risankizumab 1200 mg IV/ Placebo SC n = 90	Risankizumab 1200 mg IV/ Risankizumab 180 mg SC n = 90	Risankizumab 1200 mg IV/ Risankizumab 360 mg SC n = 92	Placebo IV/ Placebo SC n = 70
<b>Treatment-Emergent Adverse Events</b>				
Any AE	71 (78.9)	60 (66.7)	66 (71.7)	47 (67.1)
AE possibly related to study drug <sup>a</sup>	13 (14.4)	9 (10.0)	13 (14.1)	11 (15.7)
AE leading to discontinuation of study drug	0	1 (1.1)	0	4 (5.7)
AE related to COVID-19	20 (22.2)	16 (17.8)	18 (19.6)	4 (5.7)
Severe AE	6 (6.7)	1 (1.1)	0	6 (8.6)
Serious AE	8 (8.9)	5 (5.6)	0	8 (11.4)
All deaths	0	0	0	0
<b>Most Frequent Adverse Events (<math>\geq 10\%</math> in any treatment group)</b>				
COVID-19	16 (17.8)	13 (14.4)	18 (19.6)	3 (4.3)
Colitis ulcerative	9 (10.0)	9 (10.0)	11 (12.0)	13 (18.6)
<b>Treatment-Emergent Adverse Events of Special Interest<sup>b</sup></b>				
Hypersensitivity	4 (4.4)	7 (7.8)	7 (7.6)	4 (5.7)
Hepatic events	1 (1.1)	2 (2.2)	7 (7.6)	2 (2.9)
Serious infections	2 (2.2)	1 (1.1)	0	1 (1.4)
Herpes zoster	1 (1.1)	1 (1.1)	0	0
Injection site reactions	2 (2.2)	1 (1.1)	4 (4.3)	1 (1.4)
Opportunistic infection excluding tuberculosis and herpes zoster	0	0	1 (1.1)	0

Reported here are maintenance safety outcomes at week 52 for all patients who received risankizumab 1200 mg or placebo during induction and were randomized to maintenance. Treatment groups were named according to treatments received during induction/maintenance.

<sup>a</sup>As assessed by study investigator.

<sup>b</sup>No active tuberculosis, malignancies, adjudicated MACE, serious hypersensitivity, or adjudicated anaphylactic reactions occurred in any treatment group.

AE, Adverse event; COVID-19, coronavirus disease 2019; E, event; IV, intravenous; MACE, major adverse cardiovascular event; PY, patient year; SC, subcutaneous.

## eResults 1. Results for the Dose-Ranging Phase 2b Induction Substudy

### Patient Characteristics

For the dose-ranging, placebo-controlled phase 2b induction substudy, 240 patients were enrolled and randomized to receive risankizumab 600 mg ( $n = 61$ ), 1200 mg ( $n = 61$ ), 1800 mg ( $n = 58$ ), or placebo ( $n = 60$ ) IV at weeks 0, 4, or 8. High completion rates across treatment groups (risankizumab 600 mg, 90.2%; 1200 mg, 95.1%; 1800 mg, 98.3%; placebo, 88.3%) were seen for the 12-week induction substudy (eFigure 2). A total of 17 patients discontinued (10 patients in the risankizumab treatment groups and 7 patients treated with placebo) prior to week 12. Baseline characteristics and patient demographics were similar across treatment groups (eTable 1). Mean duration of disease was  $9.7 \pm 6.9$  years across all treatments, with 100% of the patients being advanced therapy-inadequate response.

### Efficacy Outcomes

Following the prespecified MCP-Mod analysis, no prespecified dose-response models were statistically significant. However, in the pairwise comparisons, patients treated with risankizumab achieved numerically higher rates of clinical remission per Adapted Mayo score at week 12 compared with placebo, with all risankizumab groups achieving nominal significance (pairwise  $P \leq .1$ ) (eFigure 3A). Clinical remission was achieved by 7 patients (11.5%) treated with 600 mg; 6 patients (9.8%) treated with 1200 mg, and 6 patients (10.3%) treated with 1800 mg, compared with 1 patient (1.7%) treated with placebo IV (eFigure 3A).

Numerical improvements compared with placebo were observed for clinically relevant secondary endpoints with nominal  $P \leq .1$  (eFigure 3B-F). Patients receiving any risankizumab dose had improved clinical response (per Adapted Mayo score and Partial Adapted Mayo score) by week 4 compared to placebo and maintained these improvements through week 12 (eFigure 3B-D).

Endoscopic improvement in patients treated with risankizumab 600 mg (24.6%), 1200 mg (13.1%), and 1800 mg (15.5%) were numerically higher compared with placebo-treated patients (5.0%, nominal  $P \leq .1$ ), (eFigure 3E). A numerically higher proportion of patients were observed in endoscopic remission with risankizumab 600 mg (8.2%), 1200 mg (4.9%), and 1800 mg (8.6%) compared with placebo (0%,  $P \leq .1$ ), (eFigure 3F).

Reductions in inflammatory biomarkers, hs-CRP and FCP, were observed by week 4 and maintained to week 12, in patients treated with any risankizumab dose compared to placebo (**eFigure 3G-H**). Serum IL-22 levels were significantly decreased from baseline in all dose groups compared with placebo at week 12 ( $P \leq .001$ , all comparisons), (**eFigure 3I**).

Patients enrolled in the open-label phase 2b period ( $n = 340$ ) were treated with risankizumab 1800 mg, with 46.2% achieving clinical response per Adapted Mayo score at induction week 12 and randomized to the maintenance primary efficacy analysis.

### Safety Outcomes

Total adverse events and serious adverse events were reported at comparable rates among patients treated with risankizumab 600 mg (57.8% and 9.4%, respectively), 1200 mg (44.3% and 6.6%), 1800 mg (48.2% and 5.4%), and placebo (62.7% and 10.2%) (**eTable 2**). In the risankizumab groups, lower proportions of patients reported severe adverse events and adverse events leading to study drug discontinuation compared with placebo-treated patients. There were no dose-dependent patterns across the risankizumab groups in any adverse event categories. The most frequently reported adverse events were worsening of ulcerative colitis, nasopharyngitis, and headache. No patients in the risankizumab groups reported malignancy, serious hypersensitivity, adjudicated anaphylactic reaction, adjudicated MACE, or active tuberculosis. No serious hepatic events were reported or resulted in study drug discontinuation. The majority of hepatic events represented laboratory abnormalities and were found to have no reasonable possibility of being related to study drug, as assessed by the investigator. There were no deaths reported.

## **eResults 2.** Additional Safety and Efficacy Outcomes for the Phase 3 Induction and Maintenance Study

### *Changes in Liver Enzymes for the 12-Week Induction and 52-Week Maintenance Periods*

Rates for hepatic events were numerically higher in the risankizumab 360 mg group in comparison with the risankizumab 180 mg and withdrawal treatment groups with no serious hepatic events across treatment groups (**Table 4**, **eTable 7**). The majority of hepatic events were liver test increases. No elevations in liver chemistry met the criteria for Hy's Law without other cause to explain the hepatic laboratory abnormalities in either the induction or maintenance studies (**eTable 8**). Changes in liver enzymes and chemistry were assessed as not clinically meaningful for either trial (**eTables 8-9**).

### *Efficacy and Safety Outcomes for All Patients Who Responded to 12-Week Risankizumab 1200 mg Induction Therapy and Were Randomized to Maintenance*

Efficacy analysis was performed for all patients who received risankizumab 1200 mg for only one period of 12 weeks during the phase 2b/3 induction substudies who achieved clinical response and then were randomized to the 52-week maintenance period. Despite there being a smaller sample size, patients treated with risankizumab 360 mg achieved significantly higher rates of clinical remission compared with patients in the placebo SC group (44.6% vs. 27.8%, adjusted treatment difference: 18.3%;  $P \leq .001$ ) at week 52 of maintenance (**eTable 4**). No difference was found for clinical remission in patients treated with the risankizumab 180 mg dose compared with placebo SC treatment. Patients treated with either risankizumab 180 mg or 360 mg achieved significance versus placebo for several clinical, endoscopic, and patient-reported outcomes.

Analysis for safety outcomes was performed for all patients who received risankizumab 1200 mg for only one period of 12 weeks during the phase 3 induction substudy 2 and were randomized to maintenance. Total adverse events were similar for all treatment groups. Higher rates of serious and severe adverse events were observed in patients treated with placebo SC (8.9%, 6.7%), compared with risankizumab 180 mg (5.6%, 1.1%) or 360 mg (0%, 0%) (**eTable 10**). The most frequent adverse events with  $\geq 10\%$  in any treatment group were COVID-19 and colitis ulcerative. Serious infections occurred at generally similar rates in patients who received risankizumab 180 mg or placebo SC. No serious infections were observed in

patients treated with risankizumab 360 mg. No deaths, active tuberculosis, opportunistic infections (excluding tuberculosis and herpes zoster), malignancies, adjudicated MACE, serious hypersensitivity, or adjudicated hypersensitivity occurred in any of the treatment groups.

## Patient Narratives

### *One Nontreatment-Emergent Death Due to Adenocarcinoma of the Colon (Risankizumab 360 mg SC Group)*

A 62-year-old female was diagnosed with adenocarcinoma of the colon based on histopathology from the screening endoscopy for the induction study, which was noted later by the central reader.

The patient was a clinical responder to the 12-week risankizumab IV induction treatment and rolled over into the maintenance trial. During the maintenance study, the results from the screening biopsy were received from the blinded central reader, and a serious adverse event of adenocarcinoma was documented on day 36, with discontinuation of the study drug. The patient died due to adenocarcinoma on day 539, more than a year after the 140-day follow-up call. The investigator assessed the event of adenocarcinoma as not related to the study drug because the histopathology finding was from the screening endoscopy.

### *One Invasive Ductal Breast Carcinoma (Risankizumab 360 mg SC Group)*

A 48-year-old female with a history of a breast lump and prior exposure to infliximab, adalimumab, and vedolizumab experienced a serious event of invasive ductal breast carcinoma of the left breast on day 187. The diagnosis was confirmed by PET CT and MRI. The study drug was discontinued and a lumpectomy and sentinel lymph node biopsy were performed. The investigator assessed the event as having no reasonable possibility of being related to the study drug.

### eResults 3. Pharmacokinetics and Immunogenicity Results From Induction and Maintenance Studies

Following dosing of IV risankizumab 1200 mg at weeks 0, 4, and 8 during induction, risankizumab exposures reached a geometric mean trough concentration of 101 µg/mL at week 12. During maintenance, generally, dose-proportional risankizumab exposures were observed between the 180 mg and 360 mg doses across the time course of the studies, reaching geometric mean concentrations of 9.6 µg/mL and 23.6 µg/mL at week 52, respectively.

In evaluable patients who received 12-weeks of IV risankizumab induction therapy, the incidence of treatment-emergent anti-drug antibodies and neutralizing antibodies to risankizumab was 1.7% (n = 11/642) and 0.8% (n = 5/642), respectively. In evaluable patients who received 12 weeks of risankizumab 1200 mg induction followed by the maintenance regimen of 180 or 360 mg for up to 64 weeks of exposure, treatment-emergent anti-drug and neutralizing antibodies were detected in 8.9% (n = 8/90) and 6.7% (n=6/90) for the 180 mg dose, or 4.4% (n = 4/91) and 2.2% (n = 2/91) for the 360 mg dose, of evaluated patients, respectively.

The time to the first appearance of treatment-emergent anti-drug antibodies ranged from 4.0 to 42.0 weeks following the first risankizumab treatment during induction, and from 15.3 to 53.1 weeks for the risankizumab 360 mg group and from 15.7 to 48.1 weeks for the risankizumab 180 mg group during maintenance. No apparent impact of anti-drug antibodies on risankizumab exposure, efficacy, or safety (injection site reactions and hypersensitivity reactions) was observed.

## eReferences

1. Bretz F, Pinheiro JC, Branson M. Combining multiple comparisons and modeling techniques in dose-response studies. *Biometrics*. Sep 2005;61(3):738-48. doi:10.1111/j.1541-0420.2005.00344.x
2. Pinheiro J, Bornkamp B, Bretz F. Design and analysis of dose-finding studies combining multiple comparisons and modeling procedures. *J Biopharm Stat*. 2006;16(5):639-56. doi:10.1080/10543400600860428
3. Lon HK, Cheng L, Nudurupati S, et al. Pharmacokinetic Comparability of Risankizumab Formulations in Prefilled Syringe and Auto-injector for Subcutaneous Injection. *Clin Ther*. Mar 2021;43(3):629-636. doi:10.1016/j.clinthera.2021.01.009