ORIGINAL ARTICLE

Risankizumab versus Ustekinumab for Moderate-to-Severe Crohn's Disease

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ABSTRACT

BACKGROUND

The efficacy and safety of risankizumab as compared with ustekinumab in patients with Crohn's disease are unknown.

METHODS

In this phase 3b, multicenter, open-label, randomized, controlled trial with blinded assessment of end points, patients with moderate-to-severe Crohn's disease who had had an inadequate response to anti–tumor necrosis factor (TNF) therapy or unacceptable side effects with such therapy were randomly assigned to receive risankizumab or ustekinumab at standard doses for 48 weeks. The two primary end points, which were tested sequentially, were clinical remission at week 24 (defined as a Crohn's Disease Activity Index score of <150 [range, 0 to 600, with higher scores indicating more severe disease activity]), which was analyzed in the first 50% of patients to complete the week 24 visit, with a noninferiority margin of 10 percentage points; and endoscopic remission at week 48 (defined as a score of ≤4, a decrease of ≥2 points from baseline, and no subscore >1 in any individual variable on the Simple Endoscopic Score for Crohn's Disease [range, 0 to 56, with higher scores indicating more severe disease]), which was analyzed for superiority in 100% of the patients. Safety was assessed in all patients who received at least one dose of risankizumab or ustekinumab.

RESULTS

In the full intention-to-treat population for the efficacy analysis, 230 of 255 patients (90.2%) who received risankizumab and 193 of 265 patients (72.8%) who received ustekinumab completed all the assigned treatments. Both primary end points were met; risankizumab was noninferior to ustekinumab with respect to clinical remission at week 24 (58.6% vs. 39.5%; adjusted difference, 18.4 percentage points; 95% confidence interval [CI], 6.6 to 30.3) and superior to ustekinumab with respect to endoscopic remission at week 48 (31.8% vs. 16.2%; adjusted difference, 15.6 percentage points; 95% CI, 8.4 to 22.9; P<0.001). The incidence of adverse events appeared to be similar in the two groups.

CONCLUSIONS

In this head-to-head clinical trial of risankizumab and ustekinumab involving patients with moderate-to-severe Crohn's disease who had had unacceptable side effects with anti-TNF therapy or an inadequate response to such therapy, risankizumab was noninferior to ustekinumab with respect to clinical remission at week 24 and superior with respect to endoscopic remission at week 48. (Funded by AbbVie; ClinicalTrials.gov number, NCT04524611.)

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*A list of the members of the SEQUENCE Study Group is provided in the Supplementary Appendix, available at NEJM.org.

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A Quick Take is available at NEJM.org

Tumor necrosis factor (TNF) inhibitors (anti-TNF therapy) are the preferred first-line advanced treatment for moderate-to-severe Crohn's disease (i.e., biologic agents and small-molecule oral medications that are typically used in patients with moderate-to-severe forms of inflammatory bowel disease). However, inadequate response to a particular TNF inhibitor or unacceptable side effects with a TNF inhibitor often lead to the use of a different TNF inhibitor or to an advanced therapy with a different mechanism of action.[1-7] Because of the lack of robust data from head-to-head clinical trials, the selection of an alternative biologic agent is based mainly on evidence from indirect treatment comparisons and observational studies.[8-14] The SEAVUE (Safety and Efficacy of Adalimumab versus Ustekinumab for One Year) trial was a head-to-head trial of advanced therapies involving patients with moderate-to-severe Crohn's disease; however, this trial did not include patients who had received biologic agents, and the results from this trial showed that there were no differences between the treatments with respect to the primary end points.[15]

Interleukin-23 is a heterodimeric proinflammatory cytokine comprising a p40 subunit shared with interleukin-12 and a unique p19 subunit that plays a key role in skin, joint, and gastrointestinal inflammation.[16] Ustekinumab and risankizumab are humanized IgG1 monoclonal antibodies; ustekinumab selectively binds p40, and risankizumab selectively binds p19. The clinical efficacy of these therapies, as compared with placebo, in the treatment of plaque psoriasis, psoriatic arthritis, and Crohn's disease has been shown.[17-23] In head-to-head trials directly comparing their efficacy in psoriasis, risankizumab was superior to ustekinumab, which suggests greater efficacy with p19 blockade than with p40 blockade.[17-19,24-26] The relative efficacy of risankizumab and ustekinumab in inflammatory bowel disease has not been established.[21,22,27-30]

Here, we report the results from SEQUENCE, a direct head-to-head trial assessing the efficacy and safety of risankizumab as compared with ustekinumab in patients with moderate-to-severe Crohn's disease in whom at least one anti-TNF treatment had failed.

Methods

Trial Design and Oversight

We conducted this phase 3b, multicenter, open-label, randomized, controlled trial at 187 sites in 28 countries (see Section S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Although the investigators at each trial site and the patients were aware of the patients' group assignments, the central reader who interpreted the endoscopy results was unaware of the group assignments, which ensured that the endoscopic end points were measured objectively.

The trial was conducted in accordance with the International Council for Harmonisation guidelines for Good Clinical Practice, applicable regulations, and the principles of the Declaration of Helsinki. An independent ethics committee or institutional review board at each trial site approved the protocol, available at NEJM.org. All the patients provided written informed consent. The sponsor (AbbVie) designed the trial with input from the investigators. The sponsor and the investigators gathered the data jointly and interpreted the data, and the sponsor analyzed the data; a medical writer employed by AbbVie wrote the first draft of the manuscript. All the authors had access to the data. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. The sponsor, investigators, and participating institutions agreed to maintain the confidentiality of the data. All the authors made the decision to submit the manuscript for publication.

Patients

Patients 18 to 80 years of age were eligible to enroll in the trial if they had received a diagnosis of moderate-to-severe Crohn's disease at least 3 months before enrollment and had had unacceptable side effects with at least one anti-TNF therapy or an inadequate response to at least one anti-TNF therapy. Moderate-to-severe disease was defined as a baseline score of 220 to 450 on the Crohn's Disease Activity Index (CDAI; range, 0 to 600, with higher scores indicating more severe disease activity); a mean of at least 4 on the report of daily stool frequency (calculated as the mean number of daily occurrences of type 6 [very soft] or type 7 [liquid] stools according to the Bris-

tol Stool Chart within the 7 days before baseline; a higher stool frequency reflects more severe diarrhea) or a mean score of at least 2 on the daily abdominal pain scale (range, 0 [no pain] to 3 [severe pain], with the abdominal pain score calculated as the mean of the daily scores within the 7 days before baseline), or both; and a Simple Endoscopic Score for Crohn's Disease (SES-CD) of at least 6 for ileocolonic or colonic disease (or an SES-CD of ≥4 for isolated ileal disease) excluding the narrowing component, as confirmed by a central reader interpreting the endoscopy results.[31,32] For the SES-CD, five intestinal segments (terminal ileum, right colon, transverse colon, sigmoid and left colon, and rectum) were evaluated for four endoscopic variables (presence of ulcers, ulcerated surface, affected surface, and presence of narrowing), each scored on a scale of 0 to 3; total scores range from 0 to 56, with higher scores indicating more severe disease.

A mandatory glucocorticoid taper was initiated at week 2 according to a protocol-specified tapering schedule (Table S1). Previous exposure to any advanced therapy except for anti-TNF therapy was prohibited. Full eligibility criteria, including guidelines for concomitant medications, the list of prohibited medications, and the criteria for the required washout period are provided in Section S2.

RANDOMIZATION

Patients were randomly assigned, in a 1:1 ratio, by means of a Web-based interactive response system to receive risankizumab or ustekinumab; randomization was stratified according to the number of previously received anti-TNF therapies that had failed (1 or >1) and glucocorticoid use at baseline (yes or no). The patients received the approved dose of the treatments. In the risankizumab primary efficacy group, the patients received the selected 600-mg intravenous induction dose at weeks 0, 4, and 8, followed by a 360-mg subcutaneous maintenance dose every 8 weeks from week 12 to week 48. The patients in the ustekinumab group received a single weight-based intravenous induction dose (patients weighing ≤55 kg received 260 mg, patients weighing >55 to 85 kg received 390 mg, and patients weighing >85 kg received 520 mg) at week 0 followed by a 90-mg subcutaneous maintenance dose every 8 weeks, starting at week 8 (Fig. S1). Dose changes and crossover from one group to the other were not permitted.

Seven patients received risankizumab at a different dose (a 1200-mg induction dose, a 180-mg maintenance dose, or both), and their data were excluded from the primary efficacy analysis but were included in the safety analysis. Further details are provided in Section S3.

EFFICACY AND SAFETY EVALUATIONS

The two primary end points, which were tested sequentially, were clinical remission at week 24 (defined as a CDAI score of <150) and endoscopic remission at week 48 (defined as an SES-CD of ≤4 and a decrease of ≥2 points from baseline and no subscore >1 in any individual variable, as scored by a central reader). Clinical remission was analyzed for the noninferiority of risankizumab to ustekinumab among the first 50% of patients who completed the assessment at week 24 or withdrew from the trial.[33] Assessment of noninferiority of risankizumab to ustekinumab for clinical remission at week 24 was important to support continuation of the trial and enable assessment of superiority, given that this trial was designed before risankizumab received regulatory approval for treatment of Crohn's disease. A noninferiority margin of 10 percentage points was defined on the basis of clinical meaningfulness according to a survey of physicians published by the International Organization for the Study of Inflammatory Bowel Disease.[34] The second primary end point, endoscopic remission at week 48, was analyzed in 100% of the patients for superiority of risankizumab to ustekinumab. In the original protocol, the second primary end point was clinical remission at week 48; however, the protocol was amended on September 28, 2021, to change the end point to endoscopic remission at week 48; this change reflects the importance of endoscopic healing as a long-term treatment goal for patients with Crohn's disease in accordance with the STRIDE-II (Selecting Therapeutic Targets in Inflammatory Bowel Disease) guidelines.[35] None of the trial data were analyzed before this change was made.

Prespecified secondary end points were tested hierarchically for superiority of risankizumab to ustekinumab in all the patients in the following order: clinical remission at week 48, endoscopic response at week 48 (defined as a reduction in the SES-CD of >50% from baseline [or for

patients with isolated ileal disease and a baseline SES-CD of 4, a ≥2-point reduction from baseline], as scored by a central reader who was unaware of the patients' group assignments), endoscopic response at week 24, glucocorticoid-free endoscopic remission at week 48 (defined as not receiving glucocorticoids at the week 48 visit), and glucocorticoid-free clinical remission at week 48.

Prespecified exploratory end points evaluated at weeks 24 and 48, which were not adjusted for multiplicity, were clinical response according to the CDAI criteria (a reduction in the CDAI score of ≥100 points from baseline), clinical remission according to stool frequency (with remission defined as a mean daily stool frequency ≤2.8 and not worse than baseline) and according to the abdominal pain score (with remission defined as a mean daily abdominal pain score ≤1 and not worse than baseline), biologic remission (clinical remission according to the CDAI criteria and a fecal calprotectin level ≤250 mg per kilogram of body weight or a high-sensitivity C-reactive protein [hs-CRP] level ≤5 mg per liter), deep remission (clinical remission and endoscopic remission according to the CDAI criteria), mucosal healing (an SES-CD ulcerated surface subscore of 0 in patients with an SES-CD ulcerated surface subscore ≥1 at baseline, as scored by a central reader), the change from baseline in the scores on the mental and physical components of the 36-item Short Form Health Survey, the Inflammatory Bowel Disease Questionnaire total and domain scores, and the exposure-adjusted occurrence of Crohn's disease–related hospitalization and of hospitalization for any cause (through week 48). For both primary end points, prespecified subgroup analyses were also performed according to the patients' baseline characteristics. Details on the methods used for the calculation of the mean daily stool frequency and abdominal pain score are provided in Section S4. The mean changes in CDAI score, fecal calprotectin level, and hs-CRP level at weeks 8, 24, and 48, as well as CDAI clinical response, CDAI clinical remission, daily stool frequency and abdominal pain score, and biologic remission at week 8, were evaluated post hoc.

Safety was assessed in all patients who underwent randomization and received at least one dose of risankizumab or ustekinumab. Adverse events were coded according to the *Medical Dictionary for Regulatory Activities*, version 26.0. The severity of adverse events and laboratory abnormalities were graded with the use of the Common Terminology Criteria for Adverse Events, version 5.0.

STATISTICAL ANALYSIS

All primary efficacy analyses were performed in the full intention-to-treat population, except for the first primary end point of clinical remission at week 24, which was analyzed in approximately 50% of the intention-to-treat population (the first 50% of patients who completed the visit at week 24). Sample size and power calculations for each treatment group are provided in Section S5.

Categorical variables were analyzed with the use of the Cochran–Mantel–Haenszel test for common risk difference stratified according to the number of previous anti-TNF therapies that had failed (1 or >1) and concomitant glucocorticoid use at baseline (yes or no). Missing data (except data that were missing due to coronavirus disease 2019 [Covid-19] or geopolitical conflict) were imputed as no response, and patients with missing information that would be needed to determine end-point status were considered to have had treatment failure. Multiple imputation was incorporated to handle data that were missing due to Covid-19 or geopolitical conflict. Continuous variables were analyzed with the use of a mixed-effect model for repeated measures and included categorical fixed effects for treatment, visit, and treatment-by-visit interaction, stratification factors, and the continuous fixed covariates of baseline measurements. Additional sensitivity analyses for handling of missing data under the assumption that data were not missing at random were conducted with the use of a tipping-point analysis for the two primary end points and multiple imputation with a return-to-baseline approach for the continuous end points (Section S8). For the primary end points and the prespecified secondary end points that were tested hierarchically, treatment differences were assessed with the use of a fixed-sequence multiple-testing procedure to control for the family-wise type I error at a two-sided significance level of 0.05. For the noninferiority testing of clinical remission at week 24, noninferiority would be demonstrated if the lower limit of the 95% confidence interval for the risk difference between the risankizumab and ustekinumab groups was

greater than –10 percentage points. The superiority of risankizumab over ustekinumab with respect to endoscopic remission at week 48 was subsequently tested at a two-sided significance level of 0.05. Details and a summary of the number of patients with missing data according to the reason, as well as sensitivity analyses and supplementary analyses of the primary end points are described in Section S5. Safety data are summarized descriptively; missing data were not imputed. All analyses were performed with the use of SAS software (version 9.4 or later). For the exploratory end points, the widths of the reported confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing.

RESULTS

PATIENTS

In total, 527 patients underwent randomization and received at least one dose of risankizumab (262 patients) or ustekinumab (265 patients). The first patient's initial visit occurred in September 2020, and the last patient's week 48 visit occurred in July 2023. After 7 patients were excluded from the efficacy analysis because they had received a nonselected dose of risankizumab, the full intention-to-treat population for the efficacy analysis included 520 patients (255 patients received risankizumab and 265 patients received ustekinumab at the selected induction and maintenance doses). A subgroup of this population, comprising the first 50% of the patients to complete the week 24 visit (128 patients in the risankizumab group and 137 in the ustekinumab group), was assessed for noninferiority of risankizumab to ustekinumab with respect to the first primary end point of clinical remission at week 24.

The demographics and baseline characteristics of the patients were well balanced between the treatment groups (Table 1) and were representative of the general population with moderate-to-severe Crohn's disease (Table S2). In approximately 25% of the patients, more than one anti-TNF therapy had previously failed. Approximately 25% of the patients were taking glucocorticoids at baseline; the mean (±SD) daily prednisone-equivalent dose at baseline was 21.4±12.9 mg in the risankizumab group and 19.5±10.7 mg in the ustekinumab group.

A higher percentage of patients in the risankizumab group than in the ustekinumab group completed all the assigned treatment (90.2% [230 of 255 patients] vs. 72.8% [193 of 265 patients]) (Fig. S2 and Table S3). The primary reason for discontinuation of risankizumab was an adverse event (3.1% [8 of 255 patients]), and the primary reason for discontinuation of ustekinumab was lack of efficacy (13.2% [35 of 265 patients]). Additional details on the timing of discontinuation of treatment (before or after week 24) are provided in Table S3. The majority of the patients who withdrew from the trial before week 48 had active disease according to data collected from the exit endoscopy. Among the patients who discontinued treatment and who underwent exit endoscopy (17 patients in the risankizumab group and 44 patients in the ustekinumab group), 13 patients (76%) in the risankizumab group and 43 patients (98%) in the ustekinumab group did not meet the criteria for endoscopic remission (Table S4).

EFFICACY

Both primary end points, tested sequentially, were met. Risankizumab was noninferior to ustekinumab with respect to clinical remission at week 24 (58.6% [75 of 128 patients] vs. 39.5% [54 of 137 patients]; adjusted difference, 18.4 percentage points [95% confidence interval {CI}, 6.6 to 30.3], which met the prespecified noninferiority margin of 10 percentage points). Clinical remission percentages were calculated on the basis of combined estimates with Rubin's rule owing to data that were missing due to Covid-19 or geopolitical conflict. Risankizumab was superior to ustekinumab with respect to endoscopic remission at week 48 (31.8% [81 of 255 patients] vs. 16.2% [43 of 265 patients]; adjusted difference, 15.6 percentage points [95% CI, 8.4 to 22.9], $P<0.001$) (Table 2). Results from sensitivity testing (with multiple imputation of missing data) and supplementary analyses (with no imputation of values for missing evaluations ["as observed" analyses]) of the primary end points were consistent with the results of the primary analysis (Table S5). Results for the primary end points across the prespecified subgroups were also generally consistent with the results of the primary analysis (Fig. S3).

Risankizumab was superior to ustekinumab across all multiplicity-adjusted secondary end points, including clinical remission at week 48,

endoscopic response at weeks 48 and 24, and glucocorticoid-free endoscopic remission and glucocorticoid-free clinical remission at week 48 (P<0.001 for all end points) (Table 2). Furthermore, risankizumab appeared to have greater efficacy than ustekinumab across the prespecified exploratory end points, which were not adjusted for multiplicity, at weeks 24 and 48, including CDAI clinical response, clinical remission as assessed by daily stool frequency and abdominal pain score, biologic remission, mucosal healing, and deep remission, and appeared to result in improved health-related quality-of-life (Table 2, Figs. S4 and S5, and Section S7). At week 48, the incidence of hospitalization related to Crohn's disease, adjusted for exposure to the trial medications, as well as the incidence of hospitalization from any cause also appeared to be lower with risankizumab than with ustekinumab (Section S7).

Results of additional sensitivity analyses under the assumption that data were not missing at random for end-point values, including tipping-point analysis for the two primary end points and multiple imputation with a return-to-baseline approach for the continuous end points, provide further confidence in the primary analysis results and consistently support the trial conclusion (Section S8). Results of post hoc analyses of clinical remission at week 24, as well as CDAI

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Risankizumab (N=255)	Ustekinumab (N=265)
Female sex — no. (%)	119 (46.7)	134 (50.6)
Age — yr	38.0±13.1	38.3±13.8
Race or ethnic group — no. (%)†		
American Indian or Alaska Native	3 (1.2)	5 (1.9)
Asian	47 (18.4)	58 (21.9)
Black or African American	7 (2.7)	10 (3.8)
White	195 (76.5)	188 (70.9)
Multiple	0	2 (0.8)
Data missing	3 (1.2)	2 (0.8)
Hispanic or Latino ethnic group — no. (%)†		
Yes	26 (10.2)	27 (10.2)
No	229 (89.8)	238 (89.8)
Body-mass index‡	23.8±5.5	24.8±6.0
Location of disease — no. (%)		
Ileal only	42 (16.5)	45 (17.0)
Colonic only	102 (40.0)	106 (40.0)
Ileocolonic	111 (43.5)	114 (43.0)
Median CDAI score (IQR)§¶	306.0 (265.9–344.8)	307.8 (260.8–347.9)
Median duration of disease (range) — yr	7.3 (0.3–40.6)	7.3 (0.3–51.9)
Median abdominal pain score (IQR)¶‖	2.0 (1.7–2.1)	2.0 (1.6–2.3)
Median stool frequency (IQR)¶**	5.0 (4.0–7.1)	5.4 (4.1–6.9)
Median SES-CD (IQR)††	12.0 (8.0–18.0)	12.0 (8.0–19.0)
Median high-sensitivity C-reactive protein level (range) — mg/liter‡‡	8.20 (0.2–287.1)	9.40 (0.2–196.6)
Median fecal calprotectin level (range) — μg/g§§	1030 (30–26,823)	1515 (30–26,361)
Glucocorticoid use — no. (%)	58 (22.7)	71 (26.8)
Immunomodulator use — no. (%)¶¶	34 (13.3)	47 (17.7)

Table 1. (Continued.)

Characteristic	Risankizumab (N=255)	Ustekinumab (N=265)
No. of previous anti-TNF therapies that failed — no. (%)‖‖		
1	196 (76.9)	204 (77.0)
>1	59 (23.1)	61 (23.0)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. Analyses were performed in the intention-to-treat population (patients who were randomly assigned to the selected risankizumab group [600-mg induction dose, 360-mg maintenance dose] and received at least one dose of risankizumab or patients who were randomly assigned to the ustekinumab group [weight-based intravenous induction dose followed by a subcutaneous maintenance dose of 90 mg] and received at least one dose of ustekinumab). Missing values were not included in the calculation of the percentages. IQR denotes interquartile range, and TNF tumor necrosis factor.

† Race and ethnic group were reported by the patient during the screening visit.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ The Crohn's Disease Activity Index (CDAI) consists of eight factors, with each factor adjusted with a weighting factor. CDAI scores range from 0 to 600, with higher scores indicating more severe disease activity.[12]

¶ The number of patients evaluated in the risankizumab group was 251, and the number of patients evaluated in the ustekinumab group was 263.

‖ Patients reported their abdominal pain level on a scale from 0 (no pain) to 3 (severe pain); the abdominal pain score was calculated as the mean of the daily scores within the 7 days before baseline.

** Stool frequency was calculated as the mean number of daily occurrences of type 6 (very soft) or type 7 (liquid) stools according to the Bristol Stool Chart within the 7 days before baseline; a higher stool frequency reflects more severe diarrhea.

†† For the Simple Endoscopic Score for Crohn's Disease (SES-CD), five intestinal segments (terminal ileum, right colon, transverse colon, sigmoid and left colon, and rectum) were evaluated for four endoscopic variables (presence of ulcers, ulcerated surface, affected surface, and presence of narrowing), each scored on a scale of 0 to 3; total scores range from 0 to 56, with higher scores indicating more severe disease.

‡‡ The normal range for high-sensitivity C-reactive protein is 0 to 10 mg per liter. The number of patients evaluated in the risankizumab group was 246, and the number of patients evaluated in the ustekinumab group was 257.

§§ The normal value for fecal calprotectin is less than 50 μg per gram. The number of patients evaluated in the risankizumab group was 207, and the number of patients evaluated in the ustekinumab group was 215.

¶¶ Immunomodulators include thiopurines and methotrexate.

‖‖ One patient in the risankizumab group was enrolled erroneously (the patient had no history of failure of previous anti-TNF therapy).

scores, fecal calprotectin levels, and hs-CRP levels at weeks 8, 24, and 48, in the full intention-to-treat population are shown in Figures S4 and S6.

SAFETY

The percentages of patients who had any adverse event, a severe adverse event, or an adverse event leading to treatment discontinuation were similar in the two groups (Table 3). Covid-19 was the most frequently reported adverse event in both groups (Table S7). The percentage of patients who had serious adverse events was lower with risankizumab than with ustekinumab (10.3% vs. 17.4%); the treatment difference was –7.1 percentage points (95% CI, –12.9 to –1.2) (Table 3), a finding that was driven largely by serious adverse events in the gastrointestinal disorders system organ class — specifically, worsening of underlying Crohn's disease (Table S8). Crohn's disease was also the most frequently reported adverse event leading to treatment discontinuation (1.5% of patients receiving risankizumab and 3.4% of patients receiving ustekinumab) (Table S9).

The percentage of patients with serious infections was similar in the two groups (Table 3). The percentage of patients with hepatic events was also similar in the two groups, with most events involving laboratory test result abnormalities related to an increase in aminotransferase levels, which were mild to moderate in severity and were considered by the investigator to be unrelated to the trial drug they were receiving (Table 3). The percentage of patients with alanine aminotransferase or aspartate aminotransferase values at least 3 times the upper limit of the normal range was similar in the two groups (Table S10). No serious hepatic events or hepatic events that led to treatment discontinuation occurred with risankizumab. One patient discontinued ustekinumab because of nonserious ascites. One case each of skin squamous-cell carcinoma (in the risankizumab group) and anal squamous-

Table 2. Primary and Secondary End Points.*

End Point	Risankizumab (N=255)	Ustekinumab (N=265)	Adjusted Difference†	P Value†
	percent (95% CI)‡		*percentage points (95% CI)*	
Primary end points				
Clinical remission at week 24§	58.6 (50.1–67.1)	39.5 (31.3–47.7)	18.4 (6.6–30.3)¶	
Endoscopic remission at week 48‖	31.8 (26.1–37.5)	16.2 (11.8–20.7)	15.6 (8.4–22.9)	P<0.001
Secondary end points				
Clinical remission at week 48**	60.8 (54.8–66.8)	40.8 (34.8–46.7)	19.7 (11.3–28.1)	P<0.001
Endoscopic response at week 48††	45.1 (39.0–51.2)	21.9 (16.9–26.9)	23.3 (15.4–31.2)	P<0.001
Endoscopic response at week 24††	45.2 (39.1–51.3)	26.4 (21.1–31.7)	18.9 (10.9–26.9)	P<0.001
Glucocorticoid-free endoscopic remission at week 48‖‡‡	31.4 (25.7–37.1)	15.5 (11.1–19.8)	15.9 (8.8–23.1)	P<0.001
Glucocorticoid-free clinical remission at week 48**‡‡	60.8 (54.8–66.8)	40.4 (34.5–46.3)	20.1 (11.7–28.4)	P<0.001

* Unless otherwise indicated, all analyses were performed in the intention-to-treat population (patients who underwent randomization and received at least one dose of risankizumab [selected dose, 600 mg induction dose and 360 mg maintenance dose] or ustekinumab). All missing data (except those missing due to coronavirus disease 2019 [Covid-19] or geopolitical conflict) were imputed as no response, and patients with missing information that would be needed to determine end-point status were considered to have had treatment failure. Clinical remission percentages were calculated on the basis of combined estimates with Rubin's rule owing to data that were missing due to Covid-19 or geopolitical conflict. CI denotes confidence interval.

† The adjusted difference (risankizumab minus ustekinumab), the 95% confidence interval for the adjusted difference, and the P value were calculated according to the Cochran–Mantel–Haenszel test for common risk difference stratified according to the number of anti-TNF therapies that failed (1 or >1), and glucocorticoid use at baseline (yes or no).

‡ The 95% confidence interval for the percentage of patients with a response was based on the point estimate and standard error derived from multiple imputation according to Rubin's rule if there are data that were missing due to Covid-19 or geopolitical conflict. The confidence interval was based on the normal approximation to the binomial distribution if there are no data that were missing due to Covid-19 or geopolitical conflict.

§ Clinical remission (defined as a CDAI score of less than 150) was assessed in the first 50% of the intention-to-treat population to complete the visit at week 24 or withdraw from trial participation.

¶ Noninferiority was shown with respect to clinical remission at week 24 if the lower limit of the 95% confidence interval of the adjusted difference between the risankizumab and ustekinumab groups was greater than the noninferiority margin of –10 percentage points.

‖ Endoscopic remission was defined as an SES-CD of 4 or less, a decrease of at least 2 points from baseline, and no subscore of more than 1 in any individual variable.

** Clinical remission at week 48 was assessed among 100% of the intention-to-treat population.

†† Endoscopic response was defined as a decrease of more than 50% from baseline in the SES-CD (or a decrease of ≥2 points from baseline in patients with an SES-CD of 4 at baseline).

‡‡ Glucocorticoid-free was defined as not receiving glucocorticoids at the week 48 visit; glucocorticoid-free clinical remission at week 48 was assessed in 100% of the intention-to-treat population.

cell carcinoma (in the ustekinumab group) was reported (Table 3). No adjudicated anaphylactic reactions, serious hypersensitivity, active tuberculosis, or deaths were reported in either treatment group.

DISCUSSION

Data from head-to-head trials of advanced therapies are crucial for informing clinical decision making. SEQUENCE, a randomized head-to-head trial involving patients with moderate-to-severe Crohn's disease, directly compared the efficacy of two approved biologic agents among patients whose disease was refractory to anti-TNF therapy. Our trial also evaluated clinically meaningful reduction of glucocorticoid use by implementing an early mandatory glucocorticoid taper.[35]

Results showed the superiority of risankizumab over ustekinumab across numerous clinical and endoscopic end points, including glucocorticoid-free clinical remission and endoscopic remission. The SEQUENCE trial included both clinical and endoscopic primary end points, which

Table 3. Adverse Events That Emerged during Treatment.*

Adverse Event	Risankizumab (N=262)		Ustekinumab (N=265)	
	no. of patients (%)	*no. of events (events/100 person-yr)*	*no. of patients (%)*	*no. of events (events/100 person-yr)*
Any adverse event	223 (85.1)	879 (341.2)	219 (82.6)	763 (282.7)
Investigator-defined drug-related adverse event	73 (27.9)	167 (64.8)	58 (21.9)	111 (41.1)
Severe adverse event†	42 (16.0)	60 (23.3)	51 (19.2)	82 (30.4)
Serious adverse event‡	27 (10.3)	36 (14.0)	46 (17.4)	64 (23.7)
Adverse event leading to discontinuation of treatment	10 (3.8)	10 (3.9)	13 (4.9)	14 (5.2)
Death	0	0	0	0
Adverse events of special interest				
Adjudicated MACE or extended MACE§	0	0	1 (0.4)¶	1 (0.4)¶
Serious infection	8 (3.1)	10 (3.9)	11 (4.2)	14 (5.2)
Opportunistic infection, excluding tuberculosis and herpes zoster infection	1 (0.4)	1 (0.4)	0	0
Herpes zoster infection	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Malignant tumor	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
Hypersensitivity‖	28 (10.7)	37 (14.4)	24 (9.1)	32 (11.9)
Hepatic event	18 (6.9)	26 (10.1)	14 (5.3)	23 (8.5)
Injection-site reaction	5 (1.9)	5 (1.9)	6 (2.3)	8 (3.0)

* The safety population includes all patients who underwent randomization and received at least one dose of ustekinumab or risankizumab (at any dose, including the 7 patients who received a nonselected dose of risankizumab) during the 48-week treatment period. The risankizumab group consisted of patients who were randomly assigned to any risankizumab dose group and received at least one dose of risankizumab. The ustekinumab group consisted of patients who were randomly assigned to the ustekinumab group and received at least one dose of ustekinumab. The total number of person-years in the risankizumab group was 257.6, and the total number in the ustekinumab group was 269.9.

† Severe adverse events were grade 3 or higher according to the Common Terminology Criteria for Adverse Events, version 5.0.

‡ Serious adverse events were defined as any of the following events: death, a life-threatening event, hospitalization, prolongation of hospitalization, a congenital anomaly, persistent or substantial disability or incapacity, an event that led to medical or surgical intervention to prevent a serious outcome.

§ Major adverse cardiovascular events (MACE) were defined as death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Extended MACE was defined as MACE along with hospitalization for unstable angina and coronary revascularization procedures.

¶ One nonfatal myocardial infarction was reported in one patient.

‖ Hypersensitivity events were identified according to the Hypersensitivity Standardized query (narrow) in the *Medical Dictionary for Regulatory Activities*, version 26.0.

reflects the importance of these treatment goals, in accordance with the STRIDE-II guidelines.[35] Both treatments had an acceptable side-effect profile, and no new safety risks were identified with either drug.

The superior efficacy of risankizumab over ustekinumab that we observed aligns with findings in previous head-to-head clinical trials involving patients with moderate-to-severe plaque psoriasis.[25,26] The reason that targeted inhibition of interleukin-23 shows greater efficacy than inhibition of both interleukin-12 and interleukin-23 is unknown; however, this greater efficacy may be attributed to a higher affinity of risankizumab for interleukin-23, an increased potency for its inhibition, or a role of interleukin-12 in protecting the gut microenvironment from inflammation.[36,37]

The main limitation of our trial is the open-label design, which could influence reporting of symptoms and safety events. To minimize bias, the central reader of endoscopy findings was

unaware of the patients' group assignments. Significant between-group differences in the objective endoscopic end points that we examined, along with the differences in fecal calprotectin and hs-CRP levels that we observed as early as week 8, corroborate the superior efficacy of risankizumab over ustekinumab notwithstanding any possible subjectivity due to open-label treatment. The veracity of these data are further supported by efficacy data that are similar to those shown in previous double-blind trials evaluating these treatments.[21,22,27,38]

In patients with moderate-to-severe Crohn's disease who had had an inadequate response to anti-TNF therapy or unacceptable side effects with such therapy, risankizumab was noninferior to ustekinumab with respect to clinical remission at week 24 and superior with respect to endoscopic remission at week 48. No new safety risks were identified in association with risankizumab in this trial.

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APPENDIX

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