ORIGINAL ARTICLE

Mirikizumab as Induction and Maintenance Therapy for Ulcerative Colitis

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ABSTRACT

BACKGROUND

Mirikizumab, a p19-directed antibody against interleukin-23, showed efficacy in the treatment of ulcerative colitis in a phase 2 trial.

METHODS

We conducted two phase 3, randomized, double-blind, placebo-controlled trials of mirikizumab in adults with moderately to severely active ulcerative colitis. In the induction trial, patients were randomly assigned in a 3:1 ratio to receive mirikizumab (300 mg) or placebo, administered intravenously, every 4 weeks for 12 weeks. In the maintenance trial, patients with a response to mirikizumab induction therapy were randomly assigned in a 2:1 ratio to receive mirikizumab (200 mg) or placebo, administered subcutaneously, every 4 weeks for 40 weeks. The primary end points were clinical remission at week 12 in the induction trial and at week 40 (at 52 weeks overall) in the maintenance trial. Major secondary end points included clinical response, endoscopic remission, and improvement in bowel-movement urgency. Patients who did not have a response in the induction trial were allowed to receive open-label mirikizumab during the first 12 weeks of the maintenance trial as extended induction. Safety was also assessed.

RESULTS

A total of 1281 patients underwent randomization in the induction trial, and 544 patients with a response to mirikizumab underwent randomization again in the maintenance trial. Significantly higher percentages of patients in the mirikizumab group than in the placebo group had clinical remission at week 12 of the induction trial (24.2% vs. 13.3%, P<0.001) and at week 40 of the maintenance trial (49.9% vs. 25.1%, P<0.001). The criteria for all the major secondary end points were met in both trials. Adverse events of nasopharyngitis and arthralgia were reported more frequently with mirikizumab than with placebo. Among the 1217 patients treated with mirikizumab during the controlled and uncontrolled periods (including the open-label extension and maintenance periods) in the two trials, 15 had an opportunistic infection (including 6 with herpes zoster infection) and 8 had cancer (including 3 with colorectal cancer). Among the patients who received placebo in the induction trial, 1 had herpes zoster infection and none had cancer.

CONCLUSIONS

Mirikizumab was more effective than placebo in inducing and maintaining clinical remission in patients with moderately to severely active ulcerative colitis. Opportunistic infection or cancer occurred in a small number of patients treated with mirikizumab. (Funded by Eli Lilly; LUCENT-1 and LUCENT-2 ClinicalTrials.gov numbers, NCT03518086 and NCT03524092, respectively.)

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

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Ulcerative colitis is a chronic disease of the colon and rectum in which inflammation of the mucosa leads to symptoms of rectal bleeding, increased stool frequency, bowel-movement urgency, and abdominal pain.[1] Current therapies are limited by increased risks of infection or cancer, nonresponse to primary therapy, or loss of clinical benefit over time.[2-4]

Interleukin-23, a proinflammatory factor, has two components: the p40 subunit, which is shared with interleukin-12, and the unique p19 subunit.[5] Ustekinumab, a monoclonal antibody targeting the p40 subunit of interleukin-12 and interleukin-23, has been approved for the treatment of ulcerative colitis and Crohn's disease.[6] Risankizumab, a monoclonal antibody against interleukin-23 subunit p19, has been approved for the treatment of Crohn's disease.[7-9] Guselkumab, an interleukin-23 subunit p19 antagonist is under evaluation for the treatment of Crohn's disease.[10,11]

Mirikizumab, a humanized IgG4-variant monoclonal antibody that specifically binds to subunit p19 of interleukin-23, showed efficacy in a phase 2 trial involving patients with ulcerative colitis.[12,13] Here, we report the efficacy and safety results of the phase 3 LUCENT-1 induction and LUCENT-2 maintenance trials of mirikizumab in patients with moderately to severely active ulcerative colitis.

Methods

Trial Design and Oversight

We conducted LUCENT-1, a 12-week, randomized trial of induction therapy (induction trial), at 383 sites in 34 countries. LUCENT-2 was a 40-week, randomized, withdrawal trial of maintenance therapy (maintenance trial) that was conducted at 367 sites in 34 countries. Together, the two trials represented a 52-week treatment period. Both trials were double-blind, parallel-group, placebo-controlled trials. The trial protocols (available with the full text of this article at NEJM.org) were approved by the institutional review board responsible for oversight at each center. All the patients provided written informed consent.

A steering committee that comprised academic investigators and scientists and physicians employed by the Eli Lilly (the sponsor) designed the trials. Data were collected by IQVIA (a contract research organization) and analyzed by Eli Lilly or its designees. Data were interpreted jointly by the members of the steering committee and the sponsor. All the authors had full access to the data and contributed to the writing and critical revision of the manuscript. The authors vouch for accuracy and completeness of the data and for fidelity of the trials to the protocols.

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Patients

Eligible patients (18 to 80 years of age) had moderately to severely active ulcerative colitis at screening. The severity of ulcerative colitis was assessed by means of the modified Mayo score (on a scale from 0 to 9, with higher scores indicating greater severity); patients had to have a modified Mayo score of 4 to 9, with an endoscopic subscore (range, 0 to 3, with higher scores indicating greater severity) of 2 to 3. Blinded central reading of endoscopic videos and histologic findings was performed. Patients had to have an inadequate response to, a loss of response to, or an inability to take one or more glucocorticoids (referred to as corticosteroids in the trial protocol) or immunomodulators for the treatment of ulcerative colitis (conventional treatment failure) or biologic therapy or a Janus kinase (JAK) inhibitor for the treatment of ulcerative colitis (treatment failure with biologic agent or tofacitinib).

Patients were allowed to receive oral 5-aminosalicylic acid, oral glucocorticoids, or the immunomodulators azathioprine, 6-mercaptopurine, and methotrexate at stable doses throughout the trial. Oral glucocorticoids were maintained at stable doses during the induction trial, and the doses were tapered during the maintenance trial in patients who had had a response during the induction trial. Patients who had previous exposure to anti–interleukin-12 and anti–interleukin-23 subunit p40 or anti–interleukin-23 subunit p19 antibodies or who had had treatment failure with three or more different biologic therapies were excluded. All the patients who completed the induction trial, regardless of clinical response or trial-group assignment, were eligible to participate in the maintenance trial (Fig. S1 in the Supplementary Appendix, available at NEJM.org).

Randomization and Trial Regimens

At week 0 of the induction trial, patients were randomly assigned in a 3:1 ratio to receive

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mirikizumab (at a dose of 300 mg) or placebo, administered intravenously, every 4 weeks (i.e., at weeks 0, 4, and 8). Randomization was stratified according to treatment failure with a biologic agent or tofacitinib (yes or no), baseline glucocorticoid use (yes or no), baseline disease activity (modified Mayo score of 4 to 6 or 7 to 9), and geographic region (North America, Europe, or other). Assignment to trial groups was determined by a computer-generated random sequence with the use of an interactive Web-response system.

Patients who had a clinical response to mirikizumab therapy at week 12 (defined as a decrease of ≥2 points in the modified Mayo score, with a decrease of ≥30% from baseline, plus either a decrease from baseline of ≥1 point in the rectal bleeding subscore [range 0 to 3, with higher scores indicating greater severity] or a rectal bleeding subscore of 0 or 1) underwent randomization again in the maintenance trial. In the maintenance trial, patients were randomly assigned in a 2:1 ratio to receive blinded mirikizumab (200 mg) or placebo (mirikizumab withdrawal), administered subcutaneously, every 4 weeks for an additional 40 weeks (for a total 52-week treatment period). Randomization in the maintenance trial was stratified according to treatment failure with a biologic agent or tofacitinib (yes or no), remission status at week 12 of the induction trial (yes or no), glucocorticoid use (yes or no), and geographic region (North America, Europe, or other).

Patients in the placebo group who had a clinical response during the induction trial continued to receive blinded placebo during the maintenance trial. Patients in either group who had a loss of response at or after week 12 of the maintenance trial discontinued maintenance mirikizumab or placebo and received rescue therapy with three doses of open-label mirikizumab (300 mg), administered intravenously every 4 weeks.

Patients who did not have a response to mirikizumab or placebo during the induction trial received open-label extended induction therapy with an additional three doses of mirikizumab (300 mg), administered intravenously every 4 weeks, in the maintenance trial and were reassessed for clinical response at week 12 of the maintenance trial (i.e., at week 24 of the overall 52-week period). Patients who had a clinical response (as compared with baseline of the induction trial) at week 12 received open-label mirikizumab (200 mg), administered subcutaneously every 4 weeks, as maintenance therapy through week 40. Patients who did not have a response to extended induction therapy were withdrawn from the trial.

EFFICACY AND SAFETY ASSESSMENTS

The primary end point in the induction trial was clinical remission at week 12. Clinical remission was defined as a modified Mayo stool-frequency subscore of 0 (on a scale from 0 to 3, with higher scores indicating higher frequency) or a stool-frequency subscore of 1 with a decrease of at least 1 point from baseline, a rectal-bleeding subscore of 0, and an endoscopic subscore of 0 or 1 (excluding friability).

The seven major secondary end points at week 12 that were included in the graphical plan to adjust for multiple testing were as follows: an alternate definition of clinical remission (a stool-frequency subscore of 0 or 1, a rectal-bleeding subscore of 0, and an endoscopic subscore of 0 or 1 [excluding friability]); clinical response (defined as decreases of ≥2 points and ≥30% from baseline in the modified Mayo score, plus a rectal-bleeding subscore of 0 or 1 or a decrease of ≥1 point from baseline); endoscopic remission (defined as an endoscopic subscore of 0 or 1 [excluding friability]); remission of symptoms (a stool-frequency subscore of 0 or a subscore of 1 with a decrease of ≥1 point from baseline, and a rectal-bleeding subscore of 0); clinical response in patients with treatment failure with a biologic agent or tofacitinib; histologic–endoscopic mucosal improvement (with histologic improvement defined as endoscopic remission and according to the Geboes scoring system with neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue); and an improvement in bowel-movement urgency, assessed as any reduction in the Urgency Numeric Rating Scale (NRS), an 11-point scale that patients used to describe the severity of their daily bowel urgency (range, 0 [no urgency] to 10 [worst possible urgency]).[14] The alternate definition of clinical remission is included in the most recent Food and Drug Administration draft guidance as the preferred definition for future trials involving patients with ulcerative colitis.[15] In addition to the seven

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major secondary end points at week 12, remission of symptoms at week 4 was also included in the graphical plan as a major secondary end point.

Unless stated otherwise, all the end points in the maintenance trial were evaluated in the randomized maintenance population. The primary end point in the maintenance trial was clinical remission at week 40. The seven major secondary end points at week 40 that were included in the graphical scheme to adjust for multiplicity were as follows: the alternate definition of clinical remission; endoscopic remission; glucocorticoid-free clinical remission (defined as clinical remission at week 40, remission of symptoms at week 28, and no glucocorticoid use for ≥12 weeks before week 40); histologic–endoscopic mucosal remission (defined as endoscopic remission and a Geboes subscore of 0 for grades 2b [lamina propria neutrophils], 3 [neutrophils in epithelium], 4 [crypt destruction], and 5 [erosion or ulceration]); an improvement in bowel-movement urgency status, assessed as any reduction in the Urgency NRS score; bowel-urgency remission (i.e., no or minimal bowel urgency, defined as an Urgency NRS score of 0 or 1, in patients with a baseline Urgency NRS score of ≥3); and maintenance of clinical remission (defined as clinical remission in patients who had had clinical remission with mirikizumab therapy in the induction trial).

Additional end points in the two trials that were not included in the multiplicity-controlled testing scheme included the Inflammatory Bowel Disease Questionnaire score, levels of inflammatory biomarkers C-reactive protein and fecal calprotectin, and the serum concentration of mirikizumab. The Supplementary Appendix includes full details of the patient population, randomization, trial assessments, and procedures. A complete list of the end points is provided in Table S1.

STATISTICAL ANALYSIS

We assumed that 23% of the patients in the mirikizumab group and 8% of those in the placebo group would have clinical remission at week 12 in the induction trial and that 47% and 27%, respectively, would have clinical remission at week 40 of the maintenance trial. On the basis of these assumptions, we expected that a sample size of 1160 would provide the trials with more than 95% statistical power to show that mirikizumab was superior to placebo with regard to clinical remission.

For the induction trial to show substantial evidence regarding the efficacy of mirikizumab within a single induction-trial design, we selected a familywise error of 0.00125 to test the primary and major secondary end points with the use of a prespecified graphical scheme (Fig. S2A). In the maintenance trial, the primary and major secondary end points were controlled for multiplicity at an alpha level of 0.05 with the use of a prespecified graphical scheme (Fig. S2B). For multiplicity-controlled end points, the effect sizes are presented with 99.875% confidence intervals for the induction trial and with 95% confidence intervals for the maintenance trial. In both trials, analyses of hypotheses without multiplicity control are reported with point estimates and 95% confidence intervals, without P values; the widths of the confidence intervals are not adjusted for multiple testing and should not be used to infer definitive treatment effects.

Efficacy analyses were performed in the modified intention-to-treat populations in both trials. In each trial, the modified intention-to-treat population included all the patients who underwent randomization and received any amount of mirikizumab or placebo and excluded the patients who were affected by the electronic clinical-outcomes assessment transcription error that occurred in Poland and Turkey (see the Supplementary Appendix). The safety population in each trial included all the patients who had undergone randomization and received any amount of mirikizumab or placebo, including those who were affected by the electronic clinical-outcomes assessment transcription error. Unless otherwise specified, the baseline values for analyses in the maintenance trial refer to the values that were obtained at baseline in the induction trial.

For assessments of the primary end points and other binary efficacy end points, we used the Cochran–Mantel–Haenszel test to compare the trial groups with adjustment for stratification factors. Patients who discontinued mirikizumab or placebo or who had a clinical response in the induction trial but subsequently had a loss of response and received rescue therapy in the maintenance trial were classified as not having a response and as having treatment failure. Patients with sporadically missing responses ow-

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ing to other reasons had their data imputed as no response, because sporadic missingness of data was expected to be rare and the approach could be easily understood. Sensitivity analyses with the use of multiple imputation were also performed.

Comparisons of continuous efficacy variables with more than one postbaseline measurement were made with the use of a mixed-effects model for repeated-measures analysis with an assumption that missing data were missing at random. The model included trial group, baseline value, visit, interactions of trial group by visit and of baseline value by visit, and stratification factors as fixed factors. Type III sums of squares for the least-squares means were used for the statistical comparison. Unstructured covariance matrix was used to model the within-patient errors. Data that were collected after the administration of rescue medication in the maintenance trial were censored in the analysis. Prespecified sensitivity analyses were conducted for continuous variables with the use of an analysis of covariance. Further details of the statistical methods are provided in the Supplementary Appendix.

RESULTS

CHARACTERISTICS OF THE PATIENTS

The induction trial was conducted from June 18, 2018, to January 21, 2021, and the maintenance trial from October 19, 2018, to November 3 2021. A total of 1281 patients underwent randomization in the induction trial, including the patients who were affected by the electronic clinical-outcomes assessment error. In the modified intention-to-treat population, 1162 patients were randomly assigned to receive 300 mg of mirikizumab (868 patients) or placebo (294 patients), administered intravenously. In the maintenance trial, 544 patients who had had a clinical response to mirikizumab induction therapy were randomly assigned to receive 200 mg of mirikizumab (365 patients) or placebo (179 patients), administered subcutaneously. The total treatment period was 52 weeks (Fig. S3).

The characteristics of the patients were generally similar across the trial groups and across the two trials (Table 1 and Table S2). The percentages of patients with treatment failure with a biologic agent or tofacitinib (Table S3) and of patients with more severe endoscopic disease were higher in the open-label extended induction cohort than in the cohort of patients who had a clinical response in the induction trial. Less than 1% of the patients in each trial were Black. The representativeness of the trial population is shown in Table S10.

INDUCTION TRIAL

At week 12 of the induction trial, the percentage of patients with clinical remission was higher in the mirikizumab group than in the placebo group (24.2% vs. 13.3%; difference, 11.1 percentage points; 99.875% confidence interval [CI], 3.2 to 19.1; P<0.001) (Fig. 1A). These results were similar to those for the alternative definition of clinical remission (25.6% in the mirikizumab group vs. 14.6% in the placebo group, P<0.001) and for the sensitivity analyses (Table S4). Results favored the mirikizumab group for the major secondary end points of clinical response, endoscopic remission, remission of symptoms at weeks 4 and 12, clinical response in patients who had previous treatment failure with a biologic agent or tofacitinib, histologic–endoscopic mucosal improvement, and bowel-movement urgency (P<0.001 for all comparisons) (Fig. 1A and 1B and Fig. S5). Depending on trial group and trial period, between 3.8 and 39.1% of the patients were classified as not having had a response owing to the discontinuation of mirikizumab or placebo or the receipt of rescue therapy with mirikizumab. Between 0 and 3.3% of the patients with sporadic missingness of data that was due to other reasons were imputed as not having had a response. The frequency of missing end-point data is summarized in Table S5.

In the subgroup of patients with treatment failure with a biologic agent or tofacitinib, the percentage of patients who met all the secondary end points appeared to be greater in the mirikizumab group than in the placebo group (in an analysis not adjusted for multiplicity) (Table S6 and Fig. S6). Results of all the prespecified subgroup analyses are provided in Figure S4. The Inflammatory Bowel Disease Questionnaire score (Fig. S7A and S7C) and the levels of inflammatory biomarkers C-reactive protein and fecal calprotectin (Fig. S8A and S8C) appeared to be improved in the mirikizumab group as compared with the placebo group at week 12.

MAINTENANCE TRIAL

At week 40 of the maintenance trial, 49.9% of the patients in the mirikizumab group and 25.1%

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Table 1. Demographic and Disease Characteristics of the Patients at Baseline in the Induction Trial (Modified Intention-to-Treat Population).*

Characteristic	Placebo (N=294)	Mirikizumab (N=868)
Age — yr	41.3±13.8	42.9±13.9
Male sex — no. (%)	165 (56.1)	530 (61.1)
BMI category — no. (%)†		
Normal	149 (50.7)	451 (52.0)
Overweight, obese, or extremely obese	117 (39.8)	362 (41.7)
Disease duration — yr	6.9±7.0	7.2±6.7
Colitis on left side of colon — no./total no. (%)	188/293 (64.2)	544/868 (62.7)
Total Mayo score category — no./total no. (%)‡		
Moderate	186/282 (66.0)	519/825 (62.9)
Severe	93/282 (33.0)	297/825 (36.0)
Modified Mayo score category — no./total no. (%)§		
Moderate	138/293 (47.1)	404/868 (46.5)
Severe	155/293 (52.9)	463/868 (53.3)
Mayo endoscopic subscore indicating severe disease — no./total no. (%)‡	200/293 (68.3)	574/868 (66.1)
Outcome of previous therapy for ulcerative colitis — no. (%)		
Previous treatment failure with biologic agent or tofacitinib	118 (40.1)	361 (41.6)
Inadequate response to a biologic agent or tofacitinib	70 (23.8)	203 (23.4)
Loss of response to a biologic agent or tofacitinib	65 (22.1)	196 (22.6)
Inability to take a biologic agent or tofacitinib due to side effects	14 (4.8)	51 (5.9)
Previous treatment failure with biologic agent	117 (39.8)	360 (41.5)
Previous treatment failure with anti-TNF agent	97 (33.0)	325 (37.4)
Previous treatment failure with vedolizumab	59 (20.1)	159 (18.3)
Previous treatment failure with tofacitinib	6 (2.0)	34 (3.9)
Baseline therapy for ulcerative colitis — no. (%)		
Glucocorticoids	113 (38.4)	351 (40.4)
Immunomodulators	69 (23.5)	211 (24.3)
Aminosalicylates	217 (73.8)	646 (74.4)
Median severity of bowel urgency (IQR)¶	7 (5–8)	6 (5–8)
Median fecal calprotectin (IQR) — μg/g	1471.5 (626.5–2944.5)	1559.0 (634.0–3210.0)
Median C-reactive protein (IQR) — mg/liter	4.2 (1.2–9.5)	4.1 (1.5–9.6)

* Plus–minus values are means ±SD. The modified intention-to-treat population included all the patients who underwent randomization and received any dose of mirikizumab or placebo and excluded the patients who were affected by the electronic clinical-outcomes assessment transcription error in Poland and Turkey. IQR denotes interquartile range, and TNF tumor necrosis factor.

† The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. A BMI of 18.5 to less than 25 indicates a normal BMI; a BMI of 25 or higher indicates overweight (25 to <30), obesity (30 to <40), or extreme obesity (≥40). A total of 28 patients (9.5%) in the placebo group and 55 (6.3%) in the mirikizumab group had a BMI indicating underweight (<18.5).

‡ The Mayo score is a composite instrument that comprises four subscores: the stool-frequency subscore, the rectal-bleeding subscore, the endoscopic subscore, and the physician's global assessment subscore. Each subscore is assessed on a 4-point scale ranging from 0 to 3, with higher scores indicating greater severity. The maximum total Mayo score is 12. A score of 6 to 9 indicates moderate ulcerative colitis, and a score of 10 to 12 severe ulcerative colitis. The physician's global assessment subscore was not available for 55 patients (for 12 in the placebo group and for 43 in the mirikizumab group), so the total Mayo score could not be assessed for these patients. A total of 12 patients with mild disease (total Mayo score, 3 to 5) were enrolled.

§ The modified Mayo score is the sum of the Mayo stool-frequency, rectal-bleeding, and endoscopic subscores, with a maximum total score of 9. On the modified Mayo scoring system, a score of 4 to 6 indicates moderate ulcerative colitis, and a score of 7 to 9 severe ulcerative colitis. One patient (in the placebo group) with mild disease (modified Mayo score, <4) was inadvertently enrolled.

¶ The severity of bowel urgency was assessed by means of the Urgency Numeric Rating Scale (NRS), a patient-reported measure of the severity of the urgency (i.e., sudden or immediate need) to have a bowel movement in the past 24 hours. The Urgency NRS is an 11-point scale, with scores ranging from 0 (no urgency) to 10 (worst possible urgency).

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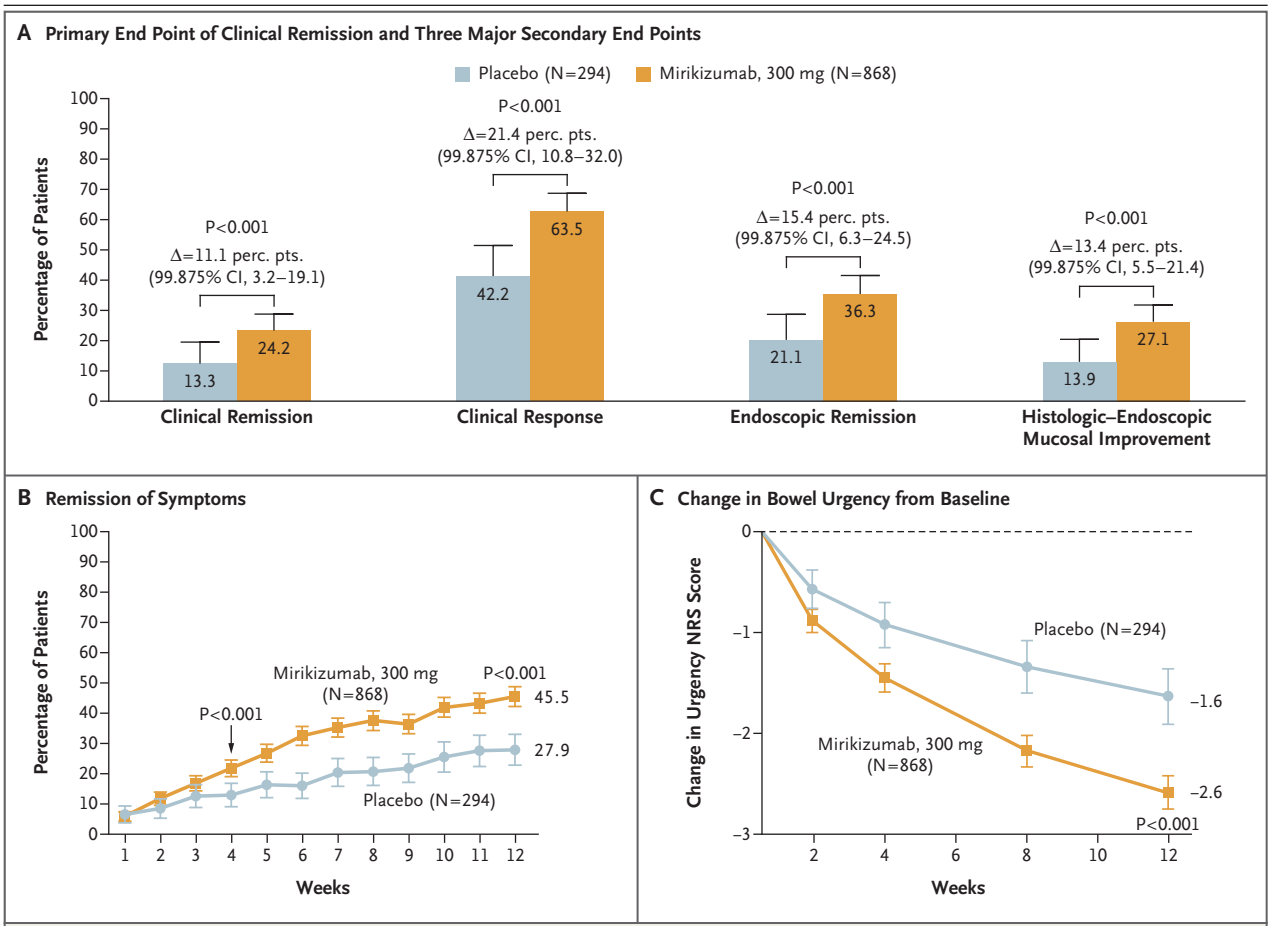

Figure 1. Primary and Major Secondary End Points in the Induction Trial.

In the induction trial, patients were randomly assigned to receive 300 mg of mirikizumab or placebo, administered intravenously. In Panel A, the difference (Δ) between percentages (shown in percentage points [perc. pts.]) is shown for each end point. The primary end point was clinical remission (defined as a modified Mayo stool-frequency subscore of 0 [on a scale from 0 to 3, with higher scores indicating higher frequency] or a stool-frequency subscore of 1 with a decrease of ≥1 point from baseline; a rectal-bleeding subscore of 0; and an endoscopic subscore of 0 or 1 [excluding friability]) at week 12. T bars indicate the upper boundary of the 99.875% confidence interval. Clinical response (defined as decreases of ≥2 points and ≥30% from baseline in the modified Mayo score; a rectal-bleeding subscore of 0 or 1 or a decrease of ≥1 point from baseline; endoscopic remission [endoscopic subscore of 0 or 1, excluding friability]; and histologic–endoscopic mucosal improvement [defined as endoscopic remission and an assessment on the Geboes scoring system of neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue). Remission of symptoms (defined as a stool-frequency subscore of 0 or a subscore of 1 with a decrease of ≥1 point from baseline, and a rectal-bleeding subscore of 0) was assessed at weeks 4 and 12 (Panel B). I bars indicate 95% confidence intervals. The Urgency Numeric Rating Scale (NRS) is a patient-reported measure of the severity for the urgency (sudden or immediate need) to have a bowel movement in the past 24 hours and is assessed on an 11-point scale, with scores ranging from 0 (no urgency) to 10 (worst possible urgency) (Panel C). Least-squares mean changes are shown, and I bars indicate 95% confidence intervals. In Panels B and C, P values are shown only for hypotheses that were controlled for multiplicity. CI denotes confidence interval.

of those in the placebo group had clinical remission (difference, 23.2 percentage points; 95% CI, 15.2 to 31.2; P<0.001) (Fig. 2A). These results were similar to those for the alternative definition of clinical remission (54.9% in the mirikizumab group vs. 27.0% in the placebo group, P<0.001) and for the sensitivity analyses. The percentages of patients with clinical remission, glucocorticoid-free clinical remission, maintenance of clinical remission, endoscopic remission, histologic–endoscopic mucosal remission, and bowel-urgency remission were all significantly greater in the mirikizumab group than in the placebo group (Fig. 2A). Among mirikizumab-treated

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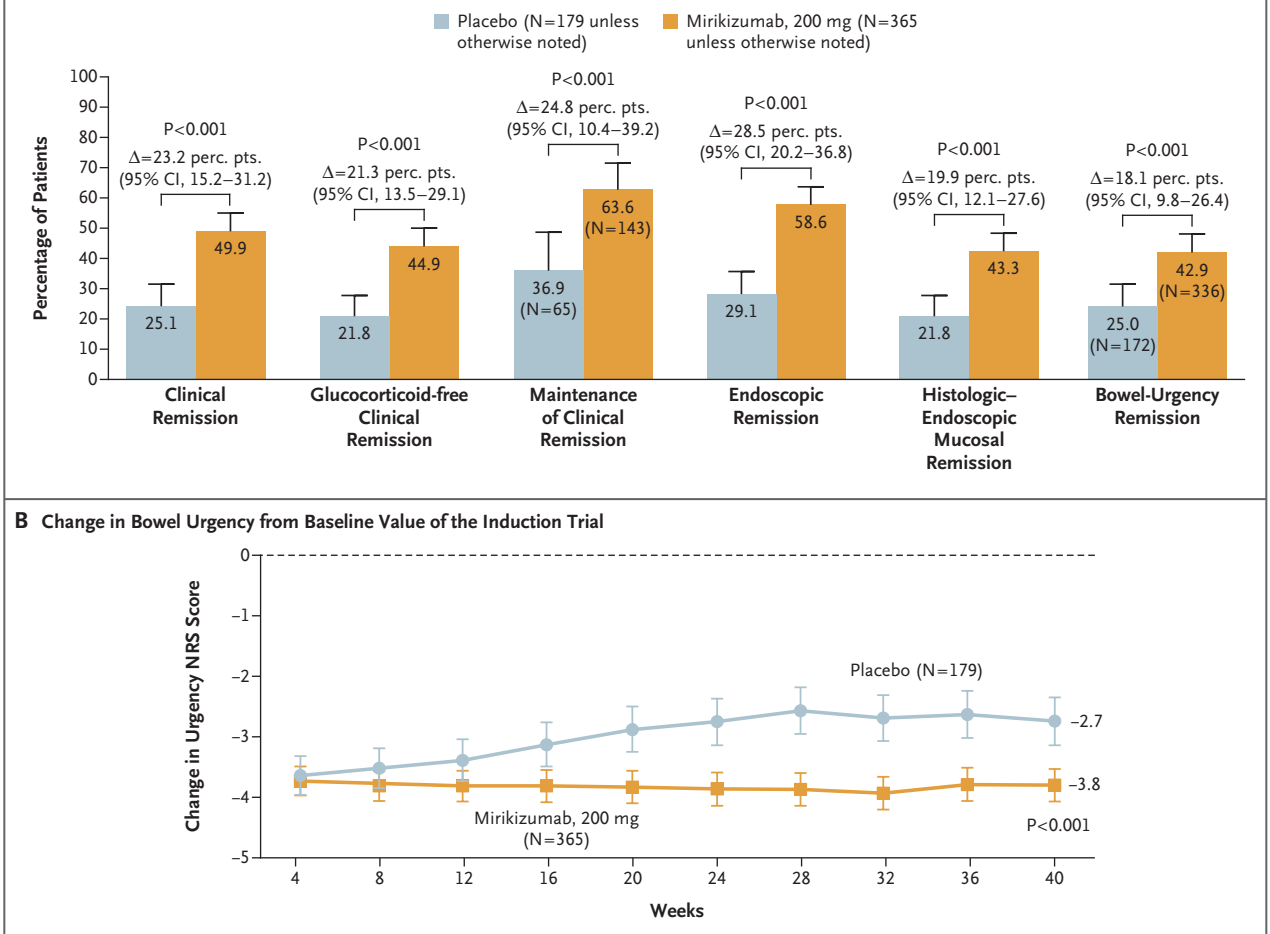

Figure 2. Primary and Major Secondary End Points in the Maintenance Trial.

In the maintenance trial, patients with a response to mirikizumab therapy in the induction trial were randomly assigned to receive 200 mg of mirikizumab or placebo, administered subcutaneously. Glucocorticoid-free clinical remission was defined as clinical remission at week 40, remission of symptoms at week 28, and no glucocorticoid use for at least 12 weeks before week 40. Maintenance of clinical remission was defined as clinical remission in patients who had had clinical remission with mirikizumab therapy in the induction trial. Histologic–endoscopic mucosal remission was defined as endoscopic remission and a Geboes subscore of 0 for grades 2b (lamina propria neutrophils), 3 (neutrophils in epithelium), 4 (crypt destruction), and 5 (erosion or ulceration). Bowel-urgency remission was defined as no or minimal bowel urgency (Urgency NRS score, 0 or 1) in patients with a baseline Urgency NRS score of 3 or higher. T bars in Panel A indicate the upper boundary of the 95% confidence interval. In Panel B, least-squares mean changes are shown, and I bars indicate 95% confidence intervals.

patients who were in clinical remission at week 40, a total of 97.8% were not taking glucocorticoids. The improvement from baseline in the Urgency NRS score remained stable throughout the maintenance trial in the mirikizumab group, whereas patients in the placebo group in the maintenance trial lost some of the improvement that had been gained during the induction trial (Fig. 2B).

In the subgroup of patients with treatment failure with biologic agents or tofacitinib, the percentages of patients who met the primary and all major secondary end points of the maintenance trial at week 40 appeared to be greater in the mirikizumab group than in the placebo group (in an analysis not adjusted for multiplicity). Results of all the prespecified subgroups are shown in Figure S4. The Inflammatory Bowel Disease Questionnaire score (Fig. S7B and S7D) and C-reactive protein and fecal calprotectin

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Table 2. Safety during the Induction and Maintenance Trials.*

Event	Induction Trial		Maintenance Trial	
	Placebo (N=321)	Mirikizumab (N=958)	Placebo (N=192)	Mirikizumab (N=389)
	number (percent)			
Any adverse event	148 (46.1)	426 (44.5)	132 (68.8)	251 (64.5)
Any adverse event, excluding ulcerative colitis	141 (43.9)	421 (43.9)	116 (60.4)	241 (62.0)
Serious adverse event	17 (5.3)	27 (2.8)	15 (7.8)	13 (3.3)
Serious adverse event, excluding ulcerative colitis	7 (2.2)	20 (2.1)	10 (5.2)	13 (3.3)
Discontinuation of mirikizumab or placebo due to adverse event	23 (7.2)	15 (1.6)	16 (8.3)	6 (1.5)
Death†	0	0	1 (0.5)	0
Common adverse events‡				
Nasopharyngitis	10 (3.1)	39 (4.1)	11 (5.7)	28 (7.2)
Arthralgia	4 (1.2)	20 (2.1)	8 (4.2)	26 (6.7)
Ulcerative colitis	24 (7.5)	17 (1.8)	40 (20.8)	26 (6.7)
Injection-site pain	—	—	6 (3.1)	17 (4.4)
Headache	9 (2.8)	32 (3.3)	2 (1.0)	16 (4.1)
Rash	2 (0.6)	5 (0.5)	0	14 (3.6)
Pyrexia	3 (0.9)	14 (1.5)	5 (2.6)	13 (3.3)
Anemia	19 (5.9)	32 (3.3)	9 (4.7)	8 (2.1)
Adverse events of interest				
Any infection	45 (14.0)	145 (15.1)	44 (22.9)	93 (23.9)
Serious infection	2 (0.6)	7 (0.7)	3 (1.6)	3 (0.8)
Opportunistic infection§	1 (0.3)	5 (0.5)	0	5 (1.3)
Candidiasis	0	1 (0.1)	0	1 (0.3)
Cytomegalovirus disease	0	2 (0.2)	0	0
Herpes zoster infection of any form	1 (0.3)	1 (0.1)	0	4 (1.0)
Tuberculosis	0	1 (0.1)	0	0
Adjudicated cerebrocardiovascular events¶	2 (0.6)	1 (0.1)	1 (0.5)	0
Cancer‖	0	2 (0.2)	1 (0.5)	1 (0.3)
Nonmelanoma skin cancer	0	0	1 (0.5)	0
Adenocarcinoma of colon	0	2 (0.2)	0	0
Gastric cancer	0	0	0	1 (0.3)
Depression**	2 (0.6)	4 (0.4)	0	4 (1.0)
Suicide or self-injury††	0	0	0	1 (0.3)
Hepatic-related event	5 (1.6)	15 (1.6)	4 (2.1)	12 (3.1)
Immediate hypersensitivity reaction‡‡	1 (0.3)	10 (1.0)	2 (1.0)	7 (1.8)
Infusion- or injection-site reaction§§	1 (0.3)	4 (0.4)	8 (4.2)	34 (8.7)

* Adverse events are reported in the safety populations of the induction trial, in which patients were assigned to receive mirikizumab (300 mg) or placebo, administered intravenously, and the maintenance trial, in which patients who had had a response to mirikizumab therapy in the induction trial were randomly assigned to receive mirikizumab (200 mg) or placebo, administered subcutaneously. The safety population in each trial included all the patients who had undergone randomization and received any amount of mirikizumab or placebo, including those patients who were affected by the electronic clinical-outcomes assessment transcription error.

† There were two deaths during the follow-up period for the induction trial: one from sudden cardiac arrest, and one from disseminated intravascular coagulation. The death in the placebo group during the maintenance trial was due to coronavirus disease 2019.

‡ Common adverse events were defined as those that occurred in at least 3% of the patients in any trial group during the induction or maintenance trial. The events are listed according to decreasing frequency in the mirikizumab group during the maintenance trial.

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Table 2. (Continued.)

§ Specific *Medical Dictionary for Regulatory Activities* (MedDRA) terms were used to identify infections that were considered to be opportunistic infections on the basis of Winthrop et al.[16] In the induction trial, one case of herpes zoster infection was reported in the placebo group, and one case of esophageal candidiasis, two of cytomegalovirus colitis, one of herpes zoster infection, and one of intestinal tuberculosis were reported in the mirikizumab group; cytomegalovirus colitis was severe in one patient. In the maintenance trial, one case of oral candidiasis and four cases of herpes zoster infection were reported in the mirikizumab group. Herpes zoster infection was severe in one patient. Other opportunistic infections during both the induction and maintenance trials were mild to moderate, and none resulted in discontinuation of mirikizumab.

¶ There were no instances of a major adverse cardiovascular event (MACE) during the induction trial. One instance of MACE (ischemic stroke) occurred in the placebo group during the maintenance trial.

‖ In the mirikizumab group during the induction trial, both cancers were colon adenocarcinoma. During the maintenance trial, nonmelanoma skin cancer (basal-cell carcinoma) occurred in one patient in the placebo group and gastric cancer in one patient in the mirikizumab group.

** The adverse event of depression excluded patients with suicide or self-injury.

†† One patient in the mirikizumab group during the maintenance trial had a suicide attempt. This patient had a medical history of depression and previous suicide attempts. The suicide attempt during the trial was not considered by the investigators to be related to mirikizumab.

‡‡ Immediate hypersensitivity reaction was defined as a hypersensitivity reaction that occurred within 24 hours after the administration of mirikizumab or placebo or on the day of administration when specific time information was missing. No serious hypersensitivity or anaphylactic reactions occurred during the induction trial. The term "hypersensitivity reactions" was used as an overarching term to describe systemic events that probably had an allergic or hypersensitivity cause. Analyses for both trial periods were based on narrow terms with the use of the following standardized queries in MedDRA: anaphylactic reaction, hypersensitivity, and angioedema. One case of anaphylaxis occurred in the placebo group during the maintenance trial.

§§ Infusion-site reaction was an adverse event of interest during the induction trial, and injection-site reaction was an adverse event of interest during the maintenance trial.

(Fig. S8B and S8D) appeared to be improved in the mirikizumab group as compared with the placebo group.

Among the 272 patients who did not have a response to mirikizumab therapy in the induction trial who then received open-label mirikizumab induction therapy in the maintenance trial, 53.7% had a clinical response and 11.4% had clinical remission by week 12 (Fig. S9A), and 144 of the 272 patients (52.9%) received mirikizumab maintenance treatment. Clinical remission was maintained in 72.2% of these patients, and 36.1% had clinical remission at week 40 (Fig. S9B). In the subgroup of patients with treatment failure with biologic agents or tofacitinib who did not have a response to mirikizumab induction therapy, 46.3% had a clinical response with extended induction therapy at week 12.

SAFETY END POINTS

The incidences of adverse events during the trials were similar in the mirikizumab groups and placebo groups during both the induction trial and the placebo-controlled maintenance trials. The most common adverse events that were reported during treatment with mirikizumab are summarized in Table 2.

Among 1217 patients treated with mirikizumab during the placebo-controlled and non–placebo-controlled (i.e., open-label extended induction and open-label maintenance) trial periods, opportunistic infections were observed in 15 (herpes zoster infection in 6 [in 5 during placebo-controlled periods and in 1 during a non–placebo-controlled period], candidiasis in 4 [in 2 during each period], cytomegalovirus disease in 4 [in 2 during each period], and intestinal tuberculosis in 1 [during a placebo-controlled period]). Opportunistic infection (herpes zoster) occurred in 1 patient who received placebo in the induction trial.

During the 52-week treatment period, among the 1217 patients who received mirikizumab, cancer was reported in 8. Adenocarcinoma of the colon was reported in 2 patients during the induction trial, and nonmelanoma skin cancer and gastric cancer in 1 patient each during the double-blind portion of the maintenance trial (Table 2). In the open-label periods of the maintenance trial, squamous-cell carcinoma was reported in 2 patients and adenocarcinoma of the colon, rectal cancer, and Kaposi's sarcoma were reported in 1 patient each (Table S8). The adverse event of colon adenocarcinoma that was observed in the open-label periods of the maintenance trial had previously been reported in the same patient by the investigator in the induction trial. No cancers were observed in patients who received placebo during the induction trial. One additional case of adenocarcinoma in a patient who had received mirikizumab in the induction trial was discovered in the post-treatment follow-

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up period after induction and is not included in the total of 8 patients with cancer.

Elevations in liver-enzyme levels were more frequent in patients who received mirikizumab than in those who received placebo (Table S9). One mirikizumab-treated patient in the open-label extended induction cohort in the maintenance trial had elevations of alanine aminotransferase and total bilirubin that met the criteria for Hy's law, with no other cause to explain the hepatic laboratory abnormalities; these elevations resolved after the discontinuation of mirikizumab.

Immediate hypersensitivity reactions were more frequent in the mirikizumab group than in the placebo group in the induction trial, although no serious hypersensitivity or anaphylactic reactions occurred. Injection-site reactions were more frequent in the mirikizumab group than in the placebo group during the placebo-controlled maintenance period. Two adverse events of injection-site pain were severe; others were mild to moderate in severity.

Depression was reported in four patients who received mirikizumab and in no patient who received placebo in the maintenance trial (Table 2). Depression was reported during the open-label maintenance period in two mirikizumab-treated patients who had not had a response to the initial induction mirikizumab therapy. One case of depression with attempted suicide was reported in a mirikizumab-treated patient who had a history of suicide attempts.

DISCUSSION

In these two trials, mirikizumab resulted in significantly higher percentages of patients who had remission (primary end point) than placebo and who met the criteria for the key secondary end points over periods of 12 weeks and 40 weeks. Current recommendations for the treatment of ulcerative colitis include increasingly rigorous goals beyond symptomatic or endoscopic improvement, such as the resolution of acute inflammatory cell infiltration that is observable on histologic testing.[2,17] Accordingly, as defined in the protocol, the histologic component for the combined end point of histologic–endoscopic mucosal remission at the end of the maintenance trial required the absence of mucosal neutrophils, which accumulate with persistent acute inflammation from ulcerative colitis.[18] Recent literature has recommended the absence of intraepithelial neutrophils as a minimal requirement for remission on the basis of histologic testing.[19,20] After 1 year of mirikizumab treatment, more than 40% of the patients in the LUCENT-1 and LUCENT-2 trials had no mucosal neutrophils.

A new aspect of the LUCENT trial program was the inclusion of end points relating to bowel urgency.[21,22] Many patients with ulcerative colitis consider control of bowel movements to be more important than rectal bleeding or stool frequency.[23,24] To address this situation, the sponsor developed and validated the patient-reported Urgency NRS.[14] In the induction trial, patients reported reductions in bowel urgency with mirikizumab therapy, which were sustained during the maintenance trial.

Herpes zoster infection occurred more often in patients in the mirikizumab groups (in two patients overall, vs. in one patient in the placebo group in the induction trial). There was no clear pattern with respect to glucocorticoid or immunomodulator use among the patients with herpes zoster infection.

Gastric cancer occurred in one mirikizumab-treated patient from Japan, where there is a known high incidence rate of gastric cancer,[25] and colorectal cancer was detected in three patients (two of whom had been treated with mirikizumab) at the end of the induction trial, the post-treatment follow-up period, or the extended induction period. Owing to the severity of mucosal inflammation, these cancers may have been present but not visualized during endoscopy at trial entry, a situation that has occurred in other phase 3 trials, although we cannot validate this.[26] Elevations in liver-enzyme levels were more frequent in the mirikizumab groups than in the placebo groups, with one patient having elevations of the alanine aminotransferase and total bilirubin levels that met the criteria for Hy's law, with no other cause to explain the hepatic laboratory abnormalities. Elevations in liver-enzyme levels have been observed with interleukin-23 subunit p19 inhibitors that are approved for other indications and with other therapies for ulcerative colitis, including anti–tumor necrosis factor agents.[9,10,27] During the maintenance trial, depression was more common in the mirikizumab group than in the

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placebo group (in four patients vs. none). Nasopharyngitis and arthralgias were also more frequent in the mirikizumab groups than in the placebo groups.

In these two phase 3 trials, we found that, over periods of 12 weeks and 40 weeks, mirikizumab therapy had efficacy in both induction and maintenance phases across clinical, symptomatic, endoscopic, and histologic measures of disease, even after treatment failure with conventional immunosuppressive agents, biologic therapies, or tofacitinib. Opportunistic infections or cancer developed in a small number of mirikizumab-treated patients. Additional and longer trials are ongoing to further assess the efficacy and safety of mirikizumab therapy in patients with ulcerative colitis (ClinicalTrials.gov number, NCT03519945) or Crohn's disease (NCT03926130 and NCT04232553).

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