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Ustekinumab as Induction and Maintenance Therapy for Ulcerative Colitis

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ABSTRACT

BACKGROUND

The efficacy of ustekinumab, an antagonist of the p40 subunit of interleukin-12 and interleukin-23, as induction and maintenance therapy in patients with ulcerative colitis is unknown.

METHODS

We evaluated ustekinumab as 8-week induction therapy and 44-week maintenance therapy in patients with moderate-to-severe ulcerative colitis. A total of 961 patients were randomly assigned to receive an intravenous induction dose of ustekinumab (either 130 mg [320 patients] or a weight-range–based dose that approximated 6 mg per kilogram of body weight [322]) or placebo (319). Patients who had a response to induction therapy 8 weeks after administration of intravenous ustekinumab were randomly assigned again to receive subcutaneous maintenance injections of 90 mg of ustekinumab (either every 12 weeks [172 patients] or every 8 weeks [176]) or placebo (175). The primary end point in the induction trial (week 8) and the maintenance trial (week 44) was clinical remission (defined as a total score of ≤2 on the Mayo scale [range, 0 to 12, with higher scores indicating more severe disease] and no subscore >1 [range, 0 to 3] on any of the four Mayo scale components).

RESULTS

The percentage of patients who had clinical remission at week 8 among patients who received intravenous ustekinumab at a dose of 130 mg (15.6%) or 6 mg per kilogram (15.5%) was significantly higher than that among patients who received placebo (5.3%) (P<0.001 for both comparisons). Among patients who had a response to induction therapy with ustekinumab and underwent a second randomization, the percentage of patients who had clinical remission at week 44 was significantly higher among patients assigned to 90 mg of subcutaneous ustekinumab every 12 weeks (38.4%) or every 8 weeks (43.8%) than among those assigned to placebo (24.0%) (P=0.002 and P<0.001, respectively). The incidence of serious adverse events with ustekinumab was similar to that with placebo. Through 52 weeks of exposure, there were two deaths (one each from acute respiratory distress syndrome and hemorrhage from esophageal varices) and seven cases of cancer (one each of prostate, colon, renal papillary, and rectal cancer and three nonmelanoma skin cancers) among 825 patients who received ustekinumab and no deaths and one case of cancer (testicular cancer) among 319 patients who received placebo.

CONCLUSIONS

Ustekinumab was more effective than placebo for inducing and maintaining remission in patients with moderate-to-severe ulcerative colitis. (Funded by Janssen Research and Development; UNIFI ClinicalTrials.gov number, NCT02407236.)

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Ulcerative colitis is a chronic inflammatory disease of the large intestine.[1,2] Current therapies are limited by increased risks of infection[3-6] or cancer[7] or by loss of clinical benefit.[8]

Ustekinumab (Stelara, Janssen Biotech) is a monoclonal antibody to the p40 subunit of interleukin-12 and interleukin-23 and has been approved for the treatment of psoriasis, psoriatic arthritis, and Crohn's disease.[9] In a phase 3 program for the treatment of Crohn's disease, ustekinumab induced a response at 8 weeks and maintained clinical benefit through 52 weeks of treatment in patients who had had treatment failure with or unacceptable side effects from corticosteroids, immunomodulators, or tumor necrosis factor (TNF) antagonists.[10] We conducted a phase 3 trial (UNIFI) of ustekinumab that involved patients with moderate-to-severe ulcerative colitis, using doses identical to those in the phase 3 program involving patients with Crohn's disease.

Methods

Trial Design and Oversight

The UNIFI trial included an 8-week randomized induction trial and a 44-week randomized-withdrawal maintenance trial (representing 52 weeks of treatment). Both were double-blind, placebo-controlled trials conducted from August 2015 through August 2018 under one protocol at 244 sites worldwide. Institutional review boards approved the protocol (available with the full text of this article at NEJM.org); all patients provided written informed consent. A steering committee of academic investigators and Janssen scientists designed the trials, analyzed and interpreted the data, and contributed to the manuscript. The first author wrote the first draft of the manuscript; all authors vouch for the veracity and completeness of the data and for the fidelity of the trials to the protocol. Editorial support was provided by Janssen.

Patients

Adult patients (≥18 years of age) were eligible if they had received a diagnosis of ulcerative colitis at least 3 months before screening and had moderate-to-severe ulcerative colitis, defined as a total score of 6 to 12 on the Mayo scale (range, 0 to 12, with higher scores indicating more severe disease) and a subscore of 2 or 3 on the endoscopic component of the Mayo scale, as determined during central review of videoendoscopy.[11,12] Subscores on each of the four components of the Mayo scale range from 0 to 3. Eligible patients were required to have had an inadequate response to or unacceptable side effects from TNF antagonists, vedolizumab, or conventional (i.e., nonbiologic) therapy. (For definitions and for more details on the patients, randomization, assessments, and end points, see the Supplementary Appendix, available at NEJM.org.)

Stable doses of aminosalicylates and immunomodulators were maintained from baseline of induction therapy through week 44 of maintenance therapy. Oral corticosteroids were maintained at a stable dose during the induction trial and tapered when patients entered the maintenance trial.

Previous treatment with interleukin-12 or interleukin-23 antagonists was prohibited. Previous TNF antagonist therapy was discontinued at least 8 weeks before trial entry, and vedolizumab was discontinued at least 4 months before trial entry; other conventional therapies were discontinued at least 2 to 4 weeks before trial entry. Among the exclusion criteria were imminent colectomy, gastrointestinal conditions that would result in surgery or confound disease-activity assessment, cancer, and active infections (including tuberculosis).

Randomization

At week 0 in the induction trial, patients were randomly assigned, in a 1:1:1 ratio, to receive a single intravenous infusion of 130 mg of ustekinumab, a weight-range–based dose that approximated 6 mg of ustekinumab per kilogram of body weight, or placebo. Randomization was performed with the use of permuted blocks, with stratification according to status with respect to previous treatment failure with biologic agents (yes or no) and geographic region (eastern Europe, Asia, or rest of world).

Patients who had a clinical response to intravenous ustekinumab at week 8 (defined as a decrease in the total Mayo score of ≥30% and of ≥3 points from baseline, with an accompanying decrease of ≥1 point on the rectal bleeding component of the Mayo scale or a rectal bleeding subscore of 0 or 1) entered the maintenance trial, as did those who did not have a response to intravenous placebo and who then received an

induction dose of intravenous ustekinumab (6 mg per kilogram) at week 8 and had a response at week 16. At week 0 in the maintenance trial, patients were randomly assigned, in a 1:1:1 ratio, to receive subcutaneous injections of 90 mg of ustekinumab every 12 weeks, 90 mg of ustekinumab every 8 weeks, or placebo through week 40 (Fig. 1). Randomization was performed with the use of permuted blocks, with stratification according to intravenous induction treatment (130 mg of ustekinumab, 6 mg of ustekinumab per kilogram, or placebo followed by 6 mg of ustekinumab per kilogram), status with respect to clinical remission (yes or no) at baseline in the maintenance trial, and oral corticosteroid use (yes or no). These patients comprised the randomized maintenance population (primary analysis population).

Patients who did not have a response to intravenous ustekinumab at week 8 received 90 mg of subcutaneous ustekinumab in a blinded manner and were reevaluated at week 16; those who had a response entered the maintenance trial and received 90 mg of subcutaneous ustekinumab every 8 weeks (i.e., patients with a delayed response to ustekinumab). Patients who had a response to intravenous placebo at week 8 received subcutaneous placebo; these patients and those who had a delayed response to ustekinumab comprised the nonrandomized maintenance population (Fig. 1).

During maintenance therapy, patients were monitored for clinical flares. Endoscopy was performed to confirm loss of response. (Details on clinical flares are provided in the Supplementary Appendix.)

ASSESSMENTS AND END POINTS

The total Mayo score[11,12] and the score on the Inflammatory Bowel Disease Questionnaire (IBDQ, with scores ranging from 32 to 224 and higher scores indicating better quality of life)[13] were assessed at weeks 0, 8, and 16 (in patients who did not have a response to induction therapy at week 8) in the induction trial and at week 20 (IBDQ score only) and week 44 in the maintenance trial. The partial Mayo score (i.e., the total Mayo score excluding the endoscopic subscore, with scores ranging from 0 to 9 and higher scores indicating more severe disease) was evaluated at weeks 2 and 4 during induction and every 4 weeks during maintenance. Concentrations of fecal biomarkers (calprotectin and lactoferrin) and serum C-reactive protein (CRP) were evaluated at all visits during induction and at weeks 8, 24, and 44 during maintenance. Mucosal biopsy samples that were obtained from patients who underwent endoscopy at week 8 during induction and at week 44 during maintenance were assessed for histologic improvement.

The primary end point in the induction trial was clinical remission (defined as a total Mayo score of ≤2 and no subscore >1) at week 8. Major secondary end points at week 8 were endoscopic improvement (defined as a Mayo endoscopic subscore of 0 or 1), clinical response, and change from baseline in the IBDQ score. The IBDQ score was a major secondary end point included in the protocol but was not included as a prespecified major secondary end point in the statistical analysis plan submitted to the Food and Drug Administration (FDA). Histo-endoscopic mucosal healing (which required both histologic improvement [defined as neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue][14,15] and endoscopic improvement) was an additional end point that was controlled for multiple comparisons at week 8. In the maintenance trial, the primary end point was clinical remission at week 44; major secondary end points were maintenance of clinical response through week 44, endoscopic improvement at week 44, corticosteroid-free clinical remission at week 44, and maintenance of clinical remission through week 44 among patients in clinical remission at baseline in the maintenance trial.

An alternative primary end point of clinical remission that excluded the subscore on the physician's global assessment component of the Mayo scale was also prespecified to support the FDA submission. This definition required an absolute stool number of 3 or fewer (average daily stool number during 3 days before a visit), a Mayo rectal bleeding subscore of 0, and a Mayo endoscopic subscore of 0 or 1.

Histologic improvement, histo-endoscopic mucosal healing, and changes in the partial Mayo score, IBDQ score, serum CRP concentration, and concentrations of fecal biomarkers were assessed separately in the induction and maintenance trials. Safety follow-up assessment (concomitant medications, adverse events, serious adverse events, and ulcerative colitis–related hospitalizations and surgical procedures) occurred

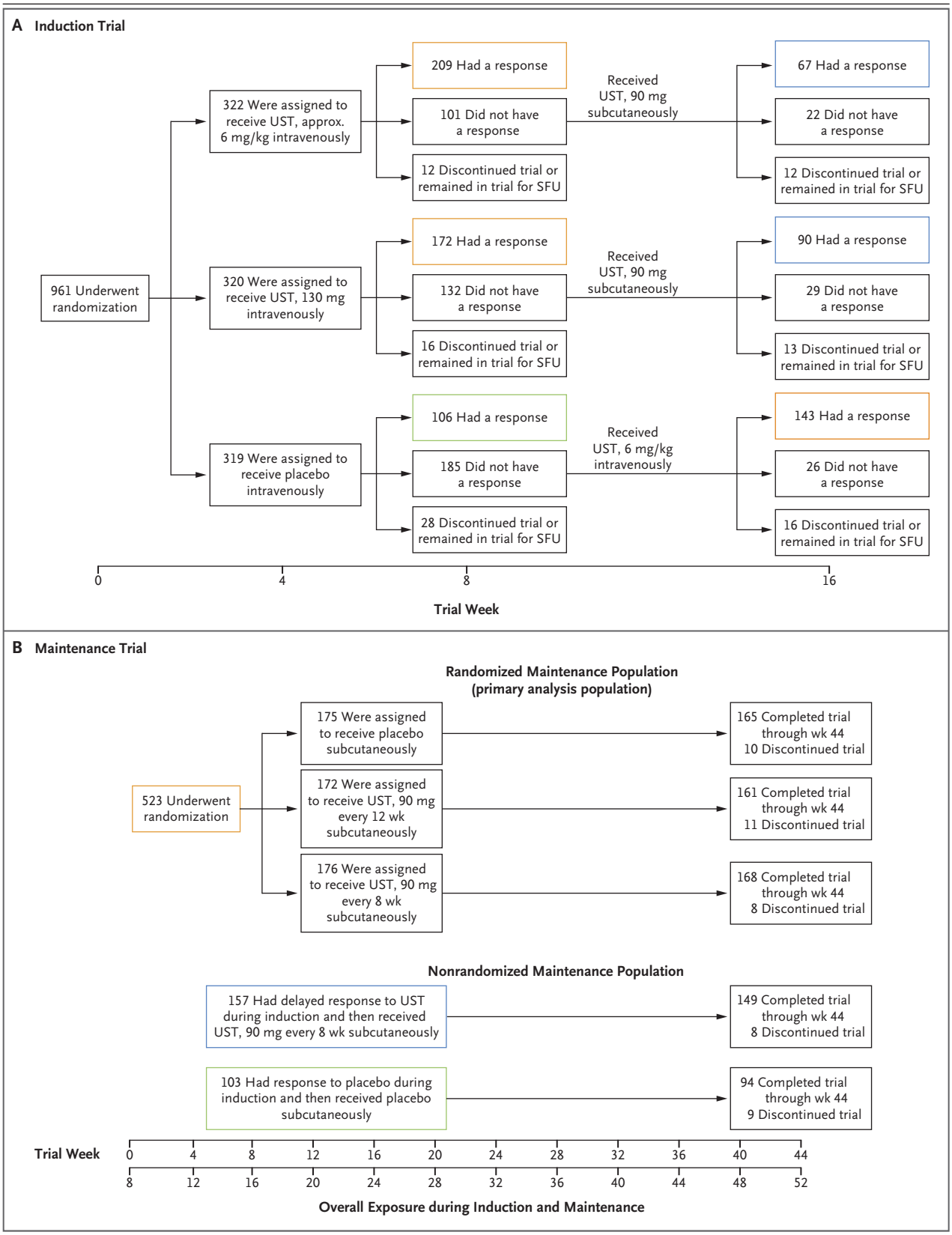

Figure 1 (facing page). Overall Trial Flow.
In the induction trial, status with respect to response or nonresponse was determined by means of an interactive Web response system and by the subscore on the endoscopic component of the Mayo scale as assessed by the local endoscopist. The patients who had a response to intravenous ustekinumab (UST) at week 8, as well as those who did not have a response to intravenous placebo and who then received an induction dose of intravenous ustekinumab (6 mg per kilogram of body weight) at week 8 and had a response at week 16, made up the randomized primary analysis population in the maintenance trial. One patient who had a response to intravenous ustekinumab (6 mg per kilogram) at week 8 and three patients who had a response to intravenous placebo did not enter the maintenance trial. Patients who had a delayed response to induction therapy with ustekinumab (i.e., those who did not have a response to intravenous ustekinumab and who then received ustekinumab subcutaneously at week 8 and had a response at week 16) entered the maintenance trial but did not undergo randomization. Patients who had a response to intravenous placebo in the induction trial entered the maintenance trial but did not undergo randomization. Baseline (week 0) in the maintenance trial is the same as week 8 or week 16 in the induction trial, depending on when patients entered maintenance (week 8 or week 16). Patients who had a response to intravenous ustekinumab at week 8 in the induction trial and then completed the maintenance trial through week 44 had 52 weeks of overall exposure; patients who had a response to ustekinumab at week 16 in the induction trial could have up to 60 weeks of overall exposure. SFU denotes safety follow-up (lasting 20 weeks after the last dose of ustekinumab or placebo).

during the induction trial through week 8 or week 16 when patients entered the maintenance trial or 20 weeks after the final induction dose for those discontinuing the trial and during the maintenance trial through week 44 (i.e., 52 weeks of treatment).

PHARMACOKINETICS AND IMMUNOGENICITY

Serum ustekinumab concentrations were evaluated at all visits during induction and every 4 weeks during maintenance. Antidrug antibodies were evaluated by means of a drug-tolerant electrochemiluminescence assay at weeks 0, 4, 8, and 16 (in patients who did not have a response to induction therapy at week 8) during induction and at weeks 4, 12, 24, 36, and 44 during maintenance. The relationship between exposure and response was assessed on the basis of quartiles of serum ustekinumab concentration at week 8 during induction (for efficacy end points in the induction trial) and at week 24 during maintenance (for efficacy end points in the maintenance trial).

STATISTICAL ANALYSIS

The primary and major secondary end points in the induction trial (including histo-endoscopic mucosal healing) and the maintenance trial were controlled for multiple comparisons. The type I error rate in each trial was controlled at an alpha level of 0.05 over the end points that were controlled for multiple comparisons with the use of a prespecified multiple-testing procedure. A different prespecified multiple-testing procedure was used to support the FDA submission. (For details on multiple-testing procedures and prespecified subgroups, see the Supplementary Appendix.)

Dichotomous end points were compared between each ustekinumab group and the placebo group with the use of a two-sided, Cochran–Mantel–Haenszel chi-square test with adjustment for stratification variables. Continuous end points were analyzed by means of analysis of covariance or analysis of covariance on van der Waerden normal scores with adjustment for baseline value and stratification variables.

Analyses of other end points were not adjusted for multiple comparisons, and results are reported with 95% confidence intervals not adjusted for multiple comparisons, without P values; inferences drawn from these results may not be reproducible. (See Tables S1A and S1B in the Supplementary Appendix and the statistical analysis plan within the protocol, available at NEJM.org.)

Unless otherwise specified, all efficacy analyses were based on the intention-to-treat principle. Data sets for the primary efficacy analyses comprise the patients who underwent randomization in the induction trial or maintenance trial. Prespecified efficacy analyses were also conducted for patients who entered the maintenance trial after having a delayed response to ustekinumab. To evaluate the consistency of the treatment effect for the primary end point, clinical remission was analyzed in prespecified subgroups.

Patients were considered not to have reached dichotomous end points if they had a prohibited change in concomitant medication for ulcerative colitis, had undergone an ostomy or colectomy before week 8 (during induction) or week 44 (during maintenance), had used a rescue medica-

tion after a clinical flare (during maintenance), or had discontinued ustekinumab or placebo owing to lack of efficacy or an adverse event of worsening disease during maintenance. For continuous end points, patients who had a treatment failure had their value at baseline in the induction trial carried forward from the time of the event onward (i.e., consistent with nonresponse for dichotomous end points).

For dichotomous end points, including all end points that were controlled for multiple comparisons, patients with missing data were considered not to have reached the end points. Prespecified sensitivity analyses including methods to account for missing data were conducted to test the robustness of the primary end point analyses for both definitions of clinical remission. (For more information on the handling of missing data, see the Supplementary Appendix.)

Assuming an incidence of clinical remission of 7% in the placebo group and 19% in each ustekinumab group, we calculated that 317 patients per induction group would provide more than 90% power for the primary end point at week 8 using a step-up Hochberg testing procedure at a two-sided alpha level of 0.05. This sample size would also provide enough patients for the primary population of the maintenance trial. Assuming an incidence of clinical remission of 20% in the group receiving placebo and 40% in the group receiving 90 mg of subcutaneous ustekinumab every 8 weeks, 109 patients per maintenance group would provide 90% power for the primary end point at week 44 at a two-sided significance level of 0.05 on the basis of the fixed-sequence testing procedure, starting with the high-dose ustekinumab group (every 8 weeks).

In the safety analyses, data for patients who received at least one dose of ustekinumab or placebo in the induction trial were analyzed according to the substance received, and data for patients who received at least one dose of ustekinumab or placebo in the maintenance trial were analyzed according to the assigned trial group. The frequency and types of adverse events were summarized. Immunogenicity analyses included patients who had at least one blood sample obtained after ustekinumab administration.

RESULTS

PATIENTS

Of 961 patients who underwent randomization, 912 (94.9%) completed the induction trial: 783 (81.5%) who entered the maintenance trial and 129 (13.4%) who did not enter the maintenance trial completed the final safety visit. In the maintenance trial, 523 patients underwent randomization (primary population) and 260 did not. Most patients (494 of 523, 94.5%) who underwent randomization in the maintenance trial completed the trial. (See Fig. S1A through S1C in the Supplementary Appendix.)

At baseline in the induction trial, patients were randomly assigned to receive a single intravenous infusion of placebo (319 patients), ustekinumab at a dose of 130 mg (320), or ustekinumab at a dose approximating 6 mg per kilogram (322). Patient characteristics were generally similar across trial groups in the induction and maintenance trials (Table 1, and Table S2 in the Supplementary Appendix).

Among 51.1% of randomly assigned patients who had previous treatment failure with biologic agents (491 of 961), a total of 98.8% (485 of 491) had had treatment failure with at least one TNF antagonist, 32.6% (160 of 491) had had treatment failure with both a TNF antagonist and vedolizumab, and 1.2% (6 of 491) had had treatment failure with vedolizumab only. Among patients who did not have previous treatment failure with biologics, 94.3% (443 of 470) had not received biologics and 5.7% (27 of 470) had received biologics but did not have documented treatment failure (Table 1; also see the Supplementary Appendix).

INDUCTION THERAPY

At week 8, the percentages of patients in clinical remission were higher in the groups that received ustekinumab at a dose of either 130 mg (15.6% [50 of 320 patients]) or 6 mg per kilogram (15.5% [50 of 322]) than in the placebo group (5.3% [17 of 319]) ($P<0.001$ for both comparisons with placebo) (Fig. 2). The results were similar for the alternative primary end point of clinical remission that excluded the subscore on the physician's global assessment component of the Mayo scale: 16.6% (53 of 320 patients) and

Table 1. Demographic and Clinical Characteristics at Baseline in the Induction Trial (Randomly Assigned Patients).*

Characteristic	Placebo (N=319)	Ustekinumab	
		130 mg (N=320)	6 mg/kg† (N=322)
Male sex — no. (%)	197 (61.8)	190 (59.4)	195 (60.6)
Age — yr	41.2±13.5	42.2±13.9	41.7±13.7
Weight — kg	72.9±16.8	73.7±16.8	73.0±19.3
Duration of disease — yr	8.0±7.2	8.1±7.2	8.2±7.8
Total Mayo score‡	8.9±1.6	8.9±1.6	8.9±1.5
Score of 6–10, indicating moderate disease — no./total no. (%)	263/319 (82.4)	271/320 (84.7)	276/321 (86.0)
Disease limited to left side of colon — no./total no. (%)	167/316 (52.8)	183/318 (57.5)	168/320 (52.5)
C-reactive protein — mg/liter§			
Median	4.7	4.5	4.8
IQR	1.4–10.0	1.6–9.9	1.8–13.7
Fecal calprotectin — mg/kg¶			
Median	1224.0	1382.0	1506.5
IQR	496.0–2224.0	564.5–2681.0	621.5–3192.5
Medications for ulcerative colitis taken at baseline			
≥1 Medication — no. (%)	283 (88.7)	290 (90.6)	294 (91.3)
Aminosalicylates — no. (%)	207 (64.9)	215 (67.2)	238 (73.9)
Corticosteroids — no. (%)‖	157 (49.2)	173 (54.1)	168 (52.2)
Median dose (IQR) — mg/day	20.0 (10.0–20.0)	20.0 (10.0–20.0)	20.0 (10.0–20.0)
Immunomodulator — no. (%)**	89 (27.9)	93 (29.1)	89 (27.6)
No history of disease refractory to treatment with biologic agents — no. (%)	158 (49.5)	156 (48.8)	156 (48.4)
Had not received biologics	151 (47.3)	145 (45.3)	147 (45.7)
Had received biologics but did not have documented treatment failure	7 (2.2)	11 (3.4)	9 (2.8)
History of treatment failure with biologics — no. (%)††	161 (50.5)	164 (51.2)	166 (51.6)
Only TNF antagonist	112 (35.1)	107 (33.4)	106 (32.9)
Vedolizumab	49 (15.4)	57 (17.8)	60 (18.6)
≥1 TNF antagonist, regardless of vedolizumab	159 (49.8)	162 (50.6)	164 (50.9)
Any TNF antagonist and vedolizumab	47 (14.7)	55 (17.2)	58 (18.0)

* Plus–minus values are means ±SD. IQR denotes interquartile range, and TNF tumor necrosis factor.
† Weight-range–based doses of ustekinumab approximate 6 mg per kilogram of body weight (with 260 mg prescribed for patients weighing ≤55 kg, 390 mg for patients weighing >55 kg and ≤85 kg, and 520 mg for patients weighing >85 kg).
‡ Total scores on the Mayo scale range from 0 to 12, with higher scores indicating more severe disease.
§ Data for C-reactive protein concentrations were available for 951 patients: 316 receiving placebo, 315 receiving 130 mg of ustekinumab, and 320 receiving 6 mg of ustekinumab per kilogram.
¶ Data for fecal calprotectin concentrations were available for 855 patients: 289 receiving placebo, 296 receiving 130 mg of ustekinumab, and 300 receiving 6 mg of ustekinumab per kilogram.
‖ Corticosteroids included budesonide and beclomethasone dipropionate. Shown is the prednisone-equivalent dose. Data on corticosteroid dose were available for 418 patients: 133 receiving placebo, 143 receiving 130 mg of ustekinumab, and 142 receiving 6 mg of ustekinumab per kilogram.
** Immunomodulators included azathioprine, mercaptopurine, and methotrexate.
†† Patients may have reported more than one reason for treatment failure with a TNF antagonist.

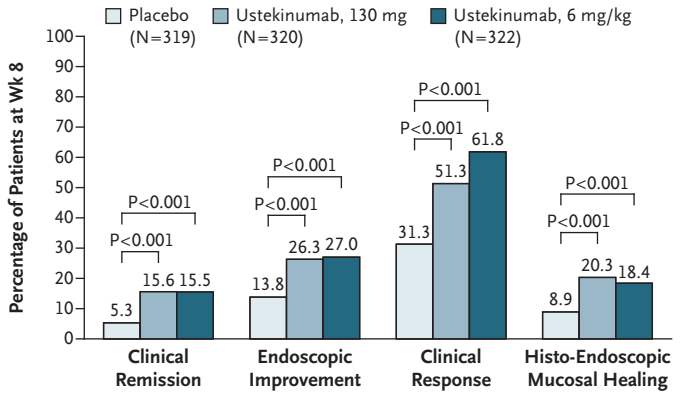

Figure 2. Patients with Clinical Remission, Endoscopic Improvement, Clinical Response, or Histo-Endoscopic Mucosal Healing at Week 8 in the Induction Trial.

Weight-range–based doses of ustekinumab approximating 6 mg per kilogram were as follows: 260 mg (weight, ≤55 kg), 390 mg (weight, >55 kg and ≤85 kg), and 520 mg (weight, >85 kg). Patients who had a prohibited change in concomitant medication for ulcerative colitis or who had undergone an ostomy or colectomy before week 8 were considered not to have met the end point. Clinical remission was defined as a total score of 2 or less on the Mayo scale (range, 0 to 12, with higher scores indicating more severe disease) and no subscore greater than 1 (range, 0 to 3) on any of the four Mayo scale components. Endoscopic improvement was defined as a Mayo endoscopic subscore of 0 or 1. Clinical response was defined as a decrease in the total Mayo score of at least 30% and of at least 3 points from baseline, with an accompanying decrease of at least 1 point on the Mayo rectal bleeding subscore or a rectal bleeding subscore of 0 or 1. Histo-endoscopic mucosal healing required both histologic improvement (defined as neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue) and endoscopic improvement. Patients with missing data on all four Mayo subscores at week 8 were considered not to be in clinical remission or not to have a clinical response at week 8. Patients who had a missing Mayo endoscopic subscore at week 8 were considered not to have endoscopic improvement. Patients who were missing any Geboes score components pertaining to histologic improvement at week 8 were considered not to have histologic improvement. The analyses for histologic improvement and histo-endoscopic mucosal healing excluded data from patients whose status with respect to these end points could not be determined at week 8 owing to a biopsy sample that could not be evaluated (i.e., a biopsy sample was obtained but could not be assessed owing to technical issues, such as errors during sample collection, preparation, or both).

18.9% (61 of 322) in the respective ustekinumab groups and 6.3% (20 of 319) in the placebo group (P<0.001 for both comparisons with placebo) (Fig. S2 in the Supplementary Appendix).

The efficacy observed in prespecified subgroups for both ustekinumab groups was consistent with that in the overall trial population. Results of analyses according to treatments received before the trial suggest benefits of ustekinumab across subgroups. For both definitions of clinical remission, the results of sensitivity analyses were consistent. (For details, see Fig. S3A through S3H and Tables S4 and S5 in the Supplementary Appendix.)

The percentages of patients who met major secondary end points or had histo-endoscopic mucosal healing were significantly higher in both ustekinumab groups than in the placebo group (Fig. 2). Through week 8, the median changes from baseline in the IBDQ score were significantly greater in both ustekinumab groups than in the placebo group. The percentage of patients who had histologic improvement at week 8 was higher in both ustekinumab groups than in the placebo group. Improvements from baseline that were observed in the partial Mayo scores and in concentrations of fecal calprotectin and lactoferrin and serum CRP support the clinical outcomes. (See Tables S6 through S11 in the Supplementary Appendix.)

Among patients who did not have a clinical response to intravenous ustekinumab and who received 90 mg of subcutaneous ustekinumab at week 8, a total of 59.7% (139 of 233) had a delayed clinical response at week 16. Among all patients in the induction trial who were initially assigned to ustekinumab, 77.6% (498 of 642) had a clinical response within 16 weeks. In addition, among patients who did not have a clinical response to intravenous placebo and who then received intravenous ustekinumab at a dose of 6 mg per kilogram, 67.9% (125 of 184) had a clinical response at week 16.

MAINTENANCE THERAPY

Among patients who had a clinical response to induction treatment with ustekinumab, the percentages of patients who had clinical remission at week 44 (52 weeks after intravenous induction) were significantly higher in the groups that received 90 mg of ustekinumab every 12 weeks (38.4% [66 of 172 patients]) or every 8 weeks (43.8% [77 of 176]) than in the placebo group (24.0% [42 of 175]) (P=0.002 and P<0.001, respectively, for the comparison with placebo) (Fig. 3). The results were similar for the alternative definition of clinical remission: 39.5% (68 of 172 patients) and 42.6% (75 of 176) in the respective ustekinumab groups and 24.6% (43 of 175) in the placebo group (P=0.002 and P<0.001, respectively, for the comparison with placebo). Efficacy among prespecified subgroups was con-

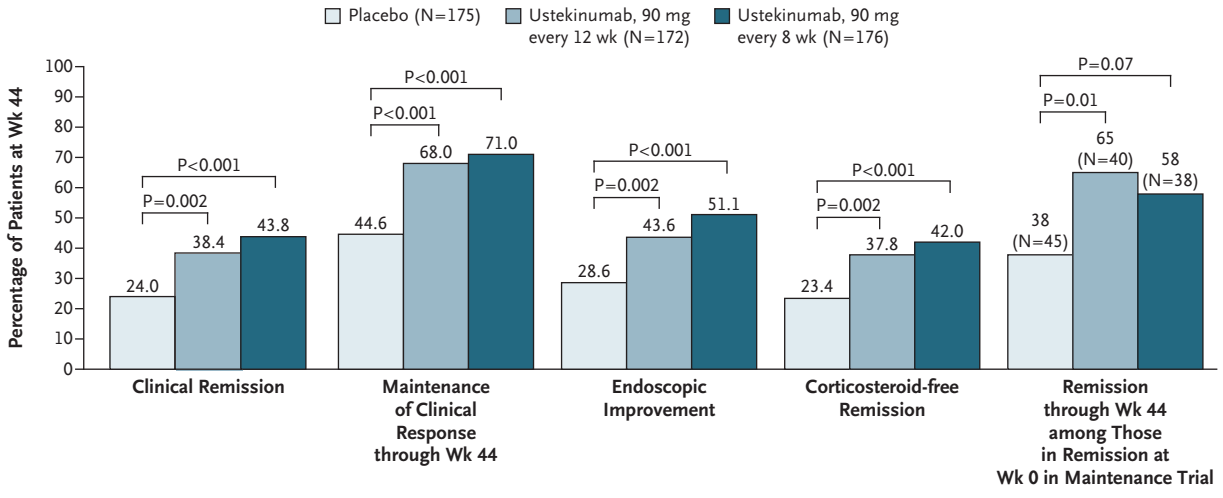

Figure 3. Patients' Responses to Maintenance Therapy.

Patients who had a clinical response to intravenous ustekinumab during the induction trial were randomly assigned to receive subcutaneous injections of placebo or one of two doses of ustekinumab on entry to the maintenance trial. Patients who had a prohibited change in medication for ulcerative colitis, had undergone an ostomy or colectomy, or had used a rescue medication after a clinical flare or who had discontinued ustekinumab or placebo owing to lack of therapeutic effect or owing to an adverse event of worsening of ulcerative colitis before the week 44 visit were considered not to have met the dichotomous end points or had their value at baseline in the induction trial carried forward from the time of the event onward for continuous end points. Patients with missing data on all four Mayo subscores at week 44 were considered not to have clinical remission, clinical response, or corticosteroid-free clinical remission at week 44. Patients who did not have clinical remission or clinical response at any time before week 44 were considered not to be in clinical remission among patients in clinical remission at week 0 in the maintenance trial or not to have maintenance of clinical response through week 44. Patients who had a missing value for corticosteroid use at week 44 had their last value carried forward. Patients who had a missing Mayo endoscopic subscore at week 44 were considered not to have endoscopic improvement.

sistent with that in the overall randomized population. For both definitions of clinical remission, the results of sensitivity analyses were consistent. (See Figs. S4 and S5A through S5L and Table S5 in the Supplementary Appendix.)

The percentages of patients with maintenance of clinical response through week 44, endoscopic improvement at week 44, or corticosteroid-free clinical remission (with either definition of clinical remission) at week 44 were significantly higher in both ustekinumab groups than in the placebo group (Fig. 3). Among patients in clinical remission at baseline in the maintenance trial, the percentage who had maintenance of clinical remission through week 44 was not significantly higher among those receiving 90 mg of ustekinumab every 8 weeks than among those receiving placebo; when the alternative definition of clinical remission was used, the percentage was significantly higher in both ustekinumab groups than in the placebo group. Results of analyses according to treatments received before the trial suggest benefits of ustekinumab across subgroups for all end points except maintenance of clinical remission. (See Fig. S4 and Table S4 in the Supplementary Appendix.)

Among patients receiving corticosteroids at baseline, the percentages of those who discontinued corticosteroid use at least 90 days before week 44 were higher in the groups that received 90 mg of ustekinumab every 12 weeks (67% [55 of 82 patients]) or every 8 weeks (77% [71 of 92]) than in the placebo group (44% [40 of 91]); 97.2% of patients in clinical remission at week 44 (both definitions) (139 of 143) were corticosteroid-free at week 44. Corticosteroids were discontinued sooner by patients receiving ustekinumab (median, 7 weeks in each group) than by those receiving placebo (median, 16 weeks) (Table S12 in the Supplementary Appendix).

The percentage of patients who had histologic improvement was higher in both ustekinumab groups than in the placebo group, as was the percentage of patients who had histo-endoscopic mucosal healing. Through week 44, median IBDQ scores were maintained or improved with

Table 2. Safety Results through the Final Safety Visit in the Induction Trial and through Week 44 in the Maintenance Trial.*

Variable	Induction†					Maintenance				
	Randomly Assigned Patients			Patients with No Response to IV Infusion		Randomized Population			Nonrandomized Population	
						Patients with Response to IV UST			Patients with Response to IV Placebo	Patients with Delayed Response to UST
	Placebo (N=319)	UST, 130 mg (N=321)	UST, 6 mg/kg‡ (N=320)	IV Placebo→ IV UST, 6 mg/kg‡§ (N=184)	IV UST→ SC UST, 90 mg§ (N=233)	Placebo¶ (N=175)	UST, 90 mg/12 wk (N=172)	UST, 90 mg/8 wk (N=176)	SC Placebo‖ (N=103)	SC UST, 90 mg/8 wk (N=157)
Average duration of follow-up — wk	8.7	8.6	8.6	10.2	11.5	42.3	41.8	42.2	40.8	41.8
Average no. of administrations	1.0	1.0	1.0	1.0	1.0	7.1	7.3	7.4	6.9	7.2
Death — no. (%)	0	0	1 (0.3)	0	0	0	0	0	0	1 (0.6)
Any adverse event — no. (%)	153 (48.0)	133 (41.4)	162 (50.6)	55 (29.9)	64 (27.5)	138 (78.9)	119 (69.2)	136 (77.3)	79 (76.7)	117 (74.5)
Common adverse events — no. (%)**										
Nasopharyngitis	1 (0.3)	1 (0.3)	2 (0.6)	0	0	28 (16.0)	31 (18.0)	26 (14.8)	13 (12.6)	19 (12.1)
Ulcerative colitis	18 (5.6)	9 (2.8)	8 (2.5)	12 (6.5)	20 (8.6)	50 (28.6)	19 (11.0)	18 (10.2)	28 (27.2)	26 (16.6)
Headache	14 (4.4)	22 (6.9)	13 (4.1)	2 (1.1)	2 (0.9)	7 (4.0)	11 (6.4)	18 (10.2)	4 (3.9)	9 (5.7)
Arthralgia	2 (0.6)	3 (0.9)	6 (1.9)	1 (0.5)	2 (0.9)	15 (8.6)	15 (8.7)	8 (4.5)	9 (8.7)	13 (8.3)
Upper respiratory tract infection	4 (1.3)	6 (1.9)	4 (1.2)	2 (1.1)	5 (2.1)	8 (4.6)	5 (2.9)	16 (9.1)	4 (3.9)	7 (4.5)
Anemia	11 (3.4)	7 (2.2)	8 (2.5)	4 (2.2)	1 (0.4)	12 (6.9)	9 (5.2)	7 (4.0)	9 (8.7)	9 (5.7)
Influenza	0	2 (0.6)	1 (0.3)	0	2 (0.9)	8 (4.6)	6 (3.5)	10 (5.7)	7 (6.8)	7 (4.5)
Pyrexia	6 (1.9)	4 (1.2)	6 (1.9)	1 (0.5)	0	7 (4.0)	1 (0.6)	9 (5.1)	5 (4.9)	5 (3.2)
Serious adverse events — no. (%)	22 (6.9)	12 (3.7)	11 (3.4)	7 (3.8)	12 (5.2)	17 (9.7)	13 (7.6)	15 (8.5)	8 (7.8)	11 (7.0)
Infections — no. (%)††										
Any	49 (15.4)	51 (15.9)	51 (15.9)	22 (12.0)	14 (6.0)	81 (46.3)	58 (33.7)	86 (48.9)	44 (42.7)	58 (36.9)
Serious	5 (1.6)	2 (0.6)	1 (0.3)	3 (1.6)	2 (0.9)	4 (2.3)	6 (3.5)	3 (1.7)	2 (1.9)	2 (1.3)
Adverse events leading to discontinuation of ustekinumab or placebo — no. (%)	NA‡‡	NA	NA			20 (11.4)	9 (5.2)	5 (2.8)	13 (12.6)	12 (7.6)

Cancer, excluding NMSC — no. (%)	0	0	0	0	2 (0.9)	0	1 (0.6)	1 (0.6)	1 (1.0)	0
Adverse events associated with an infusion or injection-site reactions — no. (%)§§	6 (1.9)	7 (2.2)	3 (0.9)	5 (2.7)	6 (2.6)	4 (2.3)	1 (0.6)	5 (2.8)	0	4 (2.5)

* IV denotes intravenous, NA not applicable, NMSC nonmelanoma skin cancer, SC subcutaneous, and UST ustekinumab.
† Included are data through the final safety follow-up visit 20 weeks after the final dose of ustekinumab or placebo for patients who did not enter the maintenance trial.
‡ Weight-range–based doses of ustekinumab approximate 6 mg per kilogram (with 260 mg prescribed for patients weighing ≤55 kg, 390 mg for patients weighing >55 kg and ≤85 kg, and 520 mg for patients weighing >85 kg).
§ Included are data from week 8 onward.
¶ Shown are patients who had a clinical response to intravenous ustekinumab during the induction trial and were randomly assigned to receive placebo subcutaneously on entry to the maintenance trial.
‖ Shown are patients who had a clinical response to intravenous placebo during the induction trial and received placebo subcutaneously on entry to the maintenance trial.
** The listed adverse events were reported by at least 5% of the patients in any group during the maintenance trial.
†† Infections were assessed by the investigator.
‡‡ In the induction trial, ustekinumab or placebo was administered as a single intravenous infusion at week 0; therefore, patients could not be discontinued from further administration of ustekinumab or placebo.
§§ Adverse event associated with infusions refer to events that occurred within 1 hour after an infusion during induction.

ustekinumab every 12 weeks and every 8 weeks but worsened with placebo. Improvements in partial Mayo scores and concentrations of CRP, lactoferrin, and calprotectin that were observed at baseline in the maintenance trial were maintained in both ustekinumab groups, whereas results for these measures worsened in the placebo group. (See Tables S13 through S19 in the Supplementary Appendix.)

Among patients who had a delayed response to ustekinumab and received 90 mg every 8 weeks, 62.4% (98 of 157) had maintenance of clinical response through week 44. The percentages of patients who met this end point or other efficacy measures at week 44 were lower than those among patients who had a response to intravenous ustekinumab and were randomly assigned to 90 mg of subcutaneous ustekinumab every 8 weeks during maintenance (see the Supplementary Appendix).

The percentage of patients who had an ulcerative colitis–related hospitalization was lower in both ustekinumab groups than in the placebo group through week 8 in the induction trial and remained lower through week 44 in the maintenance trial. (Details on ulcerative colitis–related hospitalizations and surgical procedures are provided in Table S20 in the Supplementary Appendix.)

SAFETY

Through the final safety visit in the induction trial, the percentages of patients who reported at least one adverse event in the groups receiving 130 mg of ustekinumab, 6 mg of ustekinumab per kilogram, and placebo were 41.4%, 50.6%, and 48.0%, respectively. The percentages of patients in these groups with at least one serious adverse event were 3.7%, 3.4%, and 6.9%, respectively. Through week 44 in the maintenance trial, the percentages of randomly assigned patients who reported at least one adverse event in the groups receiving 90 mg of ustekinumab every 12 weeks, 90 mg of ustekinumab every 8 weeks, and placebo were 69.2%, 77.3%, and 78.9%, respectively. The percentages of patients with at least one serious adverse event were 7.6%, 8.5%, and 9.7%, respectively; the percentages of patients with a serious infection were 3.5%, 1.7%, and 2.3%, respectively. Findings in the nonrandomized population were consistent with those in the randomized population (Table 2,

and Tables S21 and S22 in the Supplementary Appendix).

Adverse events of interest that occurred among patients receiving ustekinumab or placebo through 52 weeks of treatment are summarized below and in the Supplementary Appendix. Two deaths before week 44 (sudden death attributed to hemorrhage from esophageal varices and death from acute respiratory distress syndrome [ARDS]) and one death after week 44 (a patient with failure to thrive had a cardiac arrest) occurred among patients receiving ustekinumab. Cancer occurred in 7 of 825 patients who received ustekinumab (1 each of prostate, colon, renal papillary, and rectal cancer and 3 nonmelanoma skin cancers) and 1 of 319 patients who received placebo (testicular cancer). Four patients who received ustekinumab presented with potential opportunistic infections: cytomegalovirus colitis (in 2 patients during maintenance), legionella pneumonia (in 1 patient during induction), and concurrent ophthalmic and oral herpes simplex infections (in 1 patient during maintenance). Three major cardiovascular events occurred: a nonfatal cardiac arrest (in a patient who received ustekinumab during induction and placebo during maintenance), an acute myocardial infarction (in a patient who received ustekinumab and died of ARDS complications), and a nonfatal stroke (in a patient who received placebo during induction).

PHARMACOKINETICS AND IMMUNOGENICITY

Positive associations were observed between serum ustekinumab concentrations at week 8 and clinical response at week 8 and between serum ustekinumab concentrations at week 24 and clinical remission at week 44. Among 505 patients who received ustekinumab during both induction and maintenance, antidrug antibodies developed in 4.6% (23 of 505). Among the 23 patients, 22% (5 of 23) had neutralizing antibodies, and 39% (9 of 23) had transient antibodies. (See Figs. S6 and S7 in the Supplementary Appendix.)

DISCUSSION

In this phase 3 trial of an antagonist of interleukin-12 and interleukin-23 involving patients with moderate-to-severe ulcerative colitis, ustekinumab was more effective than placebo in achieving induction of clinical remission at 8 weeks. This effect was observed in patients with or without previous treatment failure with biologic agents, including those who had not received biologics. Among patients who had a response to induction therapy with intravenous ustekinumab and who underwent a second randomization, those assigned to either regimen of subcutaneous ustekinumab were more likely to be in clinical remission at 44 weeks than those assigned to placebo. For all prespecified major secondary end points in the induction and maintenance trials, the percentages of patients were significantly higher in the ustekinumab groups than in the placebo group, except for the major secondary end point of maintenance of clinical remission through week 44 among patients in clinical remission at baseline. For that end point, the percentage of patients in the group receiving ustekinumab every 12 weeks was higher than in the placebo group for both remission definitions, but the percentage in the group receiving ustekinumab every 8 weeks was higher than in the placebo group only for the alternative definition of clinical remission that was used to support the FDA submission.

Because this program had a randomized-withdrawal design, the percentages of patients in clinical remission reported at week 44 should be interpreted in the context of the trial design. Only those patients who had a response to induction therapy with intravenous ustekinumab underwent a second randomization in the maintenance trial; therefore, the proportion of patients who had clinical remission with ustekinumab treatment would be different if all patients entered the maintenance trial regardless of the clinical outcome in the induction trial.

The therapeutic goal in patients with ulcerative colitis is to induce and maintain long-term remission, because the disease often has a relapsing and remitting course.[16,17] Endoscopic improvement in mucosal appearance is associated with better subsequent long-term outcomes in patients with ulcerative colitis.[18,19] Histologic improvement has also been associated with better long-term outcomes, including reductions in corticosteroid use and relapse.[20,21] The combination of endoscopic and histologic improvement has been suggested by the research community and regulatory bodies[21-26] as the most complete method of assessing mucosal healing.[17]

In this trial, we combined macroscopic and

microscopic evidence of mucosal improvement to define histo-endoscopic mucosal healing. Because there was no accepted definition of histologic improvement, criteria were developed with the use of data from completed prospective clinical trials involving patients with ulcerative colitis.[15] Histo-endoscopic mucosal healing, an end point that was controlled for multiple comparisons in the induction trial, was induced by both intravenous doses of ustekinumab and maintained by both subcutaneous doses. The association of this end point with long-term clinical outcomes and prevention of colon cancer requires further exploration.

In analyses of other end points, improvements in partial Mayo scores and reductions in serum and fecal concentrations of inflammatory biomarkers that were observed with induction were sustained through maintenance. Although our findings suggest that ustekinumab was effective in patients with or without previous treatment failure with biologics for both induction and maintenance therapy, the percentages of patients in whom each end point was achieved were lower across groups with previous treatment failure with biologics.

Some possible differences in dose were observed for several end points. At week 8, a higher percentage of patients who had a clinical response, larger decreases in the partial Mayo score, and greater reductions in fecal lactoferrin and calprotectin concentrations were observed with approximately 6 mg of ustekinumab per kilogram than with 130 mg of ustekinumab. At week 44, for the more objective and stringent end points (e.g., endoscopic improvement, histo-endoscopic mucosal healing, corticosteroid-free remission, and elimination of corticosteroids ≥90 days before week 44 among patients receiving corticosteroids at baseline in the maintenance trial), greater clinical benefit was observed with ustekinumab every 8 weeks than with ustekinumab every 12 weeks.

Cancers developed in seven patients who received ustekinumab (including three cases of nonmelanoma skin cancer) and in one patient who received placebo. Potential opportunistic infections developed in four patients who received ustekinumab. There were no cases of anaphylaxis or serious hypersensitivity reactions in patients who received ustekinumab.

In conclusion, in this trial involving patients with moderate-to-severe ulcerative colitis despite current or previous treatment with conventional or biologic therapy, ustekinumab was more effective than placebo for inducing and maintaining remission.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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