

## ORIGINAL ARTICLE

# Vedolizumab versus Adalimumab for Moderate-to-Severe Ulcerative Colitis

Bruce E. Sands, M.D., Laurent Peyrin-Biroulet, M.D., Ph.D., Edward V. Loftus, Jr., M.D., Silvio Danese, M.D., Jean-Frédéric Colombel, M.D., Murat Törüner, M.D., Laimas Jonaitis, M.D., Ph.D., Brihad Abhyankar, F.R.C.S., Jingjing Chen, Ph.D., Raquel Rogers, M.D., Richard A. Lirio, M.D., Jeffrey D. Bornstein, M.D., and Stefan Schreiber, M.D., Ph.D., for the VARSITY Study Group\*

## ABSTRACT

**BACKGROUND**

Biologic therapies are widely used in patients with ulcerative colitis. Head-to-head trials of these therapies in patients with inflammatory bowel disease are lacking.

**METHODS**

In a phase 3b, double-blind, double-dummy, randomized, active-controlled trial conducted at 245 centers in 34 countries, we compared vedolizumab with adalimumab in adults with moderately to severely active ulcerative colitis to determine whether vedolizumab was superior. Previous exposure to a tumor necrosis factor inhibitor other than adalimumab was allowed in up to 25% of patients. The patients were assigned to receive intravenous infusions of 300 mg of vedolizumab on day 1 and at weeks 2, 6, 14, 22, 30, 38, and 46 (plus injections of placebo) or subcutaneous injections of 40 mg of adalimumab, with a total dose of 160 mg at week 1, 80 mg at week 2, and 40 mg every 2 weeks thereafter until week 50 (plus infusions of placebo). Dose escalation was not permitted in either group. The primary outcome was clinical remission at week 52 (defined as a total score of  $\leq 2$  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). To control for type I error, efficacy outcomes were analyzed with the use of a hierarchical testing procedure, with the variables in the following order: clinical remission, endoscopic improvement (subscore of 0 to 1 on the Mayo endoscopic component), and corticosteroid-free remission at week 52.

**RESULTS**

A total of 769 patients underwent randomization and received at least one dose of vedolizumab (383 patients) or adalimumab (386 patients). At week 52, clinical remission was observed in a higher percentage of patients in the vedolizumab group than in the adalimumab group (31.3% vs. 22.5%; difference, 8.8 percentage points; 95% confidence interval [CI], 2.5 to 15.0;  $P=0.006$ ), as was endoscopic improvement (39.7% vs. 27.7%; difference, 11.9 percentage points; 95% CI, 5.3 to 18.5;  $P<0.001$ ). Corticosteroid-free clinical remission occurred in 12.6% of the patients in the vedolizumab group and in 21.8% in the adalimumab group (difference,  $-9.3$  percentage points; 95% CI,  $-18.9$  to 0.4). Exposure-adjusted incidence rates of infection were 23.4 and 34.6 events per 100 patient-years in the vedolizumab group and adalimumab group, respectively, and the corresponding rates for serious infection were 1.6 and 2.2 events per 100 patient-years.

**CONCLUSIONS**

In this trial involving patients with moderately to severely active ulcerative colitis, vedolizumab was superior to adalimumab with respect to achievement of clinical remission and endoscopic improvement, but not corticosteroid-free clinical remission. (Funded by Takeda; VARSITY ClinicalTrials.gov number, NCT02497469; EudraCT number, 2015-000939-33.)

From the Icahn School of Medicine at Mount Sinai, New York (B.E.S., J.-F.C.); Nancy University Hospital, Nancy, France (L.P.-B.); Mayo Clinic College of Medicine, Rochester, MN (E.V.L.); Humanitas University, Milan (S.D.); Ankara University School of Medicine, Ankara, Turkey (M.T.); Lithuanian University of Health Sciences, Kaunas, Lithuania (L.J.); Takeda Development Centre Europe, London (B.A.); Takeda Development Center Americas, Cambridge, MA (J.C., R.R., R.A.L., J.D.B.); and the University Hospital Schleswig-Holstein, Kiel, Germany (S.S.). Address reprint requests to Dr. Sands at the Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Pl., Box 1069, New York, NY 10029, or at bruce.sands@mssm.edu; or to Dr. Schreiber at the Department of Medicine I, University Hospital Schleswig-Holstein, Rosalind-Franklin-Str. 12, Haus 5, 24105 Kiel, Germany, or at s.schreiber@mucosa.de.

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

Drs. Sands and Schreiber contributed equally to this article.

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ULCERATIVE COLITIS IS A CHRONIC inflammatory disorder of the large bowel characterized by abdominal pain, bloody diarrhea, and fecal urgency.<sup>1</sup> Agents that are commonly used when conventional treatments (e.g., aminosalicylates, oral immunomodulators, and corticosteroids) fail include tofacitinib, a small-molecule Janus kinase inhibitor, and biologic agents, such as tumor necrosis factor (TNF) inhibitors (e.g., infliximab, adalimumab, and golimumab) and vedolizumab, an anti-integrin antibody.<sup>2,3</sup> These medications were shown to be effective in randomized, placebo-controlled trials, but whereas head-to-head trials that directly compare agents have been performed in patients with rheumatologic diseases, few such trials have been performed in patients with inflammatory bowel disease.<sup>4,5</sup>

Adalimumab, a humanized monoclonal antibody that binds and neutralizes TNF, is widely used to treat ulcerative colitis. The gut-selective, anti-integrin vedolizumab is a humanized monoclonal antibody that specifically binds to the leukocyte integrin  $\alpha_4\beta_7$ .<sup>6,7</sup> Here we report the results of the VARSITY trial, which directly compared the efficacy and safety of vedolizumab with those of adalimumab in patients with moderately to severely active ulcerative colitis.

## METHODS

### TRIAL DESIGN

The VARSITY trial, a phase 3b, randomized, double-blind, double-dummy, active-controlled superiority trial to detect treatment differences between vedolizumab and adalimumab, was conducted from July 2015 through January 2019 at 245 sites in 34 countries. (For details on the trial design, eligibility criteria, assessments, outcome measures, and statistical analyses, see the Supplementary Appendix, available with the full text of this article at NEJM.org.) The trial protocol, available at NEJM.org, was approved by an institutional review board or ethics committee at each trial site, and all the patients provided written informed consent.

### PATIENTS

Adults 18 to 85 years of age were eligible for inclusion in the trial if they had moderately to severely active ulcerative colitis, defined as a total

score of 6 to 12 on the Mayo scale<sup>8</sup> (total Mayo scores range from 0 to 12, with higher scores indicating more severe disease) and a subscore of at least 2 on the endoscopic component of the Mayo scale (subscores on each of the four components of the Mayo scale range from 0 to 3); colonic involvement of at least 15 cm; and had a confirmed diagnosis of ulcerative colitis at least 3 months before screening. Patients who had not previously used a TNF inhibitor and had no response or loss of response to conventional treatments were eligible. Patients who had discontinued treatment with a TNF inhibitor (except adalimumab) because of documented reasons other than safety were also eligible, with enrollment capped at 25%. All patients had not previously received vedolizumab.

### SCREENING ASSESSMENTS

Screening assessments included a physical examination, endoscopy (findings were read at a central location), the total Mayo score, blood and stool tests, tuberculosis screening, the score on the Inflammatory Bowel Disease Questionnaire (IBDQ; scores range from 32 to 224, with higher scores indicating a better quality of life),<sup>9</sup> and a questionnaire to identify possible symptoms of progressive multifocal leukoencephalopathy.

### RANDOMIZATION AND TREATMENTS

Patients who were assigned to the vedolizumab group received intravenous infusions of 300 mg of vedolizumab on day 1 and at weeks 2, 6, 14, 22, 30, 38, and 46 plus subcutaneous injections of placebo on day 1 (four injections), at week 2 (two injections), and every 2 weeks thereafter (single injections) until week 50. Patients who were assigned to the adalimumab group received multiple subcutaneous injections of 40 mg of adalimumab on days 1 and 2 (either four injections on day 1 or two injections per day for 2 days [total dose of 160 mg]), two injections of 40 mg at week 2 (total dose of 80 mg), and single injections of 40 mg every 2 weeks thereafter until week 50 plus intravenous infusions of placebo at day 1 and weeks 2, 6, 14, 22, 30, 38, and 46. Dose escalation was not permitted in either treatment group.

Randomization was performed at a central location with the use of computer-generated randomization schedules and was stratified ac-

ording to previous use of a TNF inhibitor (yes or no) and concomitant use of an oral corticosteroid (yes or no). Among the patients who were receiving an oral corticosteroid at baseline, the dose must have been stable ( $\leq 30$  mg per day of prednisone or equivalent) for at least 2 weeks before the first dose of a trial drug. The corticosteroid dose remained unaltered through week 6 of the trial, and after week 6, the dose was tapered intermittently if the patient had a response. Patients who had a loss of response during the tapering period were permitted to receive the baseline corticosteroid dose one time only before tapering was restarted. In accordance with the protocol, patients in whom the corticosteroid dose could not be tapered were withdrawn from the trial and were considered to have treatment failures with respect to each of the outcomes. Patients who were not receiving corticosteroids at baseline but who initiated corticosteroid treatment during the trial were withdrawn because of lack of efficacy. Patients who were receiving an aminosalicylate or an immunomodulator at baseline maintained stable doses throughout the trial.

#### FOLLOW-UP ASSESSMENTS

Regular trial visits occurred through week 52, with a final safety follow-up visit at week 68. Adverse events (classified according to the *Medical Dictionary for Regulatory Activities*, version 21.0), results of laboratory tests and safety assessments, and concomitant medications were recorded throughout the trial. A partial score on the Mayo scale,<sup>10</sup> which consisted of the combined subscores (range, 0 to 9) on three of the four components of the Mayo scale (stool frequency, rectal bleeding, and physician's global assessment, with the exclusion of endoscopy), was calculated at weeks 2, 4, 6, 22, 30, 38, and 46. The total Mayo score was calculated at weeks 14 and 52, when endoscopy was performed. Measurements of the fecal calprotectin level were performed at weeks 14, 30, and 52. IBDQ assessments were performed at weeks 30 and 52.

#### OUTCOME MEASURES

The primary outcome was clinical remission at week 52 (defined as a total score of  $\leq 2$  on the Mayo scale and no subscore  $>1$  on any of the four components). Secondary outcomes were endoscopic improvement (defined as a subscore

of 0 or 1 on the Mayo endoscopic component [originally termed "mucosal healing" in the protocol]) and corticosteroid-free clinical remission at week 52, which was assessed only in patients who were receiving corticosteroids at baseline.

There were 42 prespecified outcomes (26 were prespecified in the trial protocol and another 16 in the statistical analysis plan [available with the protocol]). All outcomes other than the primary and two secondary outcomes were referred to as "additional end points" in the protocol and statistical analysis plan and are considered to be exploratory outcomes. These prespecified exploratory outcomes included durable clinical remission (defined as clinical remission at both week 14 and week 52); improvement in the subscores on the patient-reported components of the Mayo scale (stool frequency and rectal bleeding); improvement in quality of life (defined as an increase of  $\geq 16$  points in IBDQ score); histologic remission (defined as a Geboes score  $<2.0$  [on a scale from 0 to 5.4, with higher scores indicating more severe disease activity] and a Robarts Histopathology Index score  $<3$  [on a scale from 0 to 33, with higher scores indicating more severe disease activity])<sup>11,12</sup>; minimal histologic disease (defined as a Geboes score  $<3.2$  and a Robarts Histopathology Index score  $<5$ ); clinical response (defined as a reduction in the partial Mayo score [stool frequency, rectal bleeding, and physician's global assessment] of  $\geq 2$  points and of  $\geq 25\%$  from baseline, with an accompanying decrease in rectal bleeding subscore of  $\geq 1$  point or absolute rectal bleeding subscore of  $\leq 1$  point); and safety (as assessed by the incidence of adverse events).

#### TRIAL OVERSIGHT

The trial sponsor (Takeda) designed the trial in conjunction with the principal academic investigators and provided the trial drugs and placebo. A clinical research organization (IQVIA), funded by the sponsor, managed all the collection of the data, maintained the trial database in a blinded manner, and performed the data analyses. The trial investigators, the participating institutions, the clinical research organization, and the sponsor agreed to maintain data confidentiality. The initial draft of the manuscript was written by one of the authors employed by the sponsor in collaboration with the first and last authors. A medical

writer, funded by the sponsor, assisted with the preparation of subsequent drafts. All the authors interpreted the data, contributed to subsequent drafts, and made the decision to submit the manuscript for publication. The academic authors had access to the data and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

#### STATISTICAL ANALYSIS

Efficacy was analyzed according to treatment randomization group in the full-analysis set, which included all patients who underwent randomization and received at least one dose of a trial drug. Adverse events were analyzed according to the treatment actually received in the safety population, which included all the patients in the full-analysis set. Missing values for binary outcomes were imputed as nonresponses, and missing values for continuous outcomes were imputed with the use of the last-observation-carried-forward approach. We performed a prespecified sensitivity analysis of the primary efficacy outcome that used a hybrid imputation approach to assess the effect of discontinuation under different missing data mechanisms. First, under the assumption that data were not missing at random, missing data for patients who discontinued vedolizumab or adalimumab because of an adverse event or lack of efficacy were imputed as nonresponses. Second, under the assumption that data were missing at random, data that were missing for other reasons were imputed with the use of multiple imputation. This sensitivity analysis was repeated post hoc for the two secondary efficacy outcomes.

In the primary efficacy analysis, we compared the treatment groups with respect to the percentages of patients who had clinical remission at week 52 using the conventional Cochran–Mantel–Haenszel chi-square test, with adjustment for the randomization stratification factors. A hierarchical closed-testing procedure was used to control the inflation of the type I error rate due to multiple efficacy outcomes. Efficacy outcomes were tested in the following order: clinical remission at week 52, endoscopic improvement at week 52, and corticosteroid-free clinical remission at week 52 (two-tailed  $P < 0.05$  was required to proceed to the next test).

In a post hoc analysis, we assessed efficacy using the weighted statistical method described

by Cui et al.<sup>13</sup> to provide strong control of the familywise type I error rate in the presence of interim sample-size reestimation. Efficacy was also assessed in prespecified subgroup analyses that were performed on the basis of disease characteristics and previous use of a TNF inhibitor (yes or no). The exposure-adjusted incidence rate (per 100 patient-years) was defined as the number of patients who had the adverse event divided by the total exposure time among the patients. The extent of exposure for each patient was calculated as the duration between the first and last dose of a trial drug plus approximately five times the half-life of the drug.

We estimated that a sample size of 329 patients per treatment group would provide the trial with 86% power to detect a significant difference in clinical remission at week 52 (two-tailed chi-square test at  $P < 0.05$ ), assuming that remission would occur in 28% of the patients in the vedolizumab group and in 18% in the adalimumab group. We also estimated that this sample size would provide the trial with 80% power to detect differences in endoscopic improvement at week 52 (two-tailed chi-square test at  $P < 0.05$ ), assuming that improvement would occur in 35% of the patients in the vedolizumab group and in 25% in the adalimumab group. The sample size was increased by 100 patients after we performed a prespecified adaptive sample-size reestimation using the promising zone design.<sup>14</sup>

## RESULTS

### PATIENT CHARACTERISTICS

A total of 1285 patients were screened for eligibility, and 771 were enrolled in the trial, of whom 769 underwent randomization and received at least one dose of vedolizumab (383 patients) or adalimumab (386 patients). The characteristics of the patients were generally similar between the treatment groups (Table 1). Discontinuation of treatment because of lack of efficacy occurred in 41 patients in the vedolizumab group and in 82 patients in the adalimumab group. (Also see Fig. S1 and Table S2 in the Supplementary Appendix.)

### EFFICACY

#### Clinical Remission

Clinical remission at week 52 (primary outcome) was observed in a higher percentage of patients

in the vedolizumab group than in the adalimumab group (31.3% [120 of 383] vs. 22.5% [87 of 386],  $P=0.006$ ) — a difference of 8.8 percentage points (95% confidence interval [CI], 2.5 to 15.0) after adjustment with the Cochran–Mantel–Haenszel test (Fig. 1A). A sensitivity analysis to evaluate the effect of withdrawals showed that clinical remission at week 52 occurred in 37.2% of the patients in the vedolizumab group and in 25.9% in the adalimumab group (adjusted difference, 11.3 percentage points; 95% CI, 4.6 to 18.0). (See Tables S3 and S4 in the Supplementary Appendix.)

Among the patients who had not previously used a TNF inhibitor, clinical remission at week 52 was observed in 34.2% in the vedolizumab group and in 24.3% in the adalimumab group; among the patients who had previous exposure to a TNF inhibitor other than adalimumab, the corresponding percentages were 20.3% and 16.0% (Fig. 1A). The treatment effects in other subgroups defined according to demographic and disease characteristics were generally consistent with those in the overall population (Fig. S2 in the Supplementary Appendix; Fig. S3 provides the percentages of patients who had clinical remission at week 52 among those who were receiving an oral corticosteroid or immunomodulator at baseline and among those who were not).

At week 14, clinical remission in the overall population was observed in 26.6% of the patients (102 of 383) in the vedolizumab group and in 21.2% (82 of 386) in the adalimumab group (difference, 5.3 percentage points; 95% CI,  $-0.7$  to 11.4) (Fig. S4 in the Supplementary Appendix). Durable clinical remission occurred in 18.3% of the patients (70 of 383) in the vedolizumab group and in 11.9% (46 of 386) in the adalimumab group (difference, 6.3 percentage points; 95% CI, 1.3 to 11.3).

#### Endoscopic Improvement

At week 52, endoscopic improvement (first secondary outcome) was observed in a higher percentage of patients in the vedolizumab group than in the adalimumab group (39.7% [152 of 383] vs. 27.7% [107 of 386],  $P<0.001$ ) — a difference of 11.9 percentage points (95% CI, 5.3 to 18.5) after adjustment with the Cochran–Mantel–Haenszel test (Fig. 1B). A sensitivity analysis to evaluate the effect of withdrawals showed that

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

Characteristic	Adalimumab (N=386)	Vedolizumab (N=385)
Age — yr	40.5±13.4	40.8±13.7
Male sex — no. (%)	216 (56.0)	234 (60.8)
White race — no. (%)†	341 (88.3)	345 (89.6)
Body weight — kg	73.4±18.4	72.7±17.0
Current smoker — no. (%)‡	23 (6.0)	19 (4.9)
Duration of ulcerative colitis — yr§	6.4±6.0	7.3±7.2
Total score on the Mayo scale¶	8.7±1.5	8.7±1.6
Fecal calprotectin level — µg/g	2771±4064	2929±5920
Previous treatment with a TNF inhibitor with documented reason for discontinuation — no. (%)	81 (21.0)	80 (20.8)
Previous therapy with a TNF inhibitor with documented failure — no. (%)	79 (20.5)	72 (18.7)
Inadequate response	40 (50.6)	36 (50.0)
Loss of response	29 (36.7)	24 (33.3)
Side effects	3 (3.8)	7 (9.7)
Missing data	7 (8.9)	5 (6.9)
Concomitant use of medications for ulcerative colitis — no. (%)		
Corticosteroids only**	140 (36.3)	139 (36.1)
Immunomodulators only††	100 (25.9)	101 (26.2)

\* Plus–minus values are means ±SD. TNF denotes tumor necrosis factor.

† Race was reported by the patient.

‡ Data on smoking status were missing for two patients in the vedolizumab group.

§ One patient in the adalimumab group had ulcerative colitis of unknown duration.

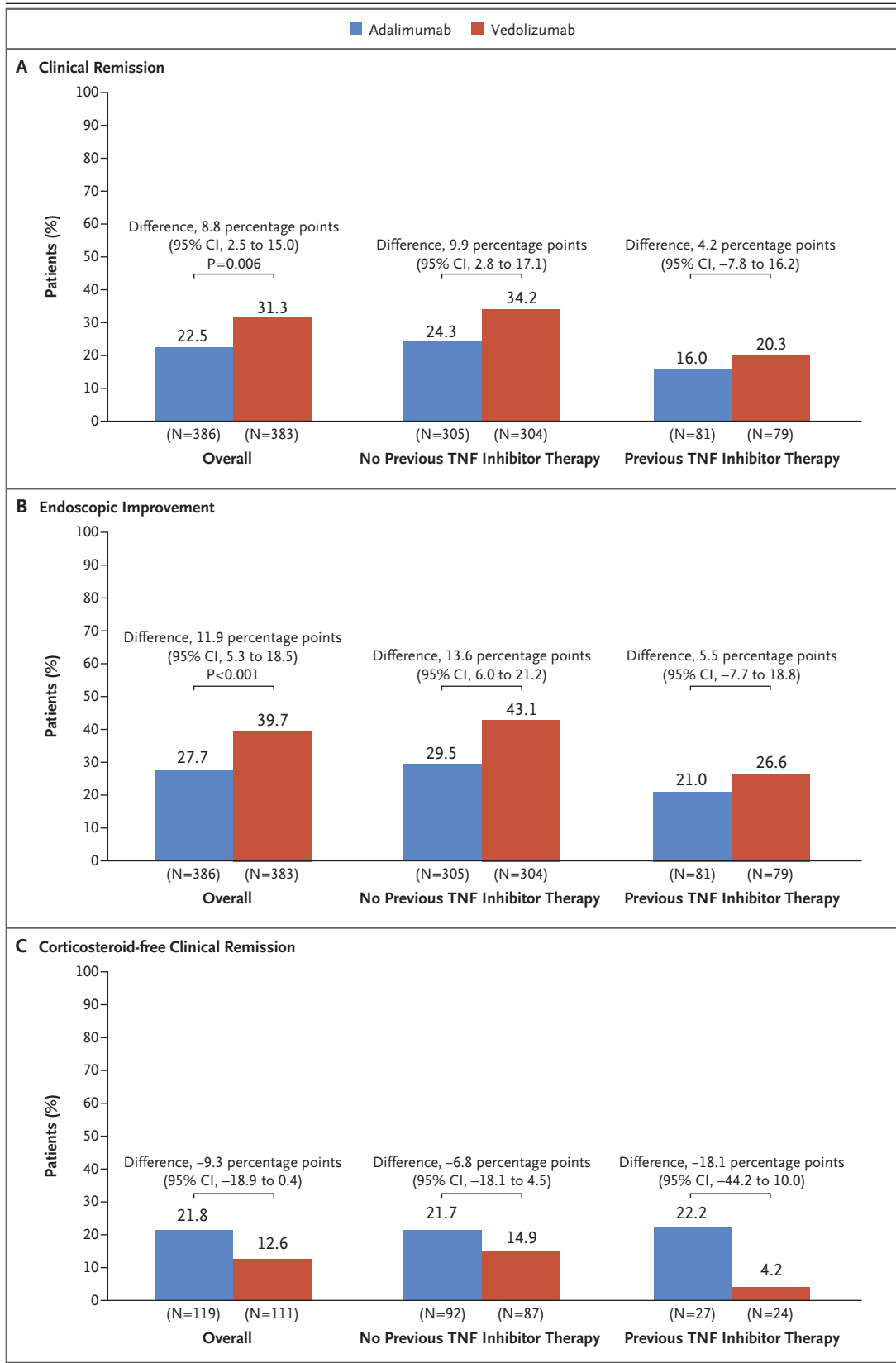
¶ The total score on the Mayo scale ranges from 0 to 12, with a higher score indicating more active disease. The four components of the Mayo scale are stool frequency, rectal bleeding, endoscopy (sigmoidoscopy), and physician's global assessment. Total Mayo scores were available for 384 patients in the adalimumab group and 380 patients in the vedolizumab group.

|| Data on the fecal calprotectin level were available for 332 patients in the adalimumab group and 341 patients in the vedolizumab group.

\*\* Concomitant use of corticosteroids was determined according to the report in the interactive Web response system.

†† Concomitant use of immunomodulators was determined according to the report in the electronic case-report form. The commonly used immunomodulators, in order from most to least used, were azathioprine, mercaptopurine, and methotrexate.

endoscopic improvement at week 52 occurred in 46.8% of the patients in the vedolizumab group and in 33.6% in the adalimumab group (adjusted difference, 13.2 percentage points; 95% CI, 6.0 to 20.3). Among the patients who had not previously used a TNF inhibitor, endoscopic improvement at week 52 occurred in 43.1% in the vedolizumab group and in 29.5% in the adalimumab group, and among the patients who had previ-



**Figure 1 (facing page). Efficacy Outcomes at Week 52 in the Full-Analysis Set and in Subgroups Defined According to Previous Treatment with a TNF Inhibitor.**

Shown are the percentages of patients who had clinical remission at week 52 (Panel A), endoscopic improvement at week 52 (Panel B), and corticosteroid-free remission at week 52 (Panel C). Efficacy was analyzed according to treatment randomization group in the full-analysis set, which included all patients who underwent randomization and received at least one dose of a trial drug. The subgroup of patients with no previous tumor necrosis factor (TNF) inhibitor therapy included those who had not previously used a TNF inhibitor and had no response or loss of response to conventional treatments; the subgroup of patients with previous TNF inhibitor therapy included those who had previous exposure to a TNF inhibitor other than adalimumab and had a documented reason for discontinuation of the therapy other than safety. The analysis of corticosteroid-free clinical remission was performed only in the subgroup of patients who were receiving corticosteroids at baseline (as determined from the electronic case report form). Point estimates, 95% confidence intervals, and P values were calculated with the use of the Cochran–Mantel–Haenszel chi-square test, with adjustment for the randomization stratification factors, or with the use of Fisher’s exact method if the numerator was five patients or fewer.

ous exposure to a TNF inhibitor other than adalimumab, the corresponding percentages were 26.6% and 21.0% (Fig. 1B). The treatment effects in the other subgroups defined according to demographic and disease characteristics were generally consistent with those in the overall population (Fig. S5 in the Supplementary Appendix). (See Fig. S3 and Tables S3 through S5 in the Supplementary Appendix.)

#### *Corticosteroid-free Clinical Remission*

At week 52, corticosteroid-free clinical remission (second secondary outcome) was observed in 12.6% of the patients (14 of 111) in the vedolizumab group and in 21.8% (26 of 119) in the adalimumab group (difference, –9.3 percentage points; 95% CI, –18.9 to 0.4) (Fig. 1C). A sensitivity analysis to evaluate the effect of withdrawals showed that corticosteroid-free clinical remission at week 52 occurred in 16.9% of the patients in the vedolizumab group and in 24.7% in the adalimumab group (adjusted difference, –7.8 percentage points; 95% CI, –18.8 to 3.1). The treatment effects in the other subgroups defined according to demographic and disease characteristics were generally consistent with

those in the overall population. (See Table S4 and Fig. S6 in the Supplementary Appendix.)

The median change in the oral corticosteroid dose from baseline to week 52 was –10.0 mg in the vedolizumab group and –7.0 mg in the adalimumab group. The median corticosteroid dose at week 52 was 0 mg (range, 0 to 40) in the vedolizumab group and 2.5 mg (range, 0 to 70) in the adalimumab group. (For absolute mean reductions in oral corticosteroid doses, see Fig. S7 in the Supplementary Appendix.)

#### *Patient-Reported Outcomes*

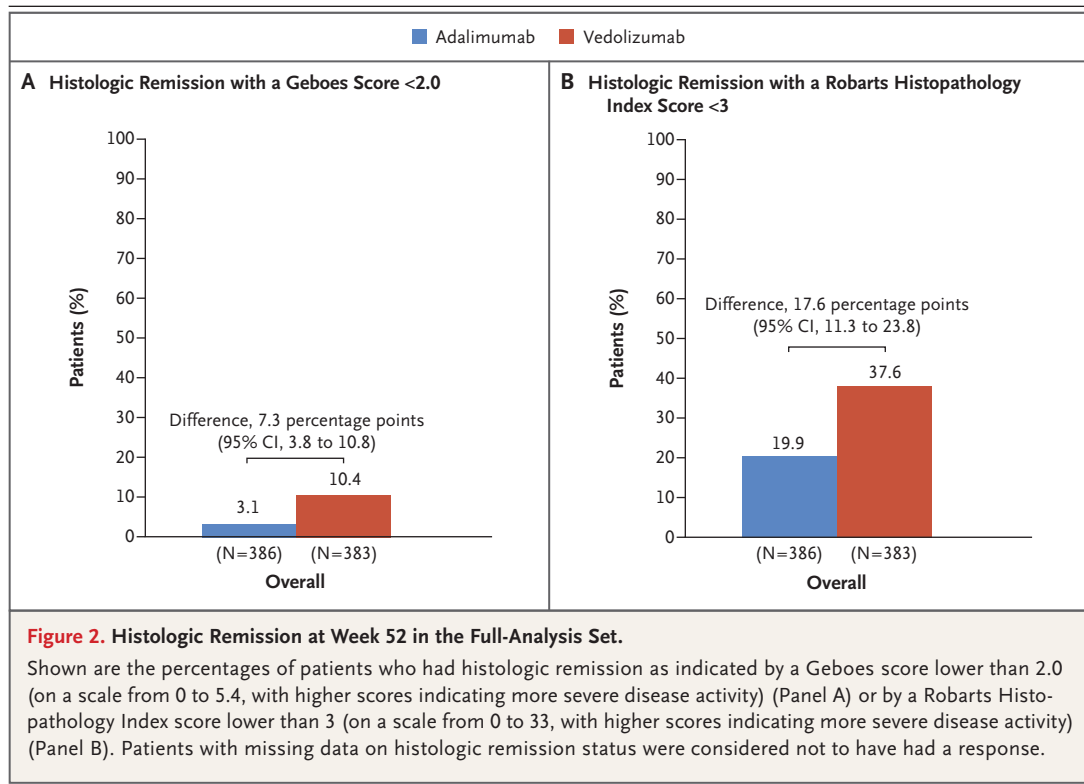
The percentage of patients who were in clinical remission at week 52 and who also had a subscore of 0 on both the rectal bleeding and endoscopic components of the Mayo scale was 22.2% (85 of 383) in the vedolizumab group and 14.0% (54 of 386) in the adalimumab group (difference, 8.2 percentage points; 95% CI, 2.8 to 13.5). In addition, 58.2% of the patients (223 of 383) in the vedolizumab group had a subscore of 0 or 1 on the stool frequency component of the Mayo scale at week 52, as compared with 44.8% (173 of 386) in the adalimumab group (difference, 13.3 percentage points; 95% CI, 6.4 to 20.3). (For patient-reported outcomes, see Table S5 in the Supplementary Appendix.)

#### *Patient Quality of Life*

Quality of life improved from baseline to week 52 (as indicated by an increase of  $\geq 16$  points in the IBDQ score) in 52.0% of the patients in the vedolizumab group and in 42.2% in the adalimumab group (difference, 9.7 percentage points; 95% CI, 2.7 to 16.7). Patient-assessed improvement at week 52 (defined as a score  $>170$  on the IBDQ) was reported in 50.1% of the patients in the vedolizumab group and in 40.4% in the adalimumab group (difference, 9.6 percentage points; 95% CI, 2.8 to 16.5). (See Table S5 in the Supplementary Appendix.)

#### *Histologic Remission*

Histologic remission at week 52 (as indicated by a Geboes score  $<2.0$ ) occurred in 10.4% of the patients (40 of 383) in the vedolizumab group and in 3.1% (12 of 386) in the adalimumab group (difference, 7.3 percentage points; 95% CI, 3.8 to 10.8) (Fig. 2A). The results were similar for histologic remission as indicated by a Robarts Histopathology Index score lower than 3 (Fig. 2B).



(Histologic remission at week 52 in the subgroups of patients defined according to previous treatment with a TNF inhibitor is shown in Fig. S8 in the Supplementary Appendix; histologic remission at week 14 was also assessed with the Geboes score and the Roberts Histopathological Index score, shown in Fig. S9.)

Minimal histologic disease activity as indicated by a Geboes score lower than 3.2 at week 52 was observed in 33.4% of the patients in the vedolizumab group and in 13.7% in the adalimumab group (difference, 19.6 percentage points; 95% CI, 13.8 to 25.5). Minimal histologic disease activity as indicated by a Roberts Histopathology Index score lower than 5 at week 52 was observed in 42.3% of the patients in the vedolizumab group and in 25.6% in the adalimumab group (difference, 16.6 percentage points; 95% CI, 10.0 to 23.1). (For details on minimal histologic disease activity, see Fig. S10 in the Supplementary Appendix.)

#### Clinical Response

The percentages of patients who had a clinical response according to the partial Mayo score are

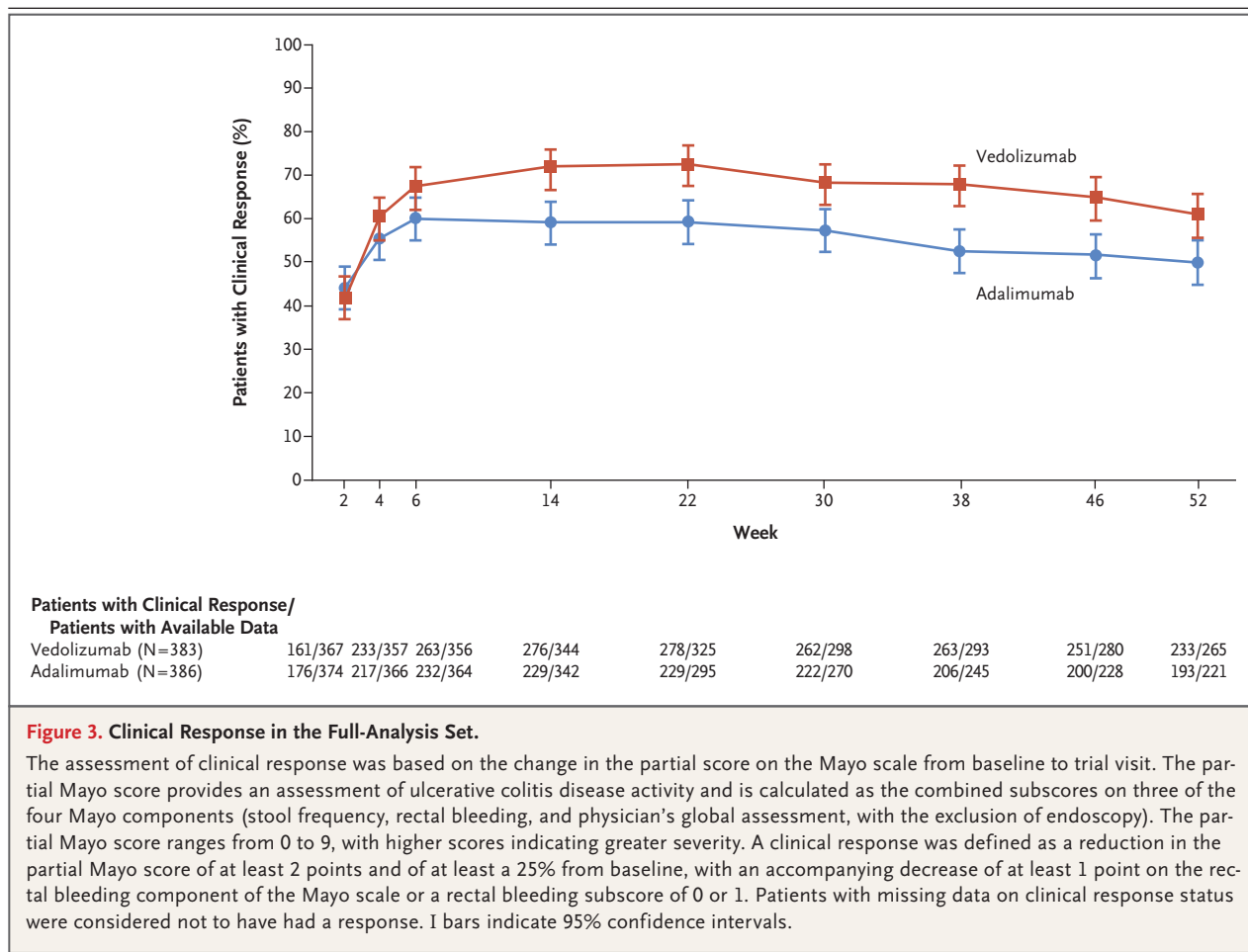
shown in Figure 3. At week 14, a clinical response according to the total Mayo score was observed in 67.1% of the patients (257 of 383) in the vedolizumab group and in 45.9% (177 of 386) in the adalimumab group (difference, 21.2 percentage points; 95% CI, 14.4 to 28.0) (Fig. S11 in the Supplementary Appendix; results of all other prespecified outcome assessments are provided in Table S5).

#### SAFETY

Adverse events occurred in 62.7% of the patients (240 of 383) in the vedolizumab group and in 69.2% (267 of 386) in the adalimumab group (Table 2). The most frequent adverse events are presented in Table S6. Serious adverse events occurred in 11.0% of the patients (42 of 383) in the vedolizumab group and in 13.7% (53 of 386) in the adalimumab group (Table S7 in the Supplementary Appendix).

Exposure-adjusted incidence rates of infections and serious infections showed that both occurred less frequently with vedolizumab than with adalimumab (infections, 23.4 vs. 34.6 events per 100 patient-years; serious infections, 1.6 vs.





2.2 events per 100 patient-years). Herpes zoster infection was less frequent with vedolizumab than with adalimumab (0.5 vs. 4.2 per 100 patient-years), although *Clostridium difficile* infection was more frequent (1.1 vs. 0.6 per 100 patient-years). No patient received a diagnosis of progressive multifocal leukoencephalopathy. One patient in the vedolizumab group died because of an exacerbation of ulcerative colitis and postoperative complications that were considered by the trial site investigator to be unrelated to vedolizumab or adalimumab (Table 2).

## DISCUSSION

In this comparative clinical trial of two biologic agents involving patients with moderately to severely active ulcerative colitis, clinical remission and endoscopic improvement, but not corticoste-

roid-free clinical remission, were observed in a higher percentage of patients in the vedolizumab group than in the adalimumab group. In the Ulcerative Colitis Long-term Remission and Maintenance with Adalimumab 2 (ULTRA2) placebo-controlled trial, clinical remission at week 52 occurred in 17.3% of the patients in the adalimumab group and in 8.5% in the placebo group.<sup>15</sup> As in the VARSITY trial, the ULTRA2 trial maintained blinding and randomization throughout the treatment period. In the GEMINI 1 placebo-controlled trial of vedolizumab, the percentages of patients who had clinical remission at week 52 were higher (41.8% of the patients in the vedolizumab group vs. 15.9% in the placebo group).<sup>16</sup> The higher percentages of patients who had a response to active therapy in the GEMINI 1 trial than in the ULTRA2 trial and our trial may have reflected differences in trial design; patients

Event	Adalimumab (N = 386)	Vedolizumab (N = 383)
<b>Adverse events that occurred during the trial period†</b>		
Any adverse event — no. of patients (%)	267 (69.2)	240 (62.7)
Mild	118 (30.6)	111 (29.0)
Moderate	109 (28.2)	92 (24.0)
Severe	40 (10.4)	37 (9.7)
Adverse events that led to discontinuation of a trial drug	25 (6.5)	17 (4.4)
Adverse events, excluding ulcerative colitis — no. of patients (%)	250 (64.8)	229 (59.8)
Serious adverse events — no. of patients (%)‡	53 (13.7)	42 (11.0)
Serious adverse events that led to discontinuation of a trial drug — no. of patients (%)	13 (3.4)	10 (2.6)
Serious adverse events, excluding ulcerative colitis — no. of patients (%)	27 (7.0)	28 (7.3)
Death — no. of patients (%)	0	1 (0.3)§
<b>Exposure-adjusted incidence rates of adverse events ¶</b>		
Infections and infestations — no. of patients/incidence rate per 100 patient-yr	124/34.6	103/23.4
Clostridia	2/0.6	5/1.1
Herpesvirus	15/4.2	2/0.5
Lower respiratory tract	7/2.0	5/1.1
Upper respiratory tract	65/18.1	55/12.5
Serious infections and infestations	8/2.2	7/1.6
Musculoskeletal and connective-tissue disorders — no. of patients/incidence rate per 100 patient-yr	44/12.3	50/11.4
Arthralgia	16/4.5	18/4.1
Skin and subcutaneous-tissue disorders — no. of patients/incidence rate per 100 patient-yr	52/14.5	38/8.6
Psoriasis	6/1.7	1/0.2

\* Adverse events were classified according to the *Medical Dictionary for Regulatory Activities* System Organ Class categorization and preferred terms, version 21.0, and were analyzed according to the treatment actually received in the safety population, which included all the patients who underwent randomization and received at least one dose of a trial drug.

† The trial period was the time from the first dose of a trial drug and up to 126 days after the last dose.

‡ No cases of progressive multifocal leukoencephalopathy have been reported.

§ The one death in the vedolizumab group was not considered by the site investigator to be related to the trial drug.

¶ The exposure-adjusted incidence rate (per 100 patient-years) was defined as the number of patients who had the adverse event divided by the total exposure time among the patients. The results included the final 68-week safety follow-up.

who had a clinical response underwent an additional randomization at week 6 in the GEMINI 1 trial, but the patients in the ULTRA2 trial and our trial underwent randomization only at baseline. In addition, the ULTRA2 trial and the GEMINI 1 trial included a higher percentage of patients who had previously received treatment with a TNF inhibitor than the VARSITY trial. Direct comparisons of efficacy between the clinical trials are difficult and further highlight

the need for direct head-to-head trials such as the VARSITY trial.

The results of the current trial suggest that corticosteroid-free clinical remission occurred in a higher percentage of patients in the adalimumab group than in the vedolizumab group. It is difficult to explain the inconsistency of the results between this secondary remission outcome and the primary remission outcome. The trial did not require a specific schedule for corticoste-

roid tapering, which can vary among practitioners. However, this limitation should not have resulted in differential effects in the two treatment groups.

There were no notable treatment differences between patients who were receiving concomitant immunomodulator therapy and those who were not. A previous pooled-analysis study suggested that the immunomodulator–adalimumab combination therapy did not provide efficacy benefits beyond adalimumab monotherapy.<sup>17</sup>

In the VARSITY trial, a subgroup of patients who had previous use of infliximab or golimumab were enrolled, and therefore the results observed among these patients in the adalimumab group reflect the efficacy in clinical practice among patients who switched to adalimumab from a drug within the same drug class. We might have postulated that adalimumab would be disadvantaged relative to vedolizumab for patients who previously received treatment with a TNF inhibitor; however, our findings did not suggest this.

Histologic remission was an exploratory outcome of this trial and was assessed with the Geboes score and the Robarts Histopathologic Index score. The results for the outcomes of histologic remission were consistent with the findings for clinical remission and endoscopic improvement.

Few differences were observed between the trial groups in terms of the most commonly reported adverse events. The exposure-adjusted incidence rate of infection was 23.4 per 100 patient-years in the vedolizumab group and 34.6 per 100 patient-years in the adalimumab group.

The double-blind, double-dummy nature of the trial meant that dose intensification in either treatment group was not practical if blinding was to be maintained. The dosing regimens selected for this trial were based on a conservative approach and use according to U.S. labels. Real-world studies have shown improved efficacy outcomes after dose intensification in both adalimumab and vedolizumab therapies.<sup>18,19</sup> Data from ongoing trials of adalimumab (ClinicalTrials.gov number, NCT02065622) and vedolizumab (NCT03029143) may further characterize the effect of higher doses on efficacy outcomes.

In conclusion, the results of our trial involving patients with moderately to severely active

ulcerative colitis show the superiority of vedolizumab over adalimumab in terms of clinical remission and endoscopic improvement but not of corticosteroid-free clinical 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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