ORIGINAL ARTICLE

Ozanimod as Induction and Maintenance Therapy for Ulcerative Colitis

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ABSTRACT

BACKGROUND

Ozanimod, a selective sphingosine-1-phosphate receptor modulator, is under investigation for the treatment of inflammatory bowel disease.

METHODS

We conducted a phase 3, multicenter, randomized, double-blind, placebo-controlled trial of ozanimod as induction and maintenance therapy in patients with moderately to severely active ulcerative colitis. In the 10-week induction period, patients in cohort 1 were assigned to receive oral ozanimod hydrochloride at a dose of 1 mg (equivalent to 0.92 mg of ozanimod) or placebo once daily in a double-blind manner, and patients in cohort 2 received open-label ozanimod at the same daily dose. At 10 weeks, patients with a clinical response to ozanimod in either cohort underwent randomization again to receive double-blind ozanimod or placebo for the maintenance period (through week 52). The primary end point for both periods was the percentage of patients with clinical remission, as assessed with the three-component Mayo score. Key secondary clinical, endoscopic, and histologic end points were evaluated with the use of ranked, hierarchical testing. Safety was also assessed.

RESULTS

In the induction period, 645 patients were included in cohort 1 and 367 in cohort 2; a total of 457 patients were included in the maintenance period. The incidence of clinical remission was significantly higher among patients who received ozanimod than among those who received placebo during both induction (18.4% vs. 6.0%, P<0.001) and maintenance (37.0% vs. 18.5% [among patients with a response at week 10], P<0.001). The incidence of clinical response was also significantly higher with ozanimod than with placebo during induction (47.8% vs. 25.9%, P<0.001) and maintenance (60.0% vs. 41.0%, P<0.001). All other key secondary end points were significantly improved with ozanimod as compared with placebo in both periods. The incidence of infection (of any severity) with ozanimod was similar to that with placebo during induction and higher than that with placebo during maintenance. Serious infection occurred in less than 2% of the patients in each group during the 52-week trial. Elevated liver aminotransferase levels were more common with ozanimod.

CONCLUSIONS

Ozanimod was more effective than placebo as induction and maintenance therapy in patients with moderately to severely active ulcerative colitis. (Funded by Bristol Myers Squibb; True North ClinicalTrials.gov number, NCT02435992.)

Ulcerative colitis is a chronic disease that is characterized by a dysregulated immune response and chronic inflammation in the colonic mucosa.[1] Conventional therapies such as aminosalicylates are modestly effective in patients with moderate, but not severe, disease.[2] Glucocorticoids have been associated with adverse events and long-term adverse health consequences and are not recommended as maintenance therapy.[2-4] Newer agents, including biologic drugs and Janus kinase inhibitors, are not effective in all patients or can lose efficacy with long-term use, and they have been associated with infections, infusion reactions, and cancers.[5,6] Thus, the need remains for new oral treatments for ulcerative colitis that are safe and glucocorticoid-sparing and that have durable efficacy.[2]

Ozanimod is a sphingosine-1-phosphate (S1P) receptor modulator that binds with high affinity to S1P subtypes 1 and 5 (S1P1 and S1P5), leading to internalization of S1P1 receptors in lymphocytes and the prevention of lymphocyte mobilization to inflammatory sites.[7-9] In a phase 2 trial, treatment with ozanimod showed significant improvements over placebo with regard to endoscopic, histologic, and clinical end points in patients with moderate-to-severe ulcerative colitis.[10] A separate phase 2 trial showed benefits with ozanimod therapy in patients with Crohn's disease.[11] To date, the safety profile of ozanimod, as characterized on the basis of studies involving more than 4000 patients with ulcerative colitis, Crohn's disease, or relapsing multiple sclerosis and healthy volunteers, is consistent across populations. Several adverse events of special interest that are known to be associated with S1P receptor modulation (e.g., bradycardia, serious or opportunistic infections, macular edema, and elevated liver-enzyme levels) were monitored in the clinical trials.[10-15] We report here the results of True North, a 52-week, phase 3 trial to evaluate ozanimod as induction and maintenance therapy in patients with moderately to severely active ulcerative colitis.

METHODS

TRIAL OVERSIGHT

We conducted this randomized, double-blind, placebo-controlled trial at 285 sites in 30 countries. The protocol, available with the full text of this article at NEJM.org, was approved by the institutional review board at each center. All the patients provided written informed consent.

The members of the steering committee designed the trial in collaboration with the sponsor (Bristol Myers Squibb). Data were compiled by the sponsor; Pharmaceutical Product Development provided assistance with statistical programming. All the authors had full access to the data. The first author wrote the first draft of the manuscript. Editorial assistance was funded by Bristol Myers Squibb. The eighth and ninth authors, both employees of the sponsor, vouch for the completeness and accuracy of the data, and the eighth author vouches for the adherence of the trial to the protocol.

PATIENTS

Eligible patients were 18 to 75 years of age and had moderately to severely active ulcerative colitis, defined as a total Mayo score of 6 to 12, with an endoscopy subscore of 2 or higher, a rectal-bleeding subscore of 1 or higher, and a stool-frequency subscore of 1 or higher. Each subscore category is rated on a scale from 0 to 3, which was summed to give a total Mayo score between 0 and 12; higher scores indicate greater activity.[16]

Patients were required to have received stable doses of oral aminosalicylates or glucocorticoids (prednisone at a dose of ≤20 mg per day or budesonide) or both for at least 2 weeks before screening endoscopy and to continue receiving the same dose for the duration of the induction period; the glucocorticoid dose had to be tapered once the patient entered the maintenance period. A documented presence of varicella–zoster virus IgG antibody or complete varicella–zoster vaccination at least 30 days before randomization was also required. Patients were excluded from the trial if they had not had a response to induction therapy with at least two biologic agents approved for the treatment of ulcerative colitis, had a clinically relevant cardiac condition, or had a history of uveitis or macular edema. The full enrollment criteria are provided in the Supplementary Appendix, available at NEJM.org.

TRIAL DESIGN

After a screening period of up to 5 weeks, patients entered a 10-week induction period. First, in cohort 1, patients were randomly assigned in a 2:1 ratio to receive ozanimod hydrochloride at a dose of 1 mg per day (equivalent to 0.92 mg of ozanimod; referred to hereafter as ozanimod)

or matched placebo once daily in a double-blind manner. Randomization was conducted by means of a centralized interactive voice- and Web-based activated response system (IxRS). Once the percentage of patients with previous exposure to a tumor necrosis factor (TNF) antagonist reached 30% in cohort 1, the IxRS assigned patients with TNF antagonist exposure to cohort 2, in which patients received open-label ozanimod at the same daily dose. Patients without previous TNF antagonist exposure continued to undergo randomization in cohort 1 until enrollment was closed, at which time such patients were assigned to cohort 2. The percentage of patients with TNF antagonist exposure was capped at 50% in cohort 2. Cohort 2 was included to increase the number of patients with a response who would be available for randomization in the maintenance phase of the trial. A 7-day period of dose escalation with ozanimod — starting at 0.25 mg on days 1 to 4 and progressing to 0.5 mg on days 5 to 7 and to 1 mg thereafter — was incorporated to minimize the risk of bradycardia that has been reported with some S1P modulators within the first few hours after administration.[17,18]

Ozanimod-treated patients who had a clinical response (defined as a reduction in the total Mayo score of ≥3 points and ≥30% from baseline or in the three-component Mayo score of ≥2 points and ≥35% from baseline, as well as a reduction in the rectal-bleeding subscore of ≥1 point or an absolute rectal-bleeding subscore of ≤1 point) at week 10 were eligible to undergo randomization again, in a 1:1 ratio, to receive either ozanimod or placebo in a double-blind manner through week 52 (maintenance period). Patients who had a clinical response while they were receiving placebo at the end of the induction period continued to receive double-blind placebo during the maintenance period. Patients without a clinical response during the induction period could enter an open-label extension trial at week 10, whereas patients who were included in the maintenance period could enter the extension trial at week 52 or after disease relapse (defined as a partial Mayo score [i.e., the rectal-bleeding subscore, stool-frequency subscore, and physician's global assessment subscore] of ≥4 points or a ≥2-point increase from week 10, as well as an endoscopy subscore of ≥2 points) (Fig. S1 in the Supplementary Appendix).

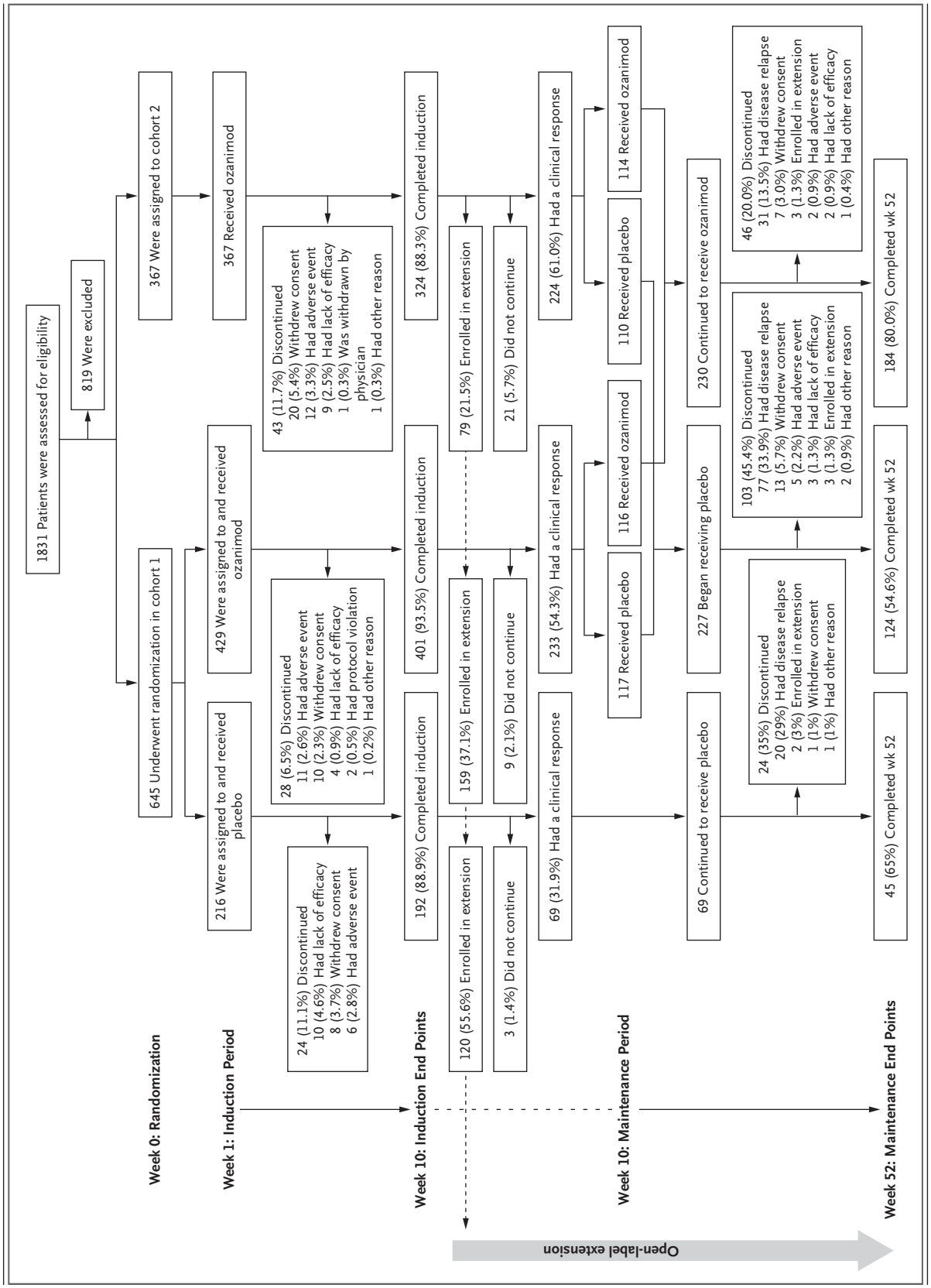
Figure 1 (facing page). Randomization and Follow-up of the Patients in the Induction and Maintenance Periods.

The most common reasons for ineligibility were disease criteria not met (in 18.1% of the patients who underwent screening), a lack of documentation of varicella–zoster virus IgG antibodies or vaccination (in 5.7%), inability to provide informed consent or to comply with protocol assessments (in 4.6%), and presence of *Clostridium difficile* or other stool pathogens (in 3.7%). In cohort 1, patients were randomly assigned to receive ozanimod or placebo; once the percentage of patients with previous exposure to a tumor necrosis factor (TNF) antagonist reached 30%, subsequent patients with TNF antagonist exposure were assigned to cohort 2, in which they received open-label ozanimod. Clinical response was defined as a reduction of at least 3 points and of at least 30% from baseline in the total Mayo score or a reduction of at least 2 points and of at least 35% from baseline in the three-component Mayo score, plus a reduction of at least 1 point in the rectal-bleeding score or an absolute rectal-bleeding score of no more than 1 point. The total Mayo score is defined as the sum of the rectal-bleeding subscore, the stool-frequency subscore, the physician's global assessment subscore, and the endoscopy subscore; overall scores range from 0 to 12 (with each subscore on a scale from 0 to 3), with higher scores indicating greater activity. The three-component Mayo score is defined as the sum of the rectal-bleeding subscore, the stool-frequency subscore, and the endoscopy subscore; overall scores range from 0 to 9 (with each subscore ranging from 0 to 3), with higher scores indicating greater activity.

ASSESSMENTS AND END POINTS

Endoscopic and histologic end points were determined by one central reader who used blinded videos of endoscopic procedures and preserved biopsy samples, respectively. Rectal bleeding and stool frequency were reported by patients in an electronic diary. The primary efficacy end point was the percentage of patients with clinical remission at week 10 (for the induction period) and at week 52 (for the maintenance period), assessed on the basis of the three-component Mayo score. Clinical remission was defined as follows: a rectal-bleeding subscore of 0; a stool-frequency subscore of 1 or less, with a decrease of at least 1 point from baseline; and an endoscopy subscore of 1 or less (all on scales from 0 [none] to 3 [most severe]).[19]

The key secondary efficacy end points were assessed in a closed, prespecified hierarchical testing procedure. The ranked secondary end points for the induction period (at week 10) were the percentages of patients with a clinical response (based on the three-component Mayo



score; see above), endoscopic improvement (defined as a mucosal endoscopy subscore of ≤1 without friability), and mucosal healing (endoscopic improvement plus histologic remission, defined as a mucosal endoscopy score of ≤1 and a Geboes score of <2.0 [on a scale from 0 to 5.4, with higher scores indicating more severe inflammation[20]]). The ranked secondary end points for the maintenance period (at week 52) were the percentages of patients with a clinical response, endoscopic improvement, maintenance of clinical remission (remission at week 52 in the subgroup of patients with remission at week 10), glucocorticoid-free remission (remission with no glucocorticoid use for ≥12 weeks), mucosal healing, and durable clinical remission (remission at weeks 10 and 52, assessed in all patients in the maintenance period).

Other prespecified end points included histologic remission and clinical remission in subgroups defined according to demographic and disease-based characteristics. Tables S1 and S2 list the prespecified efficacy end points. The time to disease relapse was examined as an exploratory end point. Reductions in rectal bleeding and stool frequency were assessed in post hoc analyses, and changes in biomarkers such as fecal calprotectin and C-reactive protein levels were examined.

Safety assessments were based on adverse events that occurred during the trial. Bradycardia, cardiac conduction abnormalities (second-degree and higher atrioventricular block), macular edema, cancer, serious or opportunistic infection, pulmonary effects, and hepatic effects were examined as adverse events of special interest on the basis of previous associations with S1P receptor modulation.[21,22] Clinical laboratory measurements were performed at a central laboratory. Assessment of vital signs, pulmonary-function testing, ophthalmologic examination (including optical coherence tomography), and electrocardiography (before and 6 hours after the first dose) were also performed. Leukocyte counts, including lymphocyte subsets, were not provided to investigators. Additional information about the methods is provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

The demographic and clinical characteristics of the patients at baseline were summarized descriptively. Efficacy analyses were based on all patients who underwent randomization and received at least one dose of ozanimod or placebo (modified intention-to-treat population). Statistical comparisons of efficacy end points for the induction period were performed in cohort 1 only. Clinical remission was analyzed with the use of a two-sided Cochran–Mantel–Haenszel test at the 5% significance level, with accounting for stratification according to glucocorticoid use at screening and previous TNF antagonist use for the induction period (week 10) and according to clinical remission status at week 10 and glucocorticoid use at week 10 for the maintenance period (week 52).

The key secondary end points were evaluated with the use of a two-sided Cochran–Mantel–Haenszel test following a closed, prespecified hierarchical testing procedure to control the overall type I error rate for multiple end points (with an alpha of 0.05 allocated for each of the induction and maintenance periods of the trial). If the primary end point in each period was significant, key secondary end points were analyzed in sequence until a 5% significance level was not reached, after which all the subsequent ranked secondary end points were to be considered exploratory. For end points that were not included in the hierarchies, point estimates and 95% confidence intervals are reported, without P values. The confidence intervals were not adjusted for multiple comparisons and should not be used to infer definitive treatment effects. Patients with missing efficacy data were considered as not having had a response. A missing-at-random assumption was not considered to be appropriate for the data. Sensitivity analyses were conducted for the primary and first key secondary end points with the use of an observed-cases analysis (assumption of data missing completely at random) and with the use of multiple imputation (assumption of data missing at random).[23]

We calculated that a sample of 600 patients (randomly assigned in a 2:1 ratio in cohort 1 in the induction period) would provide the trial with at least 90% power to detect a between-group difference of 10 percentage points in the incidence of clinical remission during the induction period. Cohort 2 (with a planned sample of 300 patients) was used to ensure that the trial would have an enrollment of 400 patients in the maintenance period, with the trial having 90% power for the primary end point. Additional details regarding the statistical analysis are provided in the Supplementary Appendix. Safety results were

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

Characteristic	Cohort 1		Cohort 2
	Placebo (N=216)	Ozanimod (N=429)	Ozanimod (N=367)
Male sex — no. (%)	143 (66.2)	245 (57.1)	214 (58.3)
Age — yr	41.9±13.6	41.4±13.5	42.1±13.7
Body-mass index†	25.1±4.5	25.4±5.5	25.9±5.8
Time since diagnosis of ulcerative colitis — yr	6.8±7.0	6.9±6.6	7.9±7.4
Extent of disease — no. (%)			
Left side of colon	134 (62.0)	268 (62.5)	237 (64.6)
Extensive	82 (38.0)	161 (37.5)	130 (35.4)
Mayo score			
Total score‡	8.9±1.4	8.9±1.5	9.1±1.5
Three-component score§	6.6±1.2	6.6±1.2	6.8±1.3
Fecal calprotectin — μg/g			
Median	1350	1080	1260
Interquartile range	345–3075	399–2532	421–2881
C-reactive protein — mg/liter			
Median	5.0	4.0	5.0
Interquartile range	2.0–12.0	1.0–9.0	2.0–11.0
Concomitant medication use — no. (%)			
Systemic glucocorticoid	70 (32.4)	119 (27.7)	124 (33.8)
Budesonide	13 (6.0)	19 (4.4)	23 (6.3)
Oral aminosalicylate	182 (84.3)	374 (87.2)	315 (85.8)
Previous medication use			
Glucocorticoid — no. (%)	162 (75.0)	322 (75.1)	286 (77.9)
Immunomodulator — no. (%)	93 (43.1)	174 (40.6)	166 (45.2)
Oral aminosalicylate — no. (%)	210 (97.2)	418 (97.4)	362 (98.6)
Vedolizumab — no. (%)	38 (17.6)	71 (16.6)	93 (25.3)
Tofacitinib — no. (%)	4 (1.9)	3 (0.7)	13 (3.5)
TNF inhibitor — no. (%)¶	65 (30.1)	130 (30.3)	159 (43.3)
Had a primary nonresponse — no./total no. (%)	21/65 (32)	49/130 (38)	60/159 (38)
Had a secondary nonresponse — no./total no. (%)	42/65 (65)	84/130 (65)	109/159 (69)
Received concomitant treatment with vedolizumab — no./total no. (%)	29/65 (45)	62/130 (48)	88/159 (55)

* Plus–minus values are means ±SD. The modified intention-to-treat population included all the patients who underwent randomization and received at least one dose of ozanimod or placebo. In cohort 1, patients were randomly assigned to receive ozanimod or placebo; once the percentage of patients with previous exposure to a tumor necrosis factor (TNF) antagonist reached 30%, subsequent patients with TNF antagonist exposure were assigned to cohort 2, in which they received open-label ozanimod.

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

‡ The total Mayo score is defined as the sum of the rectal-bleeding subscore, the stool-frequency subscore, the physician's global assessment subscore, and the endoscopy subscore. Overall scores range from 0 to 12 (with each subscore on a scale from 0 to 3), with higher scores indicating greater activity. Scores were assessed by a central reader.

§ The three-component Mayo score is defined as the sum of the rectal-bleeding subscore, the stool-frequency subscore, and the endoscopy subscore. Overall scores range from 0 to 9 (with each subscore on a scale from 0 to 3), with higher scores indicating greater activity. Scores were assessed by a central reader.

¶ Percentages in this category are based on the subgroup of patients who were treated with a TNF inhibitor. Data were from case-report forms. Patients may be classified under more than one response category if they had received more than one previous anti-TNF therapy and had a different response to each therapy. Primary nonresponse was defined as signs and symptoms of persistently active disease despite an adequate trial of induction treatment with an anti-TNF agent. Secondary nonresponse was defined as the recurrence of symptoms during maintenance therapy after a previous clinical benefit.

summarized descriptively for all patients who received at least one dose of ozanimod or placebo (safety population).

RESULTS

RANDOMIZATION AND BASELINE CHARACTERISTICS OF THE PATIENTS

The trial was conducted from May 2015 through June 2020. Of the 1831 patients who underwent screening, 1012 were enrolled in the trial. A total of 645 patients entered cohort 1 and were randomly assigned to receive either ozanimod (429 patients) or placebo (216 patients) in a double-blind manner; 367 patients received open-label ozanimod in cohort 2 (Fig. 1). In cohort 1, a total of 401 patients (93.5%) who had been assigned to receive ozanimod and 192 (88.9%) who had been assigned to receive placebo completed the induction period. The most common reasons for discontinuation in the induction period were adverse events (in 11 patients [2.6%] in the ozanimod group) and lack of efficacy (in 10 [4.6%] in the placebo group).

At the completion of the induction period, 233 patients (54.3%) in cohort 1 and 224 (61.0%) in cohort 2 had a clinical response to ozanimod therapy and underwent randomization again to receive either ozanimod (230 patients) or placebo (227 patients) in the maintenance period. A total of 184 patients (80.0%) who had been assigned to receive ozanimod and 124 (54.6%) who had been assigned to receive placebo completed the maintenance period. The most common reason for discontinuation in the maintenance period was disease relapse (in 31 patients [13.5%] in the ozanimod group and in 77 [33.9%] in the placebo group). The demographic and clinical characteristics of the patients were similar in the two groups (Table 1).

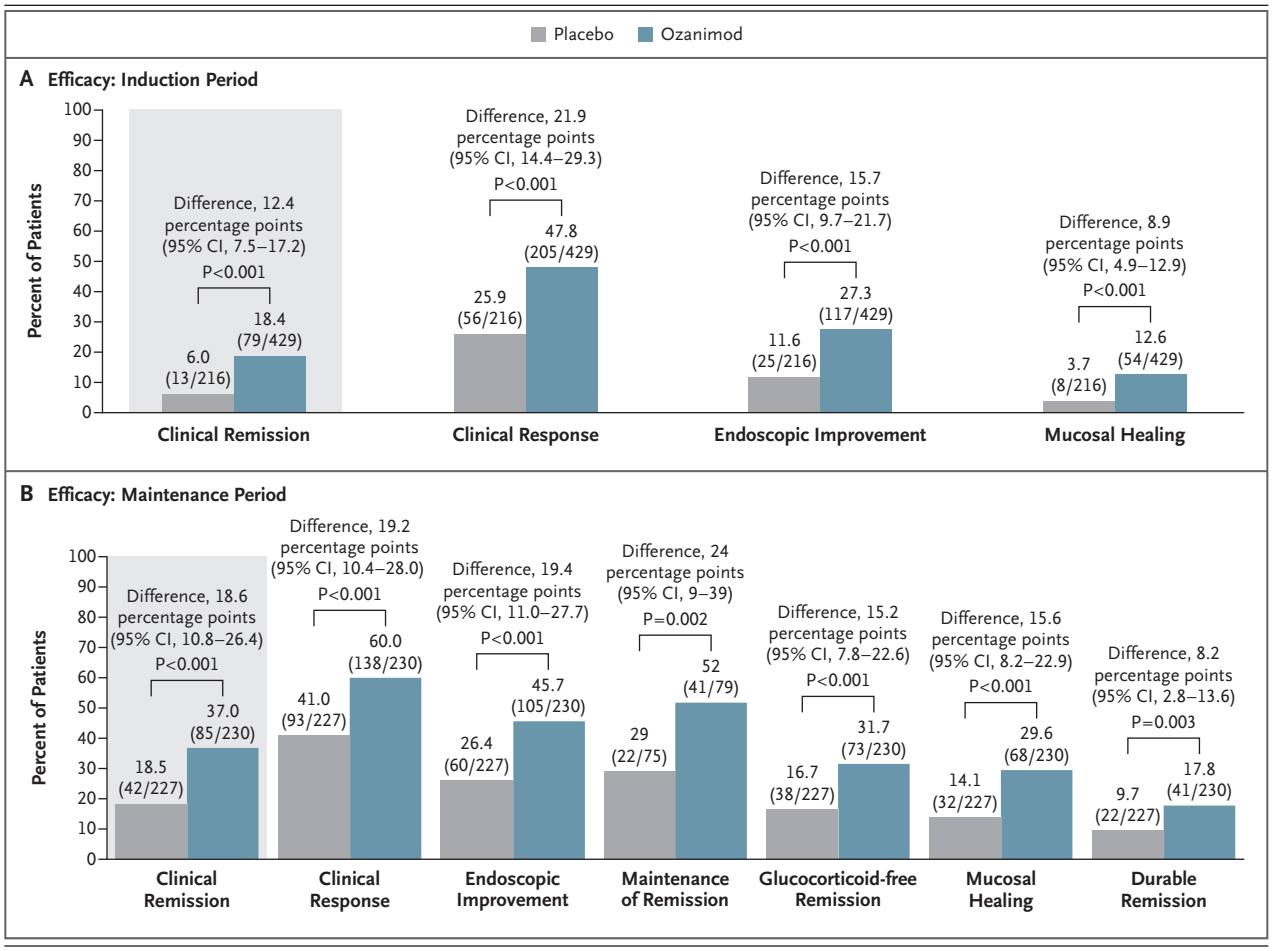
Figure 2 (facing page). Efficacy Results for Ozanimod as Induction and Maintenance Therapy, as Compared with Placebo (Modified Intention-to-Treat Population).

Panel A shows the primary end point (shaded area) and key secondary end points from the induction period (cohort 1) at week 10, and Panel B the primary end point (shaded area) and key secondary end points from the maintenance period at week 52. Percentages of patients with each end point (as well as the numbers and total numbers of patients) are shown, and between-group differences are shown in percentage points with 95% confidence intervals (CI). End points are shown in the order from the hierarchical testing procedure. The modified intention-to-treat population included all patients who underwent randomization and received at least one dose of ozanimod or placebo. Analysis in the induction period was based on the two-sided Cochran–Mantel–Haenszel test and stratified according to glucocorticoid use at screening and previous use of a TNF antagonist. Analysis in the maintenance period was based on the two-sided Cochran–Mantel–Haenszel test and stratified according to clinical remission status at week 10 of the induction period and glucocorticoid use at week 10 of the induction period. Missing data were handled with the use of a "nonresponse" imputation.

Clinical remission was defined as a rectal-bleeding subscore of 0, a stool-frequency subscore of 1 or less (plus a ≥1-point reduction from baseline), and a mucosal endoscopy subscore of 1 or less, without friability. Clinical response was defined as a reduction in the three-component Mayo score of at least 2 points and at least 35% from baseline, as well as a reduction in the rectal-bleeding subscore of at least 1 point or an absolute rectal-bleeding subscore of 1 or less. Endoscopic improvement was defined as a mucosal endoscopy subscore of 1 or less, without friability. Mucosal healing was defined as endoscopic improvement plus histologic remission (i.e., a Geboes score of <2.0 [on a scale from 0 to 5.4, with higher scores indicating more severe inflammation] and an absence of neutrophils in the epithelial crypts or lamina propria and no increase in eosinophils, no crypt destruction, and no erosions, ulcerations, or granulation tissue). Maintenance of remission was defined as clinical remission at 52 weeks in the subgroup of patients with remission at week 10. Glucocorticoid-free remission was defined as clinical remission at 52 weeks without receipt of glucocorticoids for at least 12 weeks. Durable remission was defined as remission at both weeks 10 and 52.

EFFICACY OUTCOMES IN THE INDUCTION PERIOD

At week 10, the percentage of patients with clinical remission was significantly higher in the ozanimod group than in the placebo group (18.4% vs. 6.0%, P<0.001) (Fig. 2A). Significant improvements with ozanimod as compared with placebo were also observed with regard to the three ranked key secondary end points of clinical response, endoscopic improvement, and mucosal healing (P<0.001 for all comparisons). The percentage of patients with histologic remission (an additional secondary end point) was 10.8 percentage points (95% confidence interval, 5.8 to 15.8) higher with ozanimod than with placebo (Fig. S2). Prespecified subgroup analyses for the primary end point of clinical remission during the induction period are shown in Figure S3. Efficacy results among the patients in cohort 2



were similar to the results among the patients treated with ozanimod in cohort 1 (Table S3).

EFFICACY OUTCOMES IN THE MAINTENANCE PERIOD

Among the 457 patients who had a response to ozanimod during the induction period and underwent subsequent randomization in the maintenance period, 37.0% in the ozanimod group and 18.5% in the placebo group had clinical remission at week 52 (P<0.001) (Fig. 2B). All the ranked key secondary end points were also significantly improved with ozanimod therapy, as compared with placebo, at week 52; improvement in the incidence of histologic remission (an additional secondary end point) also occurred with ozanimod therapy (Fig. 2B and Tables S4 and S6). The time to disease relapse (an exploratory end point) during the maintenance period is shown in Figure S4.

Prespecified subgroup analyses for the primary end point of clinical remission during the maintenance period are shown in Figure S5. Treatment-effect sizes in patients with TNF antagonist exposure were similar to those in patients without such exposure. Results of sensitivity analyses of the primary end point (during both the induction and maintenance periods) were consistent with those of the primary analysis (Table S5).

ADDITIONAL END POINTS

A post hoc analysis showed decreases in the rectal-bleeding and stool-frequency subscores by week 2 (i.e., 1 week after the completion of dose adjustment during the induction period) in patients receiving ozanimod (Figs. S6 and S7). Greater reductions from baseline in fecal calprotectin levels were also observed with ozanimod than with placebo in both the induction and maintenance periods (Table S7).

SAFETY

The overall incidence of adverse events was higher in the ozanimod group than in the placebo group during the maintenance period and was similar among the groups during the induction period. The overall incidence of nonserious infection with ozanimod therapy was similar to that with placebo during the induction period but was higher than that with placebo during the maintenance period (Table 2). The frequency of serious infections was less than 2% in each group. One death (in cohort 2) occurred in a patient with a history of ischemic cardiomyopathy and prolonged tobacco use, in whom influenza and acute respiratory distress syndrome developed.

In this trial that required patients to have a documented presence of varicella–zoster virus IgG antibody or complete varicella–zoster vaccination, herpes zoster infection occurred in 3 of 796 ozanimod-treated patients (0.4%) during the induction period and in 5 of 230 (2.2%) during the maintenance period (these events did not lead to hospitalization). Herpes zoster infection did not occur in any patient who did not receive ozanimod.

The absolute lymphocyte count decreased by a mean of approximately 54% from baseline to week 10 in patients who received ozanimod. Absolute lymphocyte counts of less than 200 cells per cubic millimeter occurred in 1.1% of the patients who received ozanimod (in cohort 1 or 2) and in no patients who received placebo during the induction period. Throughout the 52-week trial, 17 patients had an absolute lymphocyte count of less than 200 cells per cubic millimeter, which subsequently increased and remained at a level at or above 200 cells per cubic millimeter during ozanimod treatment. No patient with a serious or opportunistic infection had an absolute lymphocyte count of less than 200 cells per cubic millimeter.

Bradycardia occurred more frequently with ozanimod therapy than with placebo during the induction period but not during the maintenance period. No cases of second-degree type 2 atrioventricular block or third-degree atrioventricular block occurred. One patient receiving ozanimod had a hypertensive crisis on day 1 of the induction period; the event was moderate and resolved on the same day without treatment interruption. During the maintenance period, serious adverse events of hypertensive crisis occurred in 1 patient each in the ozanimod group and the placebo group; neither event resulted in discontinuation of the trial regimen.

Elevated liver aminotransferase levels were more common with ozanimod therapy than with placebo. No patients met Hy's law criteria suggestive of drug-induced liver injury or had severe liver injury. Abnormal liver-function tests led to the discontinuation of ozanimod therapy in 3 of 796 patients (0.4%) in the induction period and in 1 of 230 patients (0.4%) in the maintenance period. Macular edema occurred in 3 patients receiving ozanimod; all cases resolved after treatment discontinuation (Table 2). Cancer was diagnosed in 1 patient who received ozanimod during the induction period (basal-cell carcinoma). In the maintenance period, cancer was diagnosed in 4 patients (basal-cell carcinoma and rectal adenocarcinoma in 1 patient each who received ozanimod during the induction and maintenance periods, and adenocarcinoma of the colon and breast cancer in 1 patient each who received ozanimod during the induction period and placebo during the maintenance period) (see the Supplementary Appendix).

DISCUSSION

The results of this phase 3 trial showed that a once-daily oral formulation of ozanimod, an S1P receptor modulator, provided clinical efficacy in patients with moderately to severely active ulcerative colitis. Treatment with ozanimod led to significant improvements, as compared with placebo, in the incidence of clinical remission (primary end point) and in all key secondary clinical, endoscopic, and histologic end points at weeks 10 and 52. These results were observed in patients with active disease that had been inadequately controlled by conventional agents, as determined on the basis of required concomitant therapy with aminosalicylates or glucocorticoids at trial entry.

Cancer, opportunistic infection, and macular edema were observed in patients who received ozanimod, but the incidences were low. Patients were excluded from the trial if they had macular edema at baseline or if they did not have immunity to varicella–zoster virus or had not received

Table 2. Safety Findings through the Final Safety Visit in the Induction and Maintenance Periods.*

Variable	Induction Period			Maintenance Period†	
	Cohort 1		Cohort 2		
	Placebo (N=216)	Ozanimod (N=429)	Ozanimod (N=367)	Placebo (N=227)	Ozanimod (N=230)
Adverse event — no. (%)	82 (38.0)	172 (40.1)	146 (39.8)	83 (36.6)	113 (49.1)
Serious adverse event — no. (%)	7 (3.2)	17 (4.0)	23 (6.3)	18 (7.9)	12 (5.2)
Serious adverse event related to ozanimod or placebo — no. (%)	2 (0.9)	1 (0.2)	3 (0.8)	1 (0.4)	0
Adverse event leading to discontinuation of the regimen — no. (%)	7 (3.2)	14 (3.3)	14 (3.8)	6 (2.6)	3 (1.3)
Most frequent adverse events — no. (%)‡					
Anemia	12 (5.6)	18 (4.2)	16 (4.4)	4 (1.8)	3 (1.3)
Nasopharyngitis	3 (1.4)	15 (3.5)	10 (2.7)	4 (1.8)	7 (3.0)
Headache	4 (1.9)	14 (3.3)	10 (2.7)	1 (0.4)	8 (3.5)
Alanine aminotransferase increased§	0	11 (2.6)	6 (1.6)	1 (0.4)	11 (4.8)
Arthralgia	3 (1.4)	10 (2.3)	5 (1.4)	6 (2.6)	7 (3.0)
γ-Glutamyltransferase increased§	0	5 (1.2)	6 (1.6)	1 (0.4)	7 (3.0)
Infection — no. (%)	25 (11.6)	46 (10.7)	46 (12.5)	27 (11.9)	53 (23.0)
Serious infection	1 (0.5)	4 (0.9)	6 (1.6)	4 (1.8)	2 (0.9)
Nasopharyngitis	3 (1.4)	15 (3.5)	10 (2.7)	4 (1.8)	7 (3.0)
Upper respiratory tract infection	1 (0.5)	5 (1.2)	8 (2.2)	4 (1.8)	2 (0.9)
Herpes zoster infection¶	0	2 (0.5)	1 (0.3)	1 (0.4)	5 (2.2)
Cancer — no. (%)					
Basal-cell carcinoma	0	0	1 (0.3)	0	1 (0.4)
Rectal adenocarcinoma	0	0	0	0	1 (0.4)
Adenocarcinoma of the colon	0	0	0	1 (0.4)	0
Breast cancer	0	0	0	1 (0.4)	0
Adverse events of special interest — no. (%)					
Bradycardia	0	2 (0.5)	3 (0.8)	0	0
Hypertension	0	6 (1.4)	7 (1.9)	3 (1.3)	4 (1.7)
Hypertensive crisis	0	1 (0.2)	0	1 (0.4)	1 (0.4)
Macular edema	0	1 (0.2)	1 (0.3)	0	1 (0.4)
Laboratory assessments — no./total no. (%)					
Alanine aminotransferase					
≥2×ULN	2/216 (0.9)	25/423 (5.9)	17/359 (4.7)	12/227 (5.3)	32/230 (13.9)
≥3×ULN	1/216 (0.5)	11/423 (2.6)	7/359 (1.9)	4/227 (1.8)	7/230 (3.0)
≥5×ULN	1/216 (0.5)	4/423 (0.9)	2/359 (0.6)	1/227 (0.4)	2/230 (0.9)
Absolute lymphocyte count					
<200 cells per mm^3	0/209	9/421 (2.1)	3/360 (0.8)	0/227	5/230 (2.2)
<500 cells per mm^3	0/209	113/421 (26.8)	114/360 (31.7)	4/227 (1.8)	100/230 (43.5)

* The final safety follow-up visit was scheduled to occur 90 days (within a window of ±10 days) after the final dose of ozanimod or placebo. ULN denotes upper limit of the normal range.
† The group names indicate whether the patients received ozanimod or placebo during the maintenance period only; all the patients in the maintenance period had received ozanimod during the induction period.
‡ The most frequent events were defined as those that occurred in at least 3% of the patients who received ozanimod during the induction or maintenance period.
§ Laboratory values were flagged by the central laboratory if they fell outside the standard reference range. The investigator decided whether the laboratory value qualified as an adverse event.
¶ All the patients had documented presence of varicella–zoster virus IgG antibody or complete varicella–zoster vaccination at screening.

vaccination against varicella–zoster virus. Nonserious infections were more common with ozanimod than with placebo during the maintenance phase of the trial. The incidences of elevated alanine aminotransferase levels were higher among patients who received ozanimod than among those who received placebo. Liver events were mostly mild or moderate in severity and led to the discontinuation of the trial regimen in less than 1% of the patients. The absence of clinically significant bradycardia or cardiac conduction abnormalities may have been due to mitigation by the 7-day dose-escalation schedule.[13-15,24-26] It should be noted that the eligibility criteria for this trial excluded patients with conditions such as recent myocardial infarction, unstable angina or other clinically significant cardiovascular disease, or active or chronic infection. Overall, our results were consistent with safety findings that have previously been reported regarding ozanimod therapy in phase 3 trials involving patients with multiple sclerosis.[12,14,15]

Our trial design was informed by the increasing use of rigorous therapeutic targets beyond symptom control and endoscopic improvement in patients with ulcerative colitis, such as mucosal healing (requiring both endoscopic and histologic improvement) and reduced use of glucocorticoids.[27-30] For example, we required that the definition of mucosal healing include the absence of mucosal neutrophils, which has been associated with a reduced incidence of colectomy, hospitalization, and glucocorticoid use.[30,31] We also defined glucocorticoid-free remission as clinical remission at week 52 without glucocorticoid use for at least 12 weeks because relapse within 12 weeks after the discontinuation of glucocorticoid therapy is a defining characteristic of patients with ulcerative colitis in whom the glucocorticoid dose cannot be reduced beyond a certain threshold without relapse occurring.[32]

A potential limitation of this trial is that the trial population may not be representative of the broader patient population in a routine clinical setting. Another limitation is the lack of long-term data; the open-label extension phase of this trial is ongoing.

In this phase 3 trial, we found that ozanimod was more effective than placebo as induction and maintenance therapy in patients with moderately to severely active ulcerative colitis.

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

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