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Effects of Vedolizumab Induction Therapy for Patients With Crohn's Disease in Whom Tumor Necrosis Factor Antagonist Treatment Failed

Bruce E. Sands,[1] Brian G. Feagan,[2] Paul Rutgeerts,[3] Jean-Frédéric Colombel,[1,4] William J. Sandborn,[5] Richmond Sy,[6] Geert D'Haens,[7] Shomron Ben-Horin,[8] Jing Xu,[9] Maria Rosario,[9] Irving Fox,[9] Asit Parikh,[10] Catherine Milch,[9] and Stephen Hanauer[11]

[1]The Dr Henry D. Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, New York; [2]Robarts Clinical Trials Inc, and Robarts Research Institute, Department of Medicine, and Department of Epidemiology and Biostatistics, University of Western Ontario, London, Ontario, Canada; [3]Department of Gastroenterology, University Hospital Gasthuisberg and Katholieke Universiteit, Leuven, Belgium; [4]Département d'Hépato-Gastroentérologie et Centre d'Investigations Cliniques, Centre Hospitalier Régional Universitaire de Lille, Université Lille Nord de France, Lille, France; [5]Division of Gastroenterology, University of California San Diego, La Jolla, California; [6]Department of Gastroenterology, University of Ottawa, Ottawa, Ontario, Canada; [7]Department of Gastroenterology, Inflammatory Bowel Disease Centre of the Academic Medical Centre, Amsterdam, the Netherlands; [8]Department of Gastroenterology, Sheba Medical Center and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel; [9]Takeda Pharmaceuticals International Co, Cambridge, Massachusetts; [10]Takeda Pharmaceuticals International, Inc, Deerfield, Illinois; [11]Division of Gastroenterology, The University of Chicago Medical Center, Chicago, Illinois

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BACKGROUND & AIMS: There is an increasing need for new treatments for patients with Crohn's disease (CD) in whom previous therapy with tumor necrosis factor (TNF) antagonists has failed. We performed a placebo-controlled, phase 3, double-blind trial to evaluate the efficacy and safety of vedolizumab, an antibody against the integrin $\alpha_4\beta_7$, as induction therapy. **METHODS:** Patients with moderately to severely active CD (CD activity index [CDAI] score, 220–400 points) were assigned randomly to groups given vedolizumab (300 mg) or placebo intravenously at weeks 0, 2, and 6. The primary analysis involved 315 patients with previous TNF antagonist failure (ie, an inadequate response to, loss of response to, or intolerance of $\geq$1 TNF antagonists); we determined the proportion of patients in clinical remission (CDAI, $\leq$150 points) at week 6. Secondary analyses evaluated outcomes at weeks 6 and 10 in this population and in the overall population (N = 416), which included patients naive to TNF antagonist therapy (n = 101). **RESULTS:** Among patients who had experienced previous TNF antagonist failure, 15.2% of those given vedolizumab and 12.1% of those given placebo were in remission at week 6 (P = .433). At week 10, a higher proportion of this population given vedolizumab was in remission (26.6%) than those given placebo (12.1%) (nominal P = .001; relative risk, 2.2; 95% confidence interval, 1.3–3.6). A higher proportion of patients with previous TNF antagonist failure given vedolizumab also had a CDAI-100 response ($\geq$100-point decrease in CDAI score from baseline) at week 6 than those given placebo (39.2% vs 22.3%; nominal P = .001; relative risk, 1.8; 95% confidence interval, 1.2–2.5). Adverse event results were similar among all groups. **CONCLUSIONS:** Vedolizumab was not more effective than placebo in inducing clinical remission at week 6 among patients with CD in whom previous treatment with TNF antagonists had failed. The therapeutic benefits of vedolizumab in these patients were detectable at week 10. ClinicalTrials.gov number: NCT01224171.

Current therapies for Crohn's disease (CD), a chronic inflammatory disorder of the alimentary tract,[1] include corticosteroids; immunosuppressives (eg, azathioprine, 6-mercaptopurine, methotrexate); the tumor necrosis factor (TNF) antagonists infliximab, adalimumab, and certolizumab; and the anti–α_4 integrin monoclonal antibody natalizumab.[1–6] Treatment with TNF antagonists substantially has improved the care of patients with CD that is refractory to other treatments by inducing and maintaining remission and decreasing the need for hospitalization and surgery.[7,8] However, in controlled trials, approximately two thirds of patients did not attain or maintain remission at 1 year after TNF antagonist initiation.[9–11] In addition, patients in whom 1 TNF antagonist has failed have a substantially decreased response rate when treated with a second TNF antagonist.[12,13] Important safety

Abbreviations used in this paper: **AE, adverse event; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CDAI-100, CDAI score decrease of 100 points or more from baseline; CI, confidence interval; CNS, central nervous system; CRP, C-reactive protein; MAdCAM-1, mucosal addressin cell adhesion molecule-1; PML, progressive multifocal leukoencephalopathy; SAE, serious adverse event; TNF, tumor necrosis factor; UC, ulcerative colitis.**

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concerns are associated with the immunosuppressive effects of TNF antagonists, including an increased risk of serious infections (eg, tuberculosis).[14–16]

Natalizumab, another option for patients with CD, binds to $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrins, inhibiting T-lymphocyte adhesion to vascular cell adhesion molecule-1 and mucosal addressin cell adhesion molecule-1 (MAdCAM-1). Natalizumab is approved for multiple sclerosis in many countries and for moderate to severe CD in the United States.[3,5,6] However, an increased risk of progressive multifocal leukoencephalopathy (PML), a rare, serious infection of the central nervous system (CNS), has limited natalizumab use in patients with CD.[17,18] Because of these limitations with TNF antagonists and natalizumab, therapies for patients with TNF antagonist failure are needed, and those that selectively inhibit lymphocyte trafficking to the gut may yield important safety benefits.

Vedolizumab is a humanized, anti–$\alpha_4\beta_7$ integrin, immunoglobulin G1 monoclonal antibody.[19] Unlike natalizumab, vedolizumab specifically binds to the $\alpha_4\beta_7$ integrin and neither binds to nor inhibits the function of $\alpha_4\beta_1$ or $\alpha_E\beta_7$ integrins.[19] The drug inhibits adhesion of a discrete gut-homing subset of T lymphocytes to MAdCAM-1, but not to vascular cell adhesion molecule-1.[19] Selective inhibition of the $\alpha_4\beta_7$/MAdCAM-1 pathway should ameliorate gastrointestinal inflammation without inhibiting systemic immune responses or affecting T-cell trafficking to the CNS.[20–23]

The efficacy, safety, and tolerability of vedolizumab induction and maintenance therapies were established in the pivotal GEMINI 2 study[24] of patients with moderately to severely active CD in whom 1 or more prior CD therapies had failed. A second study (GEMINI 3) to assess efficacy, safety, and tolerability of vedolizumab induction therapy in patients with moderately to severely active CD, which focused on patients with previous TNF antagonist failure, is reported here.

Materials and Methods

Objectives

The primary objective of this study was to determine the effect of vedolizumab induction therapy on clinical remission (Crohn's Disease Activity Index [CDAI] score, ≤150 points) at week 6 in patients with CD and previous TNF antagonist failure (ie, ~75% of enrolled patients). Secondary objectives included determining the effects of vedolizumab on the CDAI-100 response (CDAI score decrease of ≥100 points from baseline) at week 6 and clinical remission at week 10 in the *TNF antagonist–failure population* and on remission at *weeks 6 and 10* in the *overall population*.

Study Design

This phase 3, randomized, placebo-controlled, double-blind, multinational, multicenter trial was initiated in November 2010 and completed in April 2012 (GEMINI 3; ClinicalTrials.gov NCT01224171; EudraCT 2009-016488-12). Institutional review boards and/or independent ethics committees at each investigational center approved the protocol (available at www.gastrojournal.org; protocol C13011), which was not amended. All patients provided written informed consent. All authors had access to the data and reviewed and approved the final manuscript before submission.

A 21-day screening period was followed by a 10-week treatment period (Figure 1). During screening, physical and neurologic examinations were performed and medical history (eg, prior and concomitant CD medications) and demographic information were obtained. Blood tests, urinalysis, and stool sample analysis for enteric pathogens and fecal calprotectin[25] also were performed. Disease activity for eligibility was assessed with the CDAI,[26] an 8-component scale (range, 0 to approximately 600; with higher scores indicating greater disease activity). Eligible patients then randomly were assigned (1:1) to receive vedolizumab 300 mg or placebo, administered intravenously in 250 mL of 0.9% sodium chloride at weeks 0, 2, and 6. After the 10-week treatment phase, patients who had no unacceptable adverse events (AEs) or did not require CD-related surgery during the study were eligible for the long-term, open-label extension (NCT00790933).

Randomization and Blinding

Investigators performed patient enrollment, monitored by an interactive voice response system. Stratified block randomization was computer-generated centrally using 8 strata and a block size of 16. Patients were stratified by previous TNF

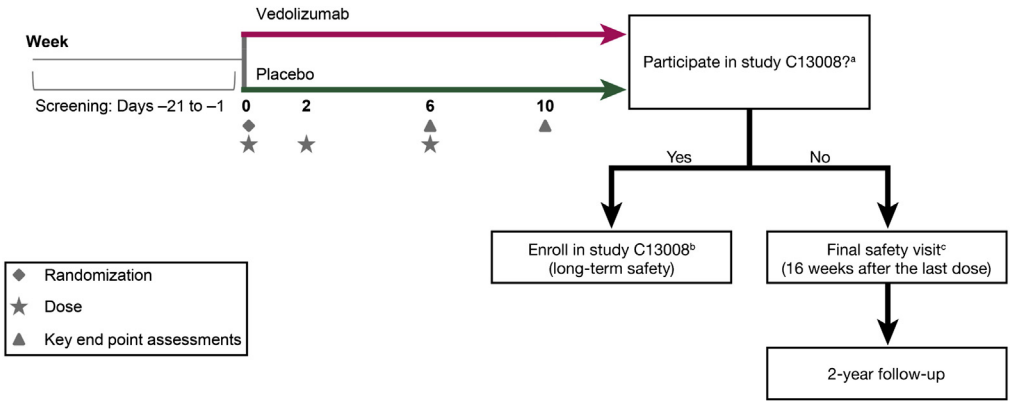

Figure 1. Study design. [a]After the week 10 assessments, patients were eligible to enroll in study C13008 if the study drug was well tolerated and no CD surgical intervention was required. [b]Eligible patients could enroll in study C13008 within 5 weeks after the final study drug dose. [c]Patients who were ineligible for or declined entry into study C13008 returned for a final on-study safety visit (week 22 or 16 weeks after the last dose) and completed the 2-year follow-up evaluation.

antagonist status (failure/no experience), concomitant oral corticosteroid use (yes/no), and concomitant immunosuppressive use (yes/no).

Randomization schedules were generated by Takeda Pharmaceuticals International Co (Cambridge, MA), and each treatment-qualified patient received a unique randomization number used to provide treatment assignments for dose preparation via the interactive voice response system. Saline bag covers and labels maintained blinding. Only the study site pharmacist was aware of treatment assignments.

Patients

Patients (at 107 sites in North America, Europe, Asia, Africa, and Australia) were between 18 and 80 years of age and had a diagnosis of CD with known involvement of the ileum and/or colon at 3 or more months before enrollment (Table 1). Diagnosis was based on clinical and endoscopic evidence, corroborated by results of histopathology (diagnosis occurred at $\geq$6 months before enrollment if a histopathology report was unavailable). All patients had CD that was moderately to severely active, as determined by a CDAI score of 220–400 points within 7 days before enrollment, and one of the following: a screening C-reactive protein (CRP) level greater than 2.87 mg/L,[25] a colonoscopy within the previous 4 months that documented ulcerations, or a fecal calprotectin level greater than 250 μg/g stool during screening in conjunction with features of active CD supported by small-bowel imaging. All patients had experienced an inadequate response, loss of response, or intolerance to TNF antagonists, immunosuppressives, or corticosteroids within the past 5 years (Supplementary Table 1).

Exclusion criteria included previous vedolizumab, natalizumab, efalizumab, or rituximab exposure, as well as concurrent lactation or pregnancy, unstable or uncontrolled medical condition, major neurologic disorder, general anesthesia within 30 days, or planned major surgery during the study. Previous malignancies with the exception of certain cancers for which the recurrence risk after adequate treatment is expected to be low (eg, nonmetastatic basal cell and squamous cell skin cancers, cervical carcinoma in situ) resulted in exclusion, as did active drug or alcohol dependence and active psychiatric disease or other complicating factor(s) that could result in nonadherence to study procedures.

Efficacy Outcomes

The primary efficacy analysis was restricted to patients with prior TNF antagonist failure (ie, TNF antagonist–failure population, prespecified as ~75% of enrolled patients), among whom the proportion of patients in clinical remission at week 6 was assessed (Figure 2). Secondary efficacy outcomes were the proportion of patients in the overall study population (including an additional ~25% of TNF antagonist–naive patients) in remission at week 6, proportions of patients in the overall and TNF antagonist–failure populations in remission at week 10, proportions of patients in the overall and TNF antagonist–failure populations with remission at both weeks 6 and week 10, and the proportion of patients in the TNF antagonist–failure population with a CDAI-100 response at week 6.

Prespecified exploratory outcomes included the proportion of patients in the overall population who had a CDAI-100 response at week 6 and proportions of patients in the overall and TNF antagonist–failure populations who had a CDAI-100 response at week 10, as well as changes from baseline to weeks 6 and 10 in CRP concentration (among patients with increased baseline CRP concentration [>2.87 mg/L]) and from baseline to week 6 in fecal calprotectin level. To summarize efficacy in important subgroups and further clarify primary and secondary outcomes, additional prespecified exploratory analyses were performed, including clinical remission and CDAI-100 response at weeks 6 and 10 and remission at both weeks 6 and 10 in patients who were naive to TNF antagonist therapy and remission at weeks 6 and 10 and CDAI-100 response at week 6 in subgroups defined by concomitant corticosteroid or immunosuppressive use.

Safety Outcomes

Adverse events, serious adverse events (SAEs), standard clinical laboratory test results, and vital signs were evaluated.

Monitoring for PML

Consistent with all vedolizumab clinical studies conducted since 2006, the development of new neurologic signs and symptoms potentially consistent with PML was monitored in a risk minimization program[27] featuring standardized questionnaires and a stepwise diagnostic algorithm overseen by an independent committee of PML experts. The committee adjudicated potential cases and provided further guidance for the investigator and study sponsor in situations of clinical uncertainty.

Pharmacokinetics and Immunogenicity

Blood samples for pharmacokinetic evaluation were collected postdose at week 0, predose and postdose at week 6, and at any time during the study visit at week 10 and any unscheduled disease exacerbation -related visit. Blood samples for anti–vedolizumab antibody assessment were collected predose at weeks 0, 6, 10, and 22, and during any unscheduled disease exacerbation–related visit.

Statistical Analyses

All efficacy analyses were performed for patients from intention-to-treat populations who had received any amount of blinded study drug; missing efficacy data were considered therapy failure. The safety population was defined as all patients who received any amount of study drug. Populations for pharmacokinetic analyses were defined as all patients who received 1 or more doses of study drug and underwent sufficient blood sampling for pharmacokinetic evaluation.

All proportion-based outcomes (Supplementary Figure 1) were analyzed using the Cochran–Mantel–Haenszel chi-square test at a statistical significance level of 0.05 with stratification according to previous TNF antagonist status, concomitant corticosteroid use, and concomitant immunosuppressive use. The Cochran–Mantel–Haenszel chi-square P value, risk difference (primary test), and associated 2-tailed 95% confidence intervals (CIs) were determined, as were the relative risk and its 2-tailed 95% CI. Secondary analyses were performed sequentially, with a P value of .05 or less required to proceed to testing of each subsequent outcome. Of the 6 secondary analyses, 4 (ie, 2 pairs of outcomes, each pair evaluating 1 end point for the 2 populations) involved simultaneous testing for the TNF antagonist–failure and overall populations (Supplementary Figure 1).

Table 1. Demographics and Baseline Characteristics

Characteristic	Placebo			Vedolizumab		
	Overall population (n = 207)	TNF antagonist–failure population (n = 157)	TNF antagonist–naive subgroup (n = 50)	Overall population (n = 209)	TNF antagonist–failure population (n = 158)	TNF antagonist–naive subgroup (n = 51)
Women, n (%)	118 (57)	95 (61)	23 (46)	118 (56)	90 (57)	28 (55)
Median age, *y* (range)	34.8 (19–77)	36.6 (19–77)	30.6 (19–60)	36.9 (20–69)	37.5 (20–69)	35.7 (20–64)
Mean body weight, *kg* (range)	71.3 (41–147)	71.2 (41–125)	71.7 (43–147)	69.5 (40–144)	70.3 (40–144)	67.1 (40–99)
Median body mass index, kg/m^2 (range)	23.3 (15–48)	23.3 (15–48)	22.9 (17–43)	23.3 (15–43)	23.3 (15–43)	22.6 (16–33)
Median Crohn's disease duration, *y* (range)	8.0 (0.3–42.9)	9.6 (1.0–42.9)	4.4 (0.3–24.8)	8.4 (0.3–41.8)	9.4 (0.5–41.8)	4.7 (0.3–40.8)
Mean CDAI score (SD)	301.3 (55.0)	306.1 (55.4)	286.1 (51.1)	313.9 (53.2)	316.1 (52.6)	307.3 (54.8)
Mean CRP level, *mg/L* (SD)	18.5 (22.0)	18.8 (23.6)	17.7 (16.1)	19.0 (23.2)	20.7 (24.7)	13.9 (16.8)
Mean fecal calprotectin level, *μg/g stool* (SD)	1426.5 (2357.8)	1459.5 (2475.0)	1321.0 (1954.0)	1148.1 (1878.6)	1249.2 (2071.6)	836.9 (1043.8)
Disease localization, n (%)						
Ileum only	29 (14)	20 (13)	9 (18)	33 (16)	21 (13)	12 (24)
Colon only	52 (25)	40 (25)	12 (24)	48 (23)	40 (25)	8 (16)
Ileocolonic (both ileum and colon)	126 (61)	97 (62)	29 (58)	128 (61)	97 (61)	31 (61)
History of Crohn's disease surgery, n (%)	89 (43)	80 (51)	9 (18)	92 (44)	73 (46)	19 (37)
History of fistulizing disease, n (%)	77 (37)	67 (43)	10 (20)	71 (34)	57 (36)	14 (27)
Corticosteroid use, n (%)	108 (52)	85 (54)	23 (46)	110 (53)	86 (54)	24 (47)
Immunosuppressive use, n (%)	69 (33)	42 (27)	27 (54)	71 (34)	43 (27)	28 (55)
Mesalamine use, n (%)[a]	61 (29)	29 (18)	32 (64)	68 (33)	37 (23)	31 (61)
Prior immunosuppressive exposure, n (%)	193 (93)	147 (94)	46 (92)	176 (84)	135 (85)	41 (80)
Prior TNF antagonist failure, n (%)[b]	157 (76)	157 (100)	-	158 (76)	158 (100)	-
1 prior TNF antagonist failure, n (%)[b]	45 (22)[c]	43 (27)[c]	-	59 (28)[c]	59 (37)[c]	-
2 prior TNF antagonist failures, n (%)[b]	90 (43)[c]	90 (57)[c]	-	82 (39)[c]	82 (52)[c]	-
3 prior TNF antagonist failures, n (%)[b]	21 (10)[c]	21 (13)[c]	-	14 (7)[c]	14 (9)[c]	-

NOTE. Missing/unreported values in the TNF antagonist–failure population: placebo, n = 3; vedolizumab, n = 3. Missing/unreported values in the overall population: placebo, n = 51; vedolizumab, n = 54.
[a]Used by patients at any time during the study.
[b]Multiple failures are counted once per patient.
[c]Data on numbers of patients with 1, 2, and 3 TNF antagonist failures were captured via electronic case report form only (not via interactive voice response system).

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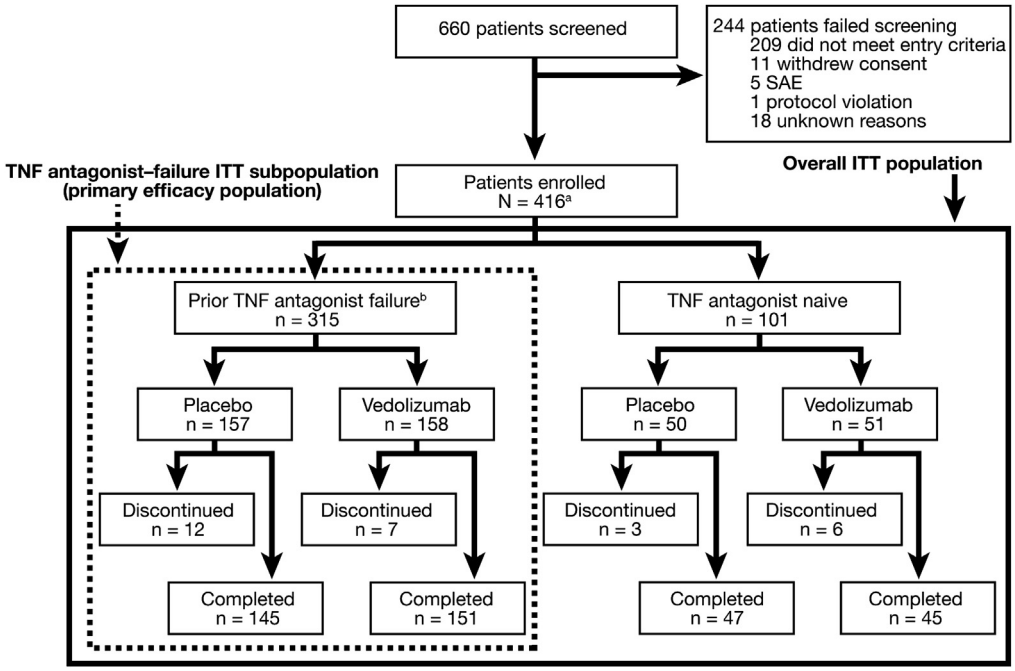

Figure 2. Patient disposition. [a]All 416 patients received at least 1 dose of blinded study drug and comprised the overall population for efficacy analyses as well as the safety population. [b]Of the 416 randomly assigned patients, 25%, 41%, and 8% had 1, 2, and 3 TNF antagonist failures, respectively. These data were captured via electronic case report form only (not via interactive voice response system). ITT, intention-to-treat.

The Hochberg method was applied to each secondary outcome pair to maintain the overall type 1 error rate at a *P* value of .05 or less. A logistic regression model, including baseline CDAI score, stratification factors, and geographic region, was conducted as a sensitivity analysis using the chi-square test at a statistical significance level of 0.05; the chi-square *P* value and odds ratio, with associated 95% CIs, were determined. Analysis of covariance models of change from baseline to week *t* for the continuous efficacy outcome variables in the vedolizumab and placebo groups was performed. For the prespecified exploratory analyses of TNF antagonist–naive patients and for those based on concomitant corticosteroid or immunosuppressive use, *P* values were determined and 95% CIs were calculated using the exact method (for categoric data with numerators $\leq$5) or the normal approximation.

Power estimates for the primary and secondary outcomes were 91% and 81%–93%, respectively, on the basis of total sample sizes of 296 for the TNF antagonist–failure population and 396 for the overall population.

Results

Patients

A total of 660 patients were screened (Figure 2), of whom 244 were excluded because of not meeting enrollment criteria (n = 209), withdrawal of consent (n = 11), having an SAE (n = 5), having a protocol violation (n = 1), or other/unknown reasons (n = 18). Of 416 randomized patients, 315 (76%) had previous failure of (ie, inadequate response to, loss of response to, or intolerance of) 1 or more TNF antagonists, and 101 patients (24%) were TNF-antagonist naive.

Demographic characteristics (Table 1) generally were similar between treatment groups in the TNF antagonist–failure population. Corticosteroids were the most common concomitant medications used at any time during the study (54% of patients), followed by immunosuppressives (34%) and mesalamine (31%). Previous immunosuppressive exposure was reported by 89% of patients. In the TNF antagonist–failure population, 2 or more TNF antagonists had failed in 66% of patients (44% of whom had a primary nonresponse), whereas 3 TNF antagonists had failed in 11% of patients.

Efficacy

For the primary outcome, the proportion of patients in clinical remission at week 6 for the TNF antagonist–failure population (Figure 3*A*), no statistically significant difference was observed between the vedolizumab (15.2%) and placebo (12.1%) groups ($P = .433$; relative risk, 1.2; 95% CI, 0.7–2.2). Because this outcome was not statistically significant, formal hypothesis testing of ranked secondary outcomes was not performed. Nominal *P* values, relative risks, and 95% CIs are presented for descriptive purposes to fully characterize the effect of vedolizumab induction treatment in this population.

Secondary and prespecified exploratory outcomes: TNF antagonist–failure population. In the TNF antagonist–failure population, greater proportions of vedolizumab-treated patients than placebo-treated patients were in clinical remission at week 10 (Figure 3*B*; vedolizumab, 26.6%; placebo, 12.1%; $P = .001$; relative risk, 2.2; 95% CI, 1.3–3.6). The between-group difference in rates of remission both weeks 6 and 10 (Figure 3*C*) was not less than 0.05 in this population (vedolizumab, 12.0%; placebo, 8.3%; $P = .276$; relative risk, 1.4; 95% CI, 0.7–2.8). Greater proportions of vedolizumab-treated patients also had a CDAI-100 response at week 6 (Figure 3*D*; vedolizumab,

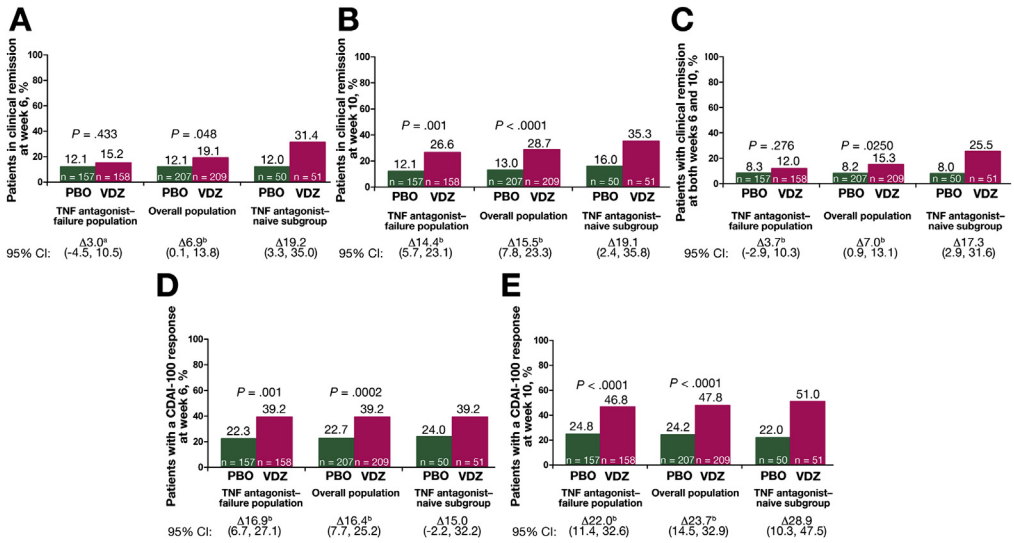

Figure 3. Treatment efficacy: clinical remission (CDAI score, ≤150 points) at (*A*) week 6, at (*B*) week 10, and at (*C*) both weeks 6 and 10; CDAI-100 response (≥100-point reduction from baseline in CDAI score) at (*D*) week 6 and at (*E*) week 10 for the TNF antagonist–failure and overall populations and the TNF antagonist–naive subgroup. [a]Primary outcome. [b]Nominal *P* values and 95% CIs are presented for descriptive purposes to fully characterize the effect of vedolizumab induction treatment in these populations. Δ, difference from placebo.

39.2%; placebo, 22.3%; $P = .001$; relative risk, 1.8; 95% CI, 1.2–2.5) and at week 10 (Figure 3*E*; vedolizumab, 46.8%; placebo, 24.8%; $P < .0001$; relative risk, 1.9; 95% CI, 1.4–2.6).

Secondary and prespecified exploratory outcomes: overall population. In the overall population, a greater proportion of vedolizumab-treated patients (19.1%) than placebo-treated patients (12.1%) was in clinical remission at week 6 (Figure 3*A*; $P = .048$; relative risk, 1.6; 95% CI, 1.0–2.5). As in the TNF antagonist–failure population, a greater proportion of the overall population was in remission at week 10 with vedolizumab than with placebo (Figure 3*B*; vedolizumab, 28.7%; placebo, 13.0%; $P < .0001$; relative risk, 2.2; 95% CI, 1.4–3.3). The nominal *P* value for the between-group difference in rates of remission at both weeks 6 and 10 was less than .05 in the overall population (Figure 3*C*; vedolizumab, 15.3%; placebo, 8.2%; $P = .025$; relative risk, 1.9; 95% CI, 1.1–3.2). Prespecified exploratory analyses in the overall population showed that the proportion of patients with a CDAI-100 response was greater with vedolizumab at week 6 (Figure 3*D*; vedolizumab, 39.2%; placebo, 22.7%; $P = .0002$; relative risk, 1.7; 95% CI, 1.3–2.3) and at week 10 (Figure 3*E*; vedolizumab, 47.8%; placebo, 24.2%; $P < .0001$; relative risk, 2.0; 95% CI, 1.5–2.6).

Prespecified exploratory outcomes: TNF antagonist–naive subgroup and effects of concomitant CD therapy. Although the TNF antagonist–naive subgroup (Figure 3) was relatively small, proportions of patients were greater with vedolizumab than with placebo for the following outcomes: clinical remission at week 6 (vedolizumab, 31.4%; placebo, 12.0%; $P = .012$; relative risk, 2.6; 95% CI, 1.1–6.2); remission at week 10 (vedolizumab, 35.3%; placebo, 16.0%; $P = .025$; relative risk, 2.2; 95% CI, 1.1–4.6); remission at both weeks 6 and 10 (vedolizumab, 25.5%; placebo, 8.0%; $P = .018$; relative risk, 3.2; 95% CI, 1.1–9.1); CDAI-100 response at week 6 (vedolizumab, 39.2%; placebo, 24.0%; $P = .088$; relative risk, 1.6; 95% CI, 0.9–2.9); and CDAI-100 response at week 10 (vedolizumab, 51.0%; placebo, 22.0%; $P = .002$; relative risk, 2.3; 95% CI, 1.3–4.2).

Prespecified exploratory subgroup analysis results by concomitant corticosteroid or immunosuppressive use for clinical remission at weeks 6 and 10 and CDAI-100 response at week 6 for the TNF antagonist–failure and overall populations are shown in Supplementary Figures 2 and 3.

Prespecified Exploratory Biomarker Outcomes: C-Reactive Protein and Fecal Calprotectin Concentrations

Among patients in the TNF antagonist–failure and overall populations with increased baseline CRP levels, median changes in CRP concentration were improved modestly from baseline to weeks 6 and 10; these improvements were more pronounced at week 10 than at week 6 (Supplementary Figure 4). Nominal *P* values for between-group differences in median change in fecal calprotectin levels from baseline to week 6 were not less than .05 among the TNF antagonist–failure population (vedolizumab, -22.1 μg/g stool; placebo, -5.0 μg/g stool; $P = .883$) or the overall population (vedolizumab, -26.2 μg/g stool; placebo, -7.8 μg/g stool; $P = .744$).

Safety

Sixty percent of placebo-treated patients and 56% of vedolizumab-treated patients experienced 1 or more AEs during the study (Table 2). Serious infection and drug-related SAEs were experienced by 1% or less of patients in both groups, and 2% of patients in both groups had SAEs

Table 2. Treatment-Emergent Adverse Events in the Overall Safety Population

Event	Overall safety population (patients who received any amount of study drug) (N = 416), No. (%)	
	Placebo (n = 207)	Vedolizumab (n = 209)
Any adverse event	124 (60)	117 (56)
Drug-related adverse event	34 (16)	34 (16)
Discontinued because of adverse events	8 (4)	4 (2)
Serious adverse events	16 (8)	13 (6)
Serious infection	0	2 (<1)
Drug-related serious adverse event	1 (<1)	1 (<1)
Discontinued because of serious adverse events	5 (2)	4 (2)
Adverse event in >1% of vedolizumab patients, categorized by preferred term		
Nausea	5 (2)	12 (6)
Headache	15 (7)	11 (5)
Upper respiratory tract infection	5 (2)	9 (4)
Arthralgia	9 (4)	10 (5)
Nasopharyngitis	8 (4)	9 (4)
Abdominal pain	6 (3)	9 (4)
Crohn's disease exacerbation	21 (10)	6 (3)
Pyrexia	13 (6)	7 (3)
Aphthous stomatitis	3 (1)	4 (2)
Vomiting	5 (2)	9 (4)
Fatigue	2 (<1)	6 (3)
Urinary tract infection	0	6 (3)
Dizziness	4 (2)	5 (2)
Anemia	1 (<1)	5 (2)
Musculoskeletal pain	0	4 (2)

leading to study discontinuation. No deaths were reported in the study.

The most common AEs in both groups were similar and included infections (vedolizumab, 19%; placebo, 17%). Gastrointestinal infections occurred in 5 (2%) vedolizumab-treated patients and in 3 (1%) placebo-treated patients. In vedolizumab-treated patients, the most common AEs were nausea, vomiting, headache, upper respiratory tract infection, arthralgia, nasopharyngitis, and abdominal pain (Table 2). Incidences of nausea, upper respiratory tract infection, arthralgia, abdominal pain, aphthous stomatitis, vomiting, fatigue, urinary tract infection, and anemia were higher with vedolizumab, whereas incidences of CD exacerbation, pyrexia, and headache were higher with placebo.

Two vedolizumab-treated patients had SAEs of infection, including 1 anal abscess and 1 urinary tract infection, which were treated successfully during the study; neither led to study discontinuation. No placebo-treated patients had SAEs of infection. Infusion-related AEs occurred in 4 (2%) vedolizumab-treated patients and in 2 (<1%) placebo-treated patients. In the 1 patient who reported new neurologic symptoms during the study and was evaluated by an independent adjudication committee, PML formally was excluded. This vedolizumab-treated patient was later withdrawn from the study because of an ependymoma and had the only reported neoplasm in the study.

Pharmacokinetics and Immunogenicity

The mean ± SD week 6 trough vedolizumab serum concentration was 26.5 ± 15.8 μg/mL (n = 195), which was similar to that observed in GEMINI 2.[24] The week 10 vedolizumab serum concentration was 28.4 ± 17.9 μg/mL (n = 190). Of 209 vedolizumab-treated patients, 3 (1%) had positive test results for antivedolizumab antibodies at any time point; 1 of these 3 patients had neutralizing antibodies, and none had persistently positive (ie, positive status at ≥2 consecutive visits) antibody status. The limited number of patients in whom antibodies were observed and the short study duration precluded meaningful analysis of potential correlations of pharmacokinetics and efficacy with immunogenicity.

Discussion

Efficacy and safety of vedolizumab induction therapy were evaluated in this randomized, blinded, placebo-controlled study of patients with moderately to severely active CD. In the TNF antagonist–failure population (~75% of patients), there were high rates of long-standing disease, prior CD surgery, history of fistulizing disease, baseline CRP and fecal calprotectin increases, and prior failure of immunosuppressives and multiple TNF antagonists.

In the TNF antagonist–failure population, vedolizumab was not statistically superior to placebo for inducing clinical remission at week 6. However, secondary and exploratory outcome results suggest that vedolizumab had clinically relevant activity in TNF antagonist–failure and TNF antagonist–naive patients.

Collectively, the primary and secondary outcome results suggest that in patients with CD and previous TNF antagonist failure, effects of vedolizumab on clinical remission may not become evident until between weeks 6 and 10. Week 10 secondary outcomes were prespecified to test the hypothesis that the time to achieve remission with vedolizumab may be 10 weeks in patients with CD, particularly in patients with previous TNF antagonist failure. Results in the TNF antagonist–failure population showed a clinically important increase over time in the proportion of vedolizumab-treated patients in remission, from 15.2% at week 6 to 26.6% at week 10. However, the remission rate in placebo-treated patients remained constant at 12.1% at weeks 6 and 10.

Similar analyses of the overall population showed more vedolizumab-treated patients (19.1%) than placebo-treated patients (12.1%) in clinical remission at week 6 (treatment difference, 7.0%; 95% CI, 0.1%–13.8%; $P = .048$). This difference resulted from the more robust effect on this outcome in the smaller TNF antagonist–naive subgroup, which comprised 24% of the overall population. On the basis of observed differences among the TNF antagonist–naive subgroups in

GEMINI 2 and 3, vedolizumab (similar to TNF antagonists) may have a more pronounced effect before the onset of structural damage, as indirectly gauged by shorter disease duration and lack of prior CD surgery. These disease characteristics were considerably more common in TNF antagonist–naive patients than in patients with prior TNF antagonist failure. Similar trends toward more pronounced effects of treatment in TNF antagonist–naive patients also have been seen with the use of a second or third TNF antagonist and with natalizumab. An increase in remission rates from week 6 to 10 also was observed among vedolizumab-treated patients in the overall population. Collectively, these findings indicate that additional benefits of vedolizumab treatment may accrue between weeks 6 and 10, regardless of previous TNF antagonist response, and could be associated with effects of an additional vedolizumab dose at week 6 or with the incremental effect of time on the drug's ability to exert a therapeutic benefit. Similar findings have been observed with natalizumab induction therapy,[6] which suggests that a gradual onset of efficacy may be an attribute of drugs that modulate lymphocyte trafficking. This observation may help with the optimization of vedolizumab induction therapy in real-world settings.

The lack of statistical significance of primary outcome results contrasts with the GEMINI 2 induction study results in patients with previous TNF antagonist failure.[24] However, several patient characteristics and design parameters differed between these 2 studies (eg, differences in upper CDAI score cut-off values, defined by entry criteria, and in mean CDAI scores, and re-randomization at week 6 in GEMINI 2). In a prespecified subgroup analysis of patients from GEMINI 2 with previous TNF antagonist failure, the proportion of patients with week 6 clinical remission was similar between vedolizumab-treated (10.5%) and placebo-treated groups (4.3%; treatment difference, 6.2%; 95% CI, -9.1% to 21.3%). In a prespecified subgroup analysis of TNF antagonist–naive patients from GEMINI 2, the week 6 remission rate was higher with vedolizumab (17.4%) than with placebo (9.2%; treatment difference, 8.2%; 95% CI, -1.4% to 17.9%). The week 6 treatment difference in patients with previous TNF antagonist failure was similar in GEMINI 3 (3.0%) and GEMINI 2 (6.2%), whereas the week 6 treatment difference in TNF antagonist–naive patients was larger in GEMINI 3 (19.2%) than in GEMINI 2 (8.2%). Observed differences in week 6 remission rates between overall populations of the 2 studies may be attributable to variations between 2 otherwise similar patient populations, including proportions of patients with previous exposure to 1, 2, or 3 TNF antagonists (GEMINI 2, 47.6%; GEMINI 3, 75.7%). The upper bound of patients' CDAI scores (GEMINI 2, 450; GEMINI 3, 400) or random variation could have accounted for the observed differences in subgroup analyses of week 6 remission rates among TNF antagonist–naive patients.

Effects of vedolizumab induction therapy were modest overall, and maintenance effects were not evaluated in this short-term study; however, the modest efficacy of vedolizumab induction therapy in GEMINI 2 was contrasted by the pronounced benefit of vedolizumab maintenance therapy over the course of 52 weeks. Among vedolizumab induction responders in GEMINI 2, week 52 clinical remission occurred in 39.0% ($P < .001$) and 36.4% ($P = .004$) of patients who continued vedolizumab every 8 and 4 weeks, respectively, and in 21.6% of patients who were assigned randomly to switch to placebo during maintenance. Effects were similar for week 52 CDAI-100 response and corticosteroid-free remission rates. In GEMINI 2, the maintenance benefit of vedolizumab was consistent between patients with previous TNF antagonist failure and in TNF antagonist–naive patients.

Observed effects of vedolizumab on disease activity biomarkers were small, but evident, and were consistent with the efficacy data. Effects on CRP concentration in patients with increased CRP levels at baseline were less pronounced than effects seen after TNF antagonist treatment in other studies.[28–30] The apparently slower CRP reduction kinetics warrant careful consideration. Previously, TNF was reported to exert a direct effect on CRP production by the liver.[31] Because vedolizumab, unlike TNF antagonists, does not antagonize TNF directly and may not affect the mesentery, an important source of CRP in CD,[32] it is scientifically plausible to speculate that the reduction in mucosal inflammation resulting from inhibition of leukocyte trafficking causes an indirect (ie, secondary) CRP concentration reduction that occurs gradually, as seen over the course of 52 weeks in GEMINI 2.[24] In contrast, TNF antagonism may result in direct and indirect effects on CRP. Week 6 assessments of fecal calprotectin, a biomarker that has been studied less extensively in CD than in ulcerative colitis (UC), did not show a clinically meaningful difference between treatment groups; however, because these assessments were not conducted at week 10, it is unclear if an effect of vedolizumab would have become more apparent over time. Future studies are warranted to evaluate the potential healing effects of vedolizumab on the ileocolonic mucosa in patients with CD and to establish an optimal methodology for analysis of drug effects on fecal calprotectin levels in CD.

Results of this short-term study support the safety of vedolizumab in patients with CD and are consistent with the drug's postulated gut-selective mechanism of action. The safety profile in GEMINI 3 generally is consistent with that in the pivotal trials GEMINI 1 (UC) and 2 (CD), in which no statistically significant differences in treatment-emergent SAE incidences occurred between the vedolizumab and placebo groups.[24,33,34] Although upper respiratory tract infection rates were similar between treatment groups in this study, across previous clinical studies, vedolizumab was associated with an increased risk of such infections.[24,33,34] This association is potentially consistent with its mechanism of action, namely antagonism of $\alpha_4\beta_7$/MAdCAM-1 interactions in upper respiratory/aerodigestive tract tissues.[35] Upper respiratory tract infections with vedolizumab generally have been mild or moderate in severity, requiring no interventions, and an increased risk of lower respiratory tract infections (eg, bronchitis and pneumonia) has not been observed. As previously noted, natalizumab, the only available biologic therapy with a mechanism that differs from that of TNF antagonists,[36] rarely is used in CD because of the risk of PML.[17,18] Consistent with the expected lack of effect

on CNS immune surveillance owing to the gut-selective blockade of lymphocyte trafficking with vedolizumab,[20,22] no PML cases have been identified in the vedolizumab development program to date. As of June 27, 2013, there were 3129 patients with CD or UC who had received vedolizumab in 11 clinical studies (including GEMINI 1, 2, 3, and the GEMINI long-term extension study) for a median of 313 days (mean, 481 days; range, 1–1977 days). Accounting for a pharmacologic effect duration of approximately 16 weeks after the last vedolizumab dose, 995 of these patients had been exposed to vedolizumab for at least 24 months. If the incidence of PML in patients receiving vedolizumab was similar to that in patients with multiple sclerosis receiving natalizumab (ie, >1 case in 500 patients) before the application of known risk-stratification factors (ie, therapy duration, previous immunosuppressive use, and JC virus seropositivity),[17] it is estimated that 6 to 7 cases would have been seen among vedolizumab-exposed patients. Although no PML cases have been reported in the integrated vedolizumab safety database, additional longer-term observational data are needed to exclude any potential of developing PML as a result of vedolizumab exposure.

In conclusion, vedolizumab was not statistically superior to placebo in achieving clinical remission at week 6 among patients with moderately to severely active CD and previous TNF antagonist failure. Several prespecified outcomes suggest that vedolizumab may lead to clinical remission in TNF antagonist–naive patients with CD and at 10 weeks in TNF antagonist–failure patients. These clinically relevant response kinetics have potential implications for bridging induction therapy to vedolizumab maintenance therapy, which has established efficacy, in patients with this lifelong condition. The safety profile of vedolizumab was generally similar to that of placebo in this short-term study and was consistent with that of longer-term vedolizumab use in previous studies.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2014.05.008.

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Author names in bold designate co-first authors.

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Reprint requests
Address requests for reprints to: Bruce E. Sands, MD, Icahn School of Medicine at Mount Sinai, 1468 Madison Ave. Box 1069, Annenberg 5, Room 12, New York, New York 10029. e-mail: bruce.sands@mssm.edu; fax: (646) 537-8647.

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Conflicts of interest
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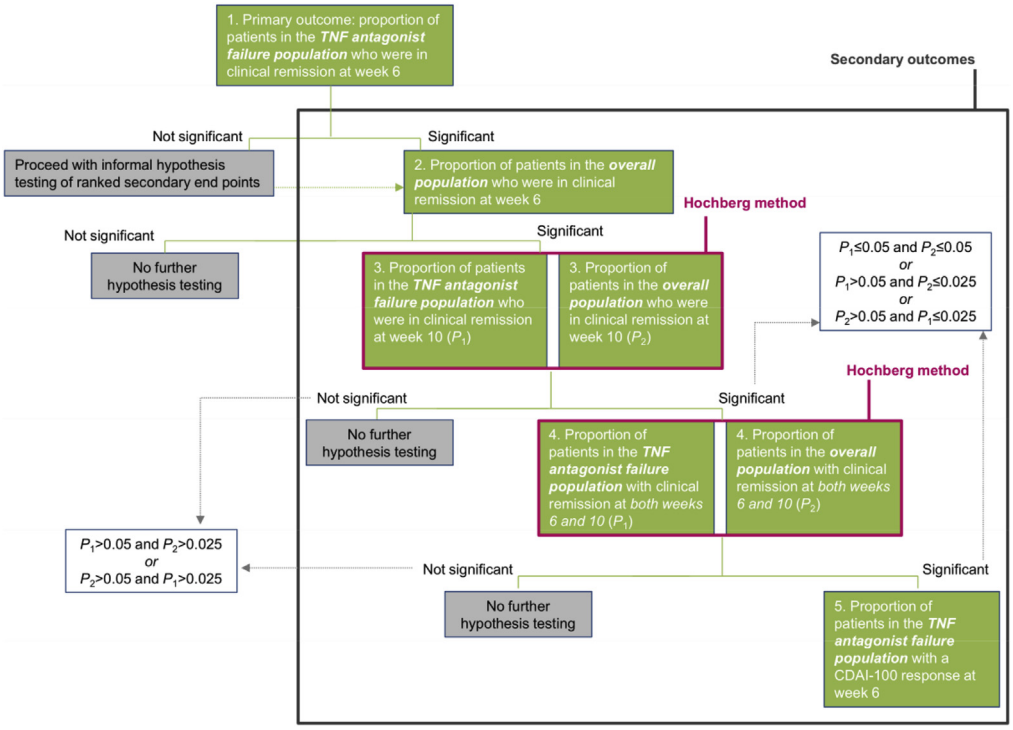
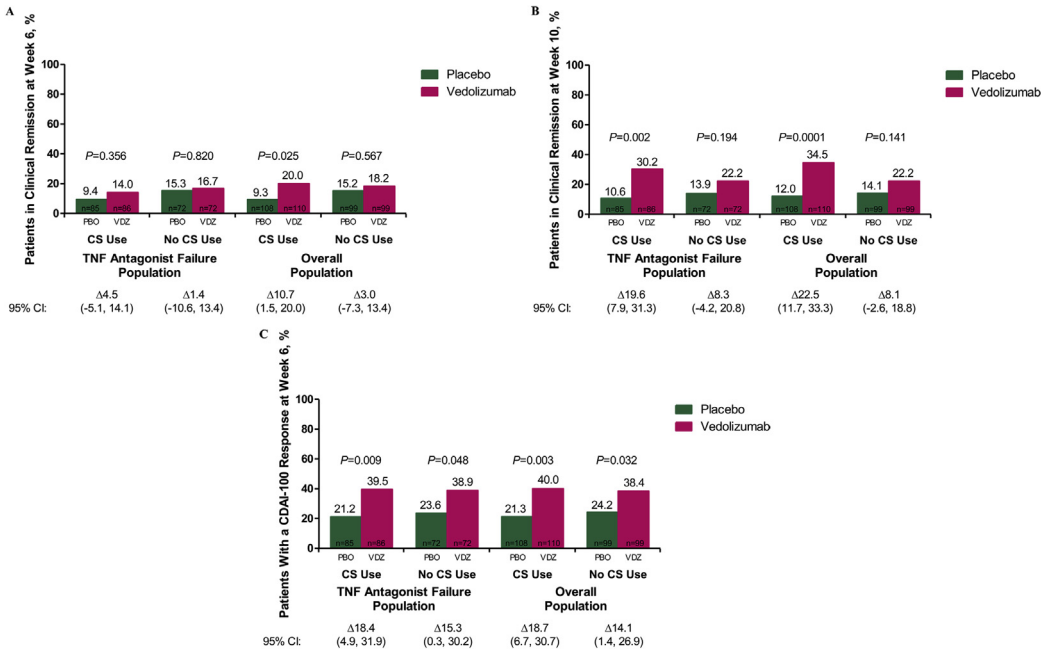
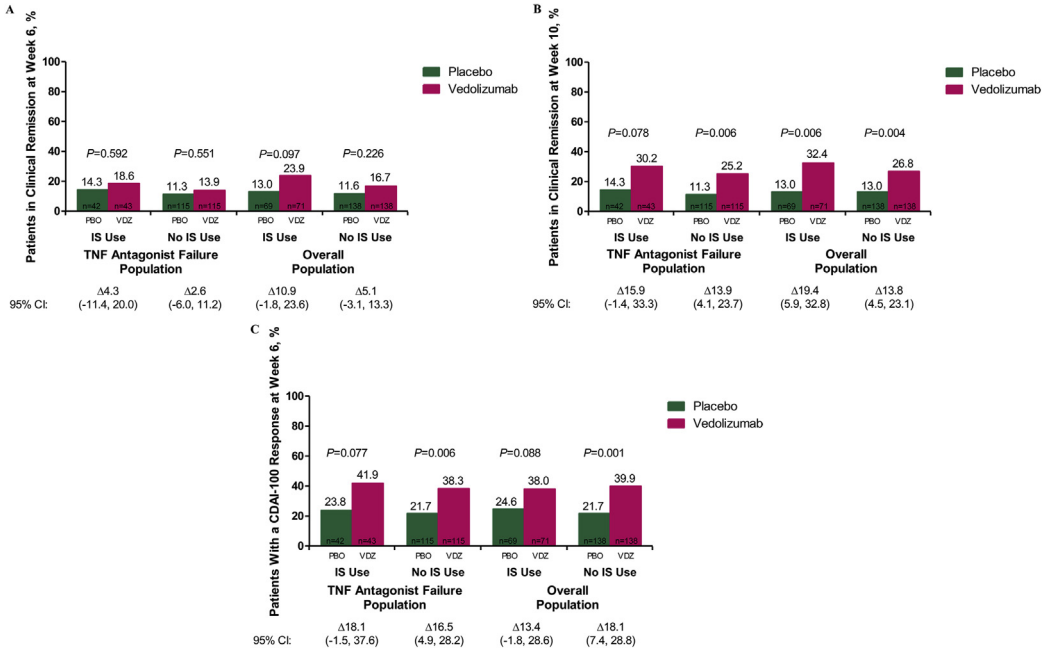


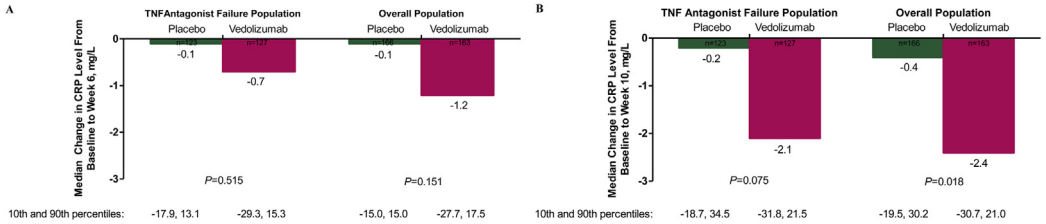
Supplementary Figure 1. Efficacy outcomes and testing order. CDAI, Crohn's Disease Activity Index; TNF, tumor necrosis factor.



Supplementary Figure 2. Clinical remission and CDAI-100 response by corticosteroid (CS) use: proportions of patients in clinical remission (CDAI score, ≤150 points) by CS use at (*A*) week 6 and (*B*) week 10 for the TNF antagonist–failure population and overall population; proportions of patients with a CDAI-100 response (≥100-point reduction from baseline in CDAI score) by CS use at (*C*) week 6 for the TNF antagonist–failure population and overall population. PBO, placebo; VDZ, vedolizumab.



Supplementary Figure 3. Clinical remission and CDAI-100 response by immunosuppressive (IS) use: proportions of patients in clinical remission (CDAI score, ≤150 points) by IS use at (*A*) week 6 and (*B*) week 10 for the TNF antagonist–failure population and overall population; proportions of patients with a CDAI-100 response (≥100-point reduction from baseline in CDAI score) by IS use at (*C*) week 6 for the TNF antagonist–failure population and overall population. PBO, placebo; VDZ, vedolizumab.



Supplementary Figure 4. Median changes in CRP concentration at (*A*) week 6 and (*B*) week 10 among patients with abnormal CRP concentrations (>2.87 mg/L) at baseline in the TNF antagonist–failure population and the overall population. CRP, C-reactive protein.

Supplementary Table 1. Definitions of Inadequate Response, Intolerance, and Loss of Response Over the Previous 5-Year Period[a]

Inadequate response to corticosteroids
Signs and symptoms of persistently active disease despite a history of at least one 4-week induction regimen that included a dose equivalent to prednisone 30 mg/day, orally for 2 weeks or intravenously for 1 week
OR
Two failed attempts to taper corticosteroids to below a dose equivalent to prednisone 10 mg/day, orally on 2 separate occasions
Intolerance to corticosteroids
History of intolerance to corticosteroids (including, but not limited to, Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, and infection)
Inadequate response to immunosuppressives
Signs and symptoms of persistently active disease despite a history of at least one 8-week regimen of azathioprine (≥1.5 mg/kg), 6-mercaptopurine (≥0.75 mg/kg), or methotrexate (≥12.5 mg/wk)
Intolerance to immunosuppressives
History of intolerance to ≥1 immunosuppressive (including, but not limited to, nausea/vomiting, abdominal pain, pancreatitis, liver function test abnormalities, lymphopenia, thiopurine methyltransferase genetic mutation, and infection)
Inadequate response to TNF antagonists
Signs and symptoms of persistently active disease despite a history of at least one 4-week induction regimen of 1 of the following agents
Infliximab: 5 mg/kg intravenously, 2 doses at least 2 weeks apart
Adalimumab: one 80-mg subcutaneous dose followed by one 40-mg dose ≥2 weeks apart
Certolizumab pegol: 400 mg subcutaneously, 2 doses ≥2 weeks apart
Intolerance to TNF antagonists
History of intolerance to at least 1 TNF antagonist (including, but not limited to, infusion-related reaction, demyelination, congestive heart failure, and infection)
Loss of response
Recurrence of symptoms during scheduled maintenance dosing after prior clinical benefit (discontinuation despite clinical benefit does not qualify)

[a]Patients who enrolled in the study had an inadequate response, did not respond or were intolerant to ≥1 corticosteroid, immunosuppressive, or TNF antagonist; US patients must have failed either immunosuppressive or TNF antagonist therapy (ie, not corticosteroids only).