Efficacy of Vedolizumab Induction and Maintenance Therapy in Patients With Ulcerative Colitis, Regardless of Prior Exposure to Tumor Necrosis Factor Antagonists

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BACKGROUND & AIMS: **The efficacy and safety of vedolizumab, a humanized immunoglobulin G1 monoclonal antibody against the integrin $\alpha4\beta7$, were demonstrated in multicenter, phase 3, randomized, placebo-controlled trials in patients with moderately to severely active ulcerative colitis (UC) or Crohn's disease. We analyzed data from 1 of these trials to determine the effects of vedolizumab therapy in patients with UC, based on past exposure to anti–tumor necrosis factor-α (TNF) antagonists.**

METHODS: **We performed a post hoc analysis of data from the GEMINI 1 study, collected from 464 patients who received vedolizumab or placebo but had not received a previous TNF antagonist (naive to TNF antagonists) and 367 patients with an inadequate response, loss of response, or intolerance to TNF antagonists (failure of TNF antagonists). Predefined outcomes of GEMINI 1 were evaluated in these subpopulations.**

RESULTS: **At Week 6, there were greater absolute differences in efficacy between vedolizumab and placebo in patients naive to TNF antagonists than patients with failure of TNF antagonists, although the risk ratios (RRs) for efficacy were similar for each group. Week 6 rates of response to vedolizumab and placebo were 53.1% and 26.3%, respectively, among patients naive to TNF antagonists (absolute difference, 26.4%; 95% confidence interval [CI], 12.4–40.4; RR, 2.0; 95% CI, 1.3–3.0); these rates were 39.0% and 20.6%, respectively, in patients with failure of TNF antagonists (absolute difference, 18.1%; 95% CI, 2.8–33.5; RR, 1.9; 95% CI, 1.1–3.2). During maintenance therapy, the absolute differences were similar but the RR for efficacy was higher for patients with failure of TNF antagonists than for patients naive to TNF antagonists, for most outcomes. Week 52 rates of remission with vedolizumab and placebo were 46.9% and 19.0%, respectively, in patients naive to TNF antagonists (absolute difference, 28.0%; 95% CI, 14.9–41.1; RR, 2.5; 95% CI, 1.5–4.0) and 36.1% and 5.3%, respectively, in patients with failure of TNF antagonists (absolute difference, 29.5%; 95% CI, 12.8–46.1; RR, 6.6; 95% CI, 1.7–26.5). No differences in adverse events were observed among groups.**

CONCLUSIONS: **Vedolizumab demonstrated significantly greater efficacy as induction and maintenance therapy for UC than placebo in patients naive to TNF antagonists and patients with TNF antagonist failure. There were numerically greater treatment differences at Week 6 among patients receiving vedolizumab who were naive to TNF antagonists than patients with TNF antagonist failure. ClinicalTrials.gov no: NCT00783718.**

Keywords: GEMINI; Inflammatory Bowel Disease; Treatment Failure; Biologic-Naive.

Abbreviations used in this paper: AD, absolute difference; ADA, antidrug antibodies; CI, confidence interval; ITT, intent-to-treat; MCS, Mayo Clinic score; PY, person-year; RR, risk ratios; TNF, tumor necrosis factor-α; TNF-failure, patients with prior TNF antagonist failure; TNF-naive, patients without prior TNF antagonist therapy; UC, ulcerative colitis.

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Ulcerative colitis (UC) is a chronic disease that results from uncontrolled inflammation of the colon. Patients experience bloody diarrhea, abdominal cramps, fatigue, and impaired health-related quality of life.[1] Although no cure exists, tumor necrosis factor-α (TNF) antagonist therapy has greatly improved medical management. However, the most effective treatments currently available fail to adequately control disease activity in many patients. Approximately 50% of patients with UC do not respond to induction therapy with TNF antagonists[2–4] or lose response over time such that after 1 year of treatment, clinical remission is observed in only 17% to 34% of patients.[2,3,5] Furthermore, the risk of serious infection (with immunosuppressants in general, and TNF antagonists specifically) is an important concern.[6,7] Thus, alternative approaches to treatment are needed.

Vedolizumab is a novel, gut-selective humanized immunoglobulin G_1 monoclonal antibody to the $\alpha_4\beta_7$ integrin that inhibits adhesion of a gut-homing subset of T lymphocytes to mucosal addressin cell adhesion molecule 1. This mechanism selectively downregulates gut inflammation while preserving systemic immune responses.[8–14] The efficacy and safety of vedolizumab induction and maintenance treatment were demonstrated in the phase 3 GEMINI 1 and GEMINI 2 studies of patients with moderately to severely active UC or Crohn's disease, respectively.[15] Here in the prespecified exploratory and post hoc analyses of GEMINI 1 data, we report the efficacy and safety of vedolizumab in patient subgroups based on their TNF antagonist treatment history.

Methods

Study Design

These results are based on subgroup analyses of data from the multicenter, phase 3, randomized, placebo-controlled GEMINI 1 trial of vedolizumab in patients with moderately to severely active UC (ClinicalTrials.gov, NCT00783718). Details of the study design are reported elsewhere.[15] Briefly, 374 patients were randomized, in a 3:2 ratio, to receive intravenous vedolizumab or placebo induction therapy on Days 1 and 15 (Cohort 1; induction intent-to-treat [ITT] population) (Supplementary Figure 1B). To fulfill sample size requirements for the subsequent maintenance trial, 521 additional patients were enrolled in an open-label group (Cohort 2) and received the same vedolizumab induction regimen as administered in the blinded study. Disease activity was defined using the Mayo Clinic score (MCS), which includes assessment of stool frequency, rectal bleeding, endoscopy, and physician's global assessment. The complete MCS ranges from 0 to 12, with higher scores indicating more active disease. Eligible patients had UC for $\geq$6 months before enrollment, MCS from 6 to 12, and endoscopic subscores of $\geq$2 within 7 days before the first dose of study drug, and evidence of disease extending $\geq$15 cm proximal to the rectum.

Vedolizumab-treated patients from both cohorts with a clinical response at Week 6 were rerandomized (1:1:1) to receive vedolizumab every 8 weeks or every 4 weeks or placebo beginning at Week 6 for up to 46 weeks (maintenance ITT population) (Supplementary Figure 1). Clinical response was defined as a reduction in the MCS of $\geq$3 points and $\geq$30% from baseline (Week 0), with an accompanying decrease of $\geq$1 point in the rectal bleeding subscore or absolute rectal bleeding subscore of 0 or 1. Patients who failed to respond to vedolizumab at Week 6 continued vedolizumab therapy every 4 weeks during maintenance. Patients who had received placebo during induction continued to receive placebo during maintenance or discontinued (Supplementary Figure 1). Patients were evaluated at Weeks 2, 4, and 6 during induction therapy and every 4 weeks thereafter until Week 52.[15]

As part of the eligibility criteria for GEMINI 1, patients had demonstrated, within the previous 5-year period, an inadequate response to, loss of response to, or intolerance of $\geq$1 of the following therapies: corticosteroids (outside the United States only), immunosuppressives (azathioprine or mercaptopurine), and/or infliximab, because this was the only TNF antagonist approved for the treatment of UC at the time of enrollment. An inadequate response to infliximab was defined as signs and symptoms of active disease despite at least one 4-week induction regimen of 2 doses of infliximab at 5 mg/kg intravenously, $\geq$2 weeks apart. Loss of response was defined as the recurrence of symptoms in a patient who had previously benefited from infliximab, and patients with intolerance had experienced treatment-related toxicity (eg, an infusion-related reaction, psoriasiform skin lesion, demyelination, congestive heart failure, infection, or other clinically meaningful adverse events). In the present analyses, the TNF-failure population comprised an aggregate of patients with inadequate response, loss of response, or intolerance to prior TNF antagonist treatment as predefined according to data captured on the case report form at baseline (Week 0) (Supplementary Figure 1B). For classification purposes, we arbitrarily declared in a hierarchical fashion that an inadequate response was considered worse than loss of response and loss of response was considered worse than intolerance. However, patients could have more than one type of failure and were evaluated by each type of failure in the present analyses. Finally, the TNF-naive population comprised patients who had never received a TNF antagonist as defined according to data captured on the interactive voice response system during screening and enrollment (Supplementary Figure 1B). Patients with prior exposure to a TNF antagonist without prior failure were excluded from the analyses; patients without prior exposure on the interactive voice response system, but who had prior

TNF antagonist failure on the case report form, were included in both TNF-naive and TNF-failure populations (Supplementary Figure 1B).

Efficacy Evaluation

In GEMINI 1, the primary outcome measure for induction therapy was a clinical response at Week 6. Secondary outcome measures were clinical remission (MCS of $\leq$2 and no subscore $>$1) and mucosal healing (Mayo Clinic endoscopic subscore of 0 or 1) at Week 6. The primary outcome for maintenance therapy was clinical remission at Week 52. Secondary measures were durable clinical response (clinical response at both Weeks 6 and 52), durable clinical remission (clinical remission at both Weeks 6 and 52), mucosal healing at Week 52, and corticosteroid-free remission at Week 52 in patients receiving corticosteroids at baseline.

In prespecified exploratory and post hoc analyses, the efficacy outcomes were evaluated in the TNF-failure and TNF-naive ITT populations, respectively. Comparisons between the treatment arms within each population were made using descriptive statistical techniques. Specifically, the absolute difference (AD) in percentages for vedolizumab and placebo and the risk ratios (RRs) were calculated for each of the dichotomous outcomes along with 95% confidence intervals (CIs). The AD was calculated using adjusted percentages based on the Cochran-Mantel-Haenszel chi-square test, with stratification according to (1) concomitant use of oral corticosteroids (yes/no), (2) previous exposure to a TNF antagonist and/or concomitant immunosuppressant use (yes/no), and additionally for Week 52 endpoints (3) enrollment in Cohort 1 or Cohort 2 in the induction phase. The RR was defined as the probability of a successful outcome with vedolizumab treatment divided by the probability of a successful outcome with placebo, adjusted for the randomization stratification factors. A RR $>$1 indicates greater efficacy with vedolizumab. RRs were considered significant if the 95% CI did not contain zero.[16] Given that the vedolizumab every-8-week and every-4-week dosing groups had similar treatment outcomes in the overall study and are generally considered to be clinically equivalent,[15] the 2 groups were evaluated as a combined vedolizumab treatment group to generate more statistically precise estimates.

Safety Evaluations

Safety data included the incidence, severity, and type of adverse events, and findings from laboratory tests and physical examinations. Adverse events were classified by preferred terms defined by the *Medical Dictionary for Regulatory Activities*, version 14.0,[17] and analyzed in the safety population, which included patients who received vedolizumab at any time during the study and patients who received placebo only.

Adverse events were reported as the number of patients experiencing the *Medical Dictionary for Regulatory Activities* preferred term per 1000 person-years (PYs) of exposure. PYs of exposure up to the first occurrence of each adverse event were calculated using *Equation 1*. For patients who did not experience the event, PYs of exposure were calculated using *Equation 2* to account for 16 weeks postdose for vedolizumab clearance or using *Equation 3* if the patient continued in the open-label extension study (ClinTrials.gov, NCT00790933). Thus, the total PYs of exposure differs for each preferred term because the number of PYs was truncated after a patient experienced the event of interest.

$$\text{Equation 1}: PYs = (\textit{Adverse event onset date}) - (\textit{Date of first dose}) + 1$$

$$\text{Equation 2}: PYs = (\textit{Date of last dose}) + (16\ \textit{weeks} \times 7\textit{days}) - (\textit{Date of first dose}) + 1$$

$$\text{Equation 3}: PYs = (\textit{Date of last dose}) - (\textit{Date of first dose}) + 1$$

Immunogenicity

Blood samples for the evaluation of antidrug antibodies (ADA) were collected within 30 minutes before dosing. Immunogenicity in the total GEMINI 1 population was determined as described elsewhere.[18] In post hoc analyses, the development of ADA in the TNF-naive and TNF-failure subpopulations was determined. The proportions of patients who had $\geq$1 positive sample and of those who had $\geq$2 consecutive samples were reported.

Results

Patients

In GEMINI 1, a total of 1406 patients were screened and 895 were enrolled in the study and randomized to treatment (Supplementary Figure 1). Approximately half (52%; n = 464) of participants were TNF antagonist naive and the remainder had been exposed to TNF antagonist therapy, with 41% (n = 367) of the total enrolled population having failed therapy according to the predefined criteria. Of note, 74 patients (15, 15, and 44 from the placebo, vedolizumab Cohort 1, and Cohort

2 treatment arms, respectively) had prior exposure without prior failure; these patients were excluded from the present analyses. Because the study protocol's predefined criteria for TNF-naive and TNF-failure status came from different sources (ie, the interactive voice response system and case report form, respectively), 10 patients (5, 2, and 3 from the placebo, vedolizumab Cohort 1, and vedolizumab Cohort 2 treatment arms, respectively) were included in both subgroups (Supplementary Figure 1). When ranked by worst outcome for the placebo group, vedolizumab Cohort 1, and Cohort 2, most prior failures were caused by inadequate response (46%, 54%, and 46%, respectively) followed by loss of response (41%, 39%, and 37%, respectively) and intolerance (13%, 7%, and 16%, respectively) (Table 1).

Patient demographics and disease characteristics at Week 0 are summarized by induction treatment group (Table 1) and maintenance ITT group (Supplementary Table 1) for TNF-naive and TNF-failure patients. Overall, the baseline demographics were similar for patients in the vedolizumab and placebo groups.

Induction Treatment in Tumor Necrosis Factor–Naive and Tumor Necrosis Factor–Failure Patients

In both TNF-naive and TNF-failure subgroups, vedolizumab therapy resulted in higher percentages of patients with clinical response, in clinical remission, and with mucosal healing at Week 6 than treatment with placebo (Table 2). TNF-naive patients had relatively higher rates of treatment response to vedolizumab induction therapy than those observed in the TNF-failure population; however, the RRs were similar (Table 2). At Week 6, 53.1% of TNF-naive patients who received vedolizumab had a clinical response (primary outcome measure) versus 26.3% of those assigned to placebo (AD: 26.4%; 95% CI, 12.4–40.4; RR: 2.0; 95% CI, 1.3–3.0). Corresponding response rates in the TNF-failure population were 39.0% versus 20.6% (AD: 18.1%; 95% CI, 2.8–33.5; RR: 1.9; 95% CI, 1.1–3.2) (Table 2). Similar observations were made for rates of clinical remission and mucosal healing (Table 2). The benefit of vedolizumab treatment in the subtypes of

Table 1. Patient Demographics and Disease Characteristics at Week 0 (Induction Population)

	TNF-naive patients[a]			TNF-failure patients[a]		
Characteristic	Placebo (n = 76)	Vedolizumab Cohort 1 (n = 130)	Vedolizumab Cohort 2 (n = 258)	Placebo (n = 63)	Vedolizumab Cohort 1 (n = 82)	Vedolizumab Cohort 2 (n = 222)
Age, *y*, mean ± SD	40.5 ± 11.7	39.7 ± 13.1	40.6 ± 13.6	41.8 ± 13.1	39.7 ± 12.5	40.2 ± 13.2
Male sex, n (%)	47 (62)	69 (53)	151 (59)	35 (56)	50 (61)	122 (55)
Weight, *kg*, mean ± SD	70.0 ± 18.8	69.2 ± 16.6	72.7 ± 19.4	74.2 ± 16.4	74.9 ± 17.0	75.3 ± 19.8
BMI, kg/m^2, mean ± SD	24.3 ± 5.7	24.1 ± 4.7	25.1 ± 6.2	25.0 ± 4.5	25.6 ± 5.0	25.5 ± 6.1
Current smoker, n (%)	7 (9)	7 (5)	17 (7)	1 (2)	4 (5)	15 (7)
Disease duration, *y*, mean ± SD	6.1 ± 6.4	5.8 ± 5.2	6.4 ± 6.2	8.0 ± 7.6	6.4 ± 5.0	8.0 ± 7.0
Mayo Clinic score, mean ± SD	8.5 ± 1.5	8.4 ± 1.8	8.5 ± 1.7	8.6 ± 1.9	8.7 ± 1.8	8.6 ± 1.8
fCal, *μg/g*, mean ± SD	2714 ± 3408	2357 ± 3595	1493 ± 1980	2196 ± 3256	3008 ± 4270	1306 ± 1604
Disease localization, n (%)						
Proctosigmoiditis	10 (13)	14 (11)	43 (17)	8 (13)	10 (12)	23 (10)
Left-sided colitis	35 (46)	66 (51)	99 (38)	20 (32)	19 (23)	76 (34)
Extensive colitis	7 (9)	14 (11)	33 (13)	9 (14)	10 (12)	24 (11)
Pancolitis	24 (32)	36 (28)	83 (32)	26 (41)	43 (52)	99 (45)
Concomitant medications, n (%)						
CS only	28 (37)	42 (32)	98 (38)	27 (43)	30 (37)	81 (36)
IS only	10 (13)	24 (18)	68 (26)	6 (10)	5 (6)	37 (17)
CS and IS	16 (21)	31 (24)	33 (13)	8 (13)	13 (16)	33 (15)
No CS and IS	22 (29)	33 (25)	59 (23)	22 (35)	34 (41)	71 (32)
Prednisone-equivalent dose, *mg*, median (min, max)	20.0 (5.0–40.0)	20.0 (2.5–40.0)	20.0 (0.6–80.0)	15.0 (5.0–30.0)	20.0 (5.0–30.0)	20.0 (1.0–176.3)
Type of TNF failure, n (%)[b]						
Inadequate response	N/A	N/A	N/A	29 (46)	44 (54)	103 (46)
Loss of response	N/A	N/A	N/A	26 (41)	32 (39)	83 (37)
Intolerance	N/A	N/A	N/A	8 (13)	6 (7)	36 (16)

BMI, body mass index; CRF, case report form; CS, corticosteroid; fCal, fecal calprotectin; IS, immunosuppressant; IVRS, interactive voice response system; N/A, not applicable; SD, standard deviation; TNF, tumor necrosis factor-α antagonist.

[a]TNF-naive patients were classified by data captured on the IVRS at screening and enrollment. Prior TNF failure was defined by data recorded on the CRF at Week 0. Patients without prior exposure on the IVRS, but who had prior TNF antagonist failure on the CRF, were included in both TNF-naive and TNF-failure populations.

[b]Each patient was counted only once according to his or her worst outcome. Inadequate response was considered worse than lost response; lost response was considered worse than intolerance.

Table 2. Outcome Measures at Week 6 and Week 52

Outcome	TNF-naive[a]				TNF-failure[a]				All patients[b]			
	Patients, n (%)		%-Point difference (95% CI)[c]	RR (95% CI)[c]	Patients, n (%)		%-Point difference (95% CI)[c]	RR (95% CI)[c]	Patients, n (%)		%-Point difference (95% CI)[c]	RR (95% CI)[c]
	Placebo	Vedolizumab			Placebo	Vedolizumab			Placebo	Vedolizumab		
Week 6	n = 76	n = 130			n = 63	n = 82			n = 149	n = 225		
Clinical response[d]	20 (26.3)	69 (53.1)	26.4 (12.4 to 40.4)	2.0 (1.3 to 3.0)	13 (20.6)	32 (39.0)	18.1 (2.8 to 33.5)	1.9 (1.1 to 3.2)	38 (25.5)	106 (47.1)	21.7 (11.6 to 31.7)	1.8 (1.4 to 2.5)
Clinical remission[e]	5 (6.6)	30 (23.1)	15.5 (5.1 to 25.9)	3.2 (1.3 to 7.9)	2 (3.2)	8 (9.8)	7.0 (-1.3 to 15.2)	3.2 (0.7 to 14.5)	8 (5.4)	38 (16.9)	11.5 (4.7 to 18.3)	3.1 (1.5 to 6.6)
Mucosal healing[f]	19 (25.0)	64 (49.2)	23.9 (10.0 to 37.7)	2.0 (1.3 to 3.0)	13 (20.6)	25 (30.5)	9.9 (-4.7 to 24.4)	1.5 (0.8 to 2.6)	37 (24.8)	92 (40.9)	16.1 (6.4 to 25.9)	1.6 (1.2 to 2.3)
Week 52	n = 79	n = 145			n = 38	n = 83			n = 126	n = 247		
Clinical remission[e]	15 (19.0)	68 (46.9)	28.0 (14.9 to 41.1)	2.5 (1.5 to 4.0)	2 (5.3)	30 (36.1)	29.5 (12.8 to 46.1)	6.6 (1.7 to 26.5)	20 (15.9)	107 (43.3)	27.7 (17.6 to 37.8)	2.7 (1.8 to 4.2)
Durable clinical response[g]	21 (26.6)	88 (60.7)	34.3 (20.7 to 47.8)	2.3 (1.6 to 3.4)	6 (15.8)	37 (44.6)	26.4 (8.5 to 44.3)	2.6 (1.2 to 5.7)	30 (23.8)	134 (54.3)	30.6 (20.1 to 41.2)	2.3 (1.6 to 3.2)
Mucosal healing[f]	19 (24.1)	87 (60.0)	35.9 (22.3 to 49.5)	2.5 (1.6 to 3.8)	3 (7.9)	37 (44.6)	34.9 (17.1 to 52.8)	5.4 (1.8 to 16.3)	25 (19.8)	133 (53.8)	34.2 (23.7 to 44.8)	2.7 (1.9 to 4.0)
Durable clinical remission[h]	10 (12.7)	37 (25.5)	12.8 (1.8 to 23.8)	2.0 (1.1 to 3.8)	1 (2.6)	14 (16.9)	13.4 (0.4 to 26.3)	5.5 (0.8 to 38.2)	11 (8.7)	55 (22.3)	13.6 (5.5 to 21.8)	2.6 (1.4 to 4.7)
	n = 43	n = 83			n = 23	n = 45			n = 72	n = 143		
Corticosteroid-free remission[i]	8 (18.6)	37 (44.6)	26.3 (8.7 to 43.9)	2.4 (1.2 to 4.7)	1 (4.3)	12 (26.7)	21.3 (1.7 to 40.8)	5.9 (0.8 to 43.5)	10 (13.9)	55 (38.5)	24.6 (11.7 to 37.6)	2.8 (1.5 to 5.1)

CRF, case report form; IVRS, interactive voice response system; RR, risk ratio; TNF, tumor necrosis factor-α antagonist.

[a]TNF-naive patients were classified by data captured on the IVRS at screening and enrollment. Prior TNF failure was defined by data recorded on the CRF at Week 0. Patients without prior exposure on the IVRS, but who had prior TNF antagonist failure on the CRF, were included in both TNF-naive and TNF-failure populations.

[b]Week 6 data for all patients previously reported in Feagan et al[15] and are shown here for comparison; represents the total population, including patients who may have had prior exposure, but not failure to a TNF antagonist.

[c]Adjusted based on the Cochran-Mantel-Haenszel chi-square test, with stratification according to (1) concomitant use of oral corticosteroids (yes/no), (2) previous exposure to TNF antagonist and/or concomitant immunomodulator use (yes/no), and additionally for Week 52 endpoints (3) enrollment in Cohort 1 or Cohort 2 in the induction phase.

[d]Defined as reduction in complete Mayo score of $\geq$3 points and $\geq$30% from baseline with an accompanying decrease in rectal bleeding subscore of $\geq$1 point or absolute rectal bleeding subscore of $\leq$1 point.

[e]Defined as complete Mayo score of $\leq$2 points and no individual subscore $>$1 point.

[f]Defined as Mayo endoscopic subscore of $\leq$1.

[g]Defined as clinical response at both Weeks 6 and 52.

[h]Defined as clinical remission at both Weeks 6 and 52.

[i]Defined as patients using oral corticosteroids at baseline who have discontinued corticosteroids and are in clinical remission at Week 52.

TNF-failure patients was most apparent in patients with loss of response to a TNF antagonist; however, results from the subgroup analyses should be interpreted with caution based on the relatively small number of patients available (Figure 1).

Maintenance Treatment in Tumor Necrosis Factor–Naive and Tumor Necrosis Factor–Failure Patients

At Week 52, a significantly higher percentage of vedolizumab-treated patients were in clinical remission, durable clinical remission, and corticosteroid-free remission and had a durable clinical response and mucosal healing than patients assigned to placebo (Table 2). In distinction to the induction study, the magnitude of treatment difference between vedolizumab and placebo was similar for both the TNF-naive and TNF-failure populations for almost all outcomes, with the exception that the AD for durable clinical response was lower in TNF-failure patients (Table 2). In addition, the RRs with vedolizumab exposure for the TNF-failure subgroup were more than 2 times the RRs for the TNF-naive subgroup for all Week 52 outcomes excluding durable clinical response (Table 2).

For the primary outcome measure, 46.9% of TNF-naive patients were in clinical remission after 52 weeks of vedolizumab treatment versus 19.0% of those who received placebo (AD: 28.0%; 95% CI, 14.9–41.1; RR: 2.5; 95% CI, 1.5–4.0). Corresponding values in the TNF-failure population were 36.1% versus 5.3% (AD: 29.5%; 95% CI, 12.8–46.1; RR: 6.6; 95% CI, 1.7–26.5) (Table 2). Among patients receiving corticosteroids at

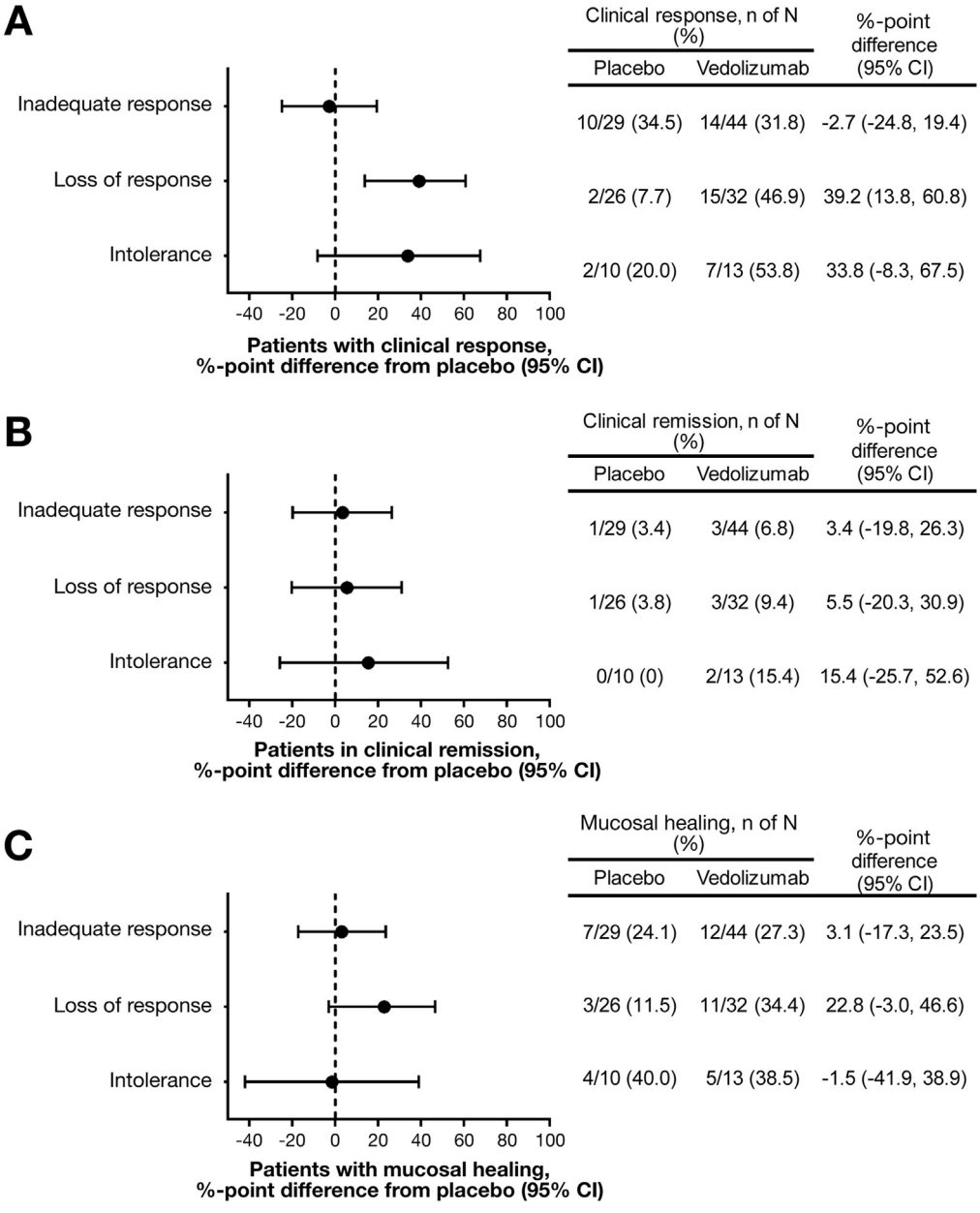


Figure 1. Induction endpoints in TNF-failure patients by type of failure. Forest plots show difference from placebo and 95% CIs for percentages of patients (*A*) with clinical response, (*B*) in clinical remission, and (*C*) with mucosal healing at Week 6. Patients with more than one type of TNF antagonist failure were evaluated by each type of failure; thus the number of patients in the subgroups may total more than the number of enrolled patients. CI, confidence interval; TNF, tumor necrosis factor-α antagonist.

baseline, 44.6% of TNF-naive patients were in remission and corticosteroid-free following vedolizumab maintenance treatment versus 18.6% of those who received placebo (AD: 26.3%; 95% CI, 8.7–43.9; RR: 2.4; 95% CI, 1.2–4.7) (Table 2). Corresponding values for TNF-failure patients were 26.7% versus 4.3% (AD: 21.3%; 95% CI, 1.7–40.8; RR: 5.9; 95% CI, 0.8–43.5) (Table 2). Results for the every-8-week and every-4-week dosing groups separately are given in Supplementary Table 2.

In general, although the numbers of patients in the subgroups were small, efficacy endpoints at Week 52 favored vedolizumab treatment over placebo irrespective of the type of TNF failure (Figure 2). However, TNF-failure patients with loss of response had the lowest percentages meeting Week 52 endpoints with maintenance vedolizumab therapy than any other classification of failure (Figure 2).

Safety

No clinically important differences in safety were observed between the vedolizumab and placebo treatment groups (Table 3 and Supplementary Table 3). The proportion of TNF-naive patients with adverse events and serious adverse events with maintenance vedolizumab therapy were 74% and 9%, respectively, versus 75% and 16%, respectively, for placebo (Table 3). The proportion of TNF-failure patients with adverse events and serious adverse events was 88% and 17%, respectively, with vedolizumab and 84% and 11%, respectively, with placebo (Table 3). When adjusted for exposure, adverse events and serious adverse events occurred in more patients per 1000 PYs with placebo than with vedolizumab in both TNF-naive and TNF-failure subgroups (Table 3). Overall, more individual events occurred with an exposure-adjusted incidence rate of $\geq$100 patients per 1000 PYs with vedolizumab treatment in the TNF-failure population (ie, arthralgia, fatigue, nausea, cough, oropharyngeal pain, and bronchitis) than in patients who were TNF-naive (Table 3).

Immunogenicity

Among all patients treated with vedolizumab continuously (ITT and non-ITT combined), 15 (6%) TNF-failure patients were ADA-positive and 3 (1%) patients were persistently positive (ie, had 2 or more consecutive ADA-positive samples). Among those who were TNF antagonist naive, 9 (3%) had at least 1 ADA-positive sample and 3 (1%) patients were persistently ADA-positive.

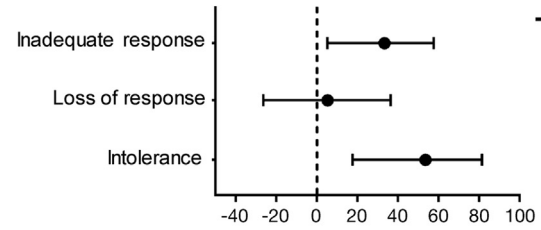
Discussion

These analyses show that vedolizumab had a consistent benefit for inducing and maintaining clinical response and remission in both TNF-naive and TNF-failure patients with moderately to severely active UC. Furthermore, no increased rates of serious infections were observed with vedolizumab treatment relative to placebo in either subgroup. The data also highlight that, in absolute terms, greater efficacy was evident for vedolizumab induction therapy in TNF-naive patients than those who had previously failed a TNF antagonist. The AD in Week 6 remission rates was higher in patients who were TNF-naive (AD, 15.5%) compared with those who had failed therapy (AD, 7.0%). In contrast, in the maintenance phase of the trial, the AD in remission rates observed between these populations and placebo was the same, supporting the notion that similar clinically meaningful effects are observed among both TNF-failure and TNF-naive populations.

It is notable that, in maintenance, the absolute remission rates were substantially lower in the TNF-failure population for both vedolizumab-treated patients and those assigned to placebo. In the latter group, the rate of remission at Week 52 was 5.3%. However, inspection of the RRs for clinical remission at Week 52 is consistent with the presence of a relatively greater response to vedolizumab in the TNF-failure population (TNF-failure: RR, 6.6; 95% CI, 1.7–26.5 vs TNF-naive, RR, 2.5; 95% CI, 1.5–4.0). This relative difference should be interpreted with caution given that the comparison was not prespecified and the RR estimate for the TNF-failure population is imprecise. The relatively low placebo response rate in the TNF-failure group could be attributed to the presence of a greater proportion of patients with more refractory disease and poor prognostic factors, such as pancolitis and long disease duration.[19] However, the high RR values with assignment to vedolizumab in this relatively refractory group of patients is more difficult to explain. One possibility is that failure of a TNF antagonist selected for a group of patients who were more likely to respond to vedolizumab in the long term on a mechanistic basis and, therefore, had relatively poor results if assigned to placebo during the maintenance phase of the trial. This possibility should be evaluated in well-designed translational medicine studies.

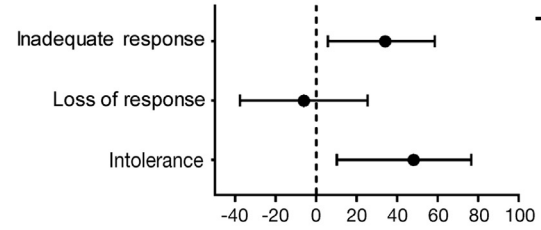
At the time of GEMINI 1 study enrollment, infliximab was the only TNF antagonist approved for the treatment of UC. Although treatment options in the class now include adalimumab[3] and golimumab,[4,5] experience in Crohn's disease and UC has documented relatively lower efficacy when these TNF antagonists are used as second-line treatment for infliximab-failure patients.[20–22] Although largely speculative, several potential explanations exist for this experience, including the possibility that inflammation in these patients may be predominately driven by mechanisms other than TNF; that failure patients may be more likely to have poor pharmacokinetics, which may be particularly problematic for subcutaneously administered therapies; and that development of immunogenicity to infliximab may predispose patients to sensitization with other members of the anti-TNF class.[23,24] Although therapeutic drug monitoring (ie, measurement of drug and ADA

A



	Clinical remission, n of N (%)		%-point difference (95% CI)
	Placebo	Vedolizumab	
Inadequate response	0/19 (0)	11/33 (33.3)	33.3 (5.2, 57.7)
Loss of response	2/13 (15.4)	7/34 (20.6)	5.2 (-26.5, 36.4)
Intolerance	1/10 (10.0)	14/22 (63.6)	53.6 (17.5, 81.3)

B



	Durable clinical response, n of N (%)		%-point difference (95% CI)
	Placebo	Vedolizumab	
Inadequate response	1/19 (5.3)	13/33 (39.4)	34.1 (5.8, 58.5)
Loss of response	5/13 (38.5)	11/34 (32.4)	-6.1 (-37.6, 25.4)
Intolerance	2/10 (20.0)	15/22 (68.2)	48.2 (10.3, 76.6)

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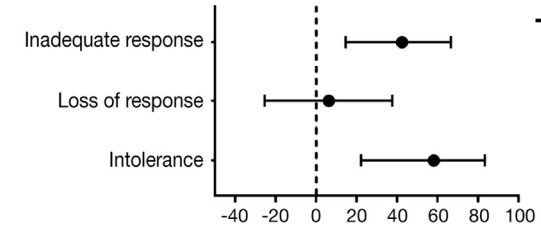
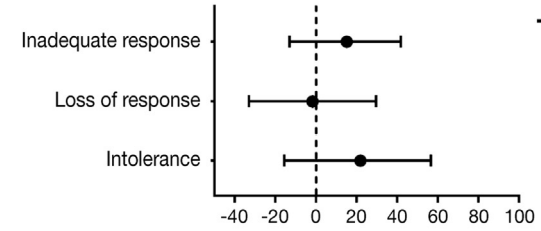


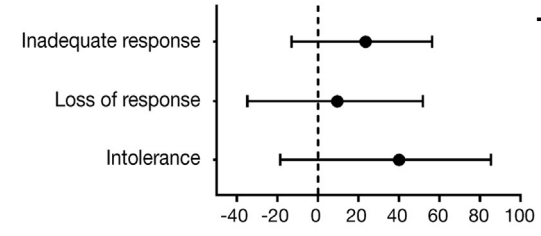
	Mucosal healing, n of N (%)		%-point difference (95% CI)
	Placebo	Vedolizumab	
Inadequate response	0/19 (0)	14/33 (42.4)	42.4 (14.5, 66.5)
Loss of response	3/13 (23.1)	10/34 (29.4)	6.3 (-25.4, 37.6)
Intolerance	1/10 (10.0)	15/22 (68.2)	58.2 (22.2, 83.3)

D



	Durable clinical remission, n of N (%)		%-point difference (95% CI)
	Placebo	Vedolizumab	
Inadequate response	0/19 (0)	5/33 (15.2)	15.2 (-13.1, 41.8)
Loss of response	1/13 (7.7)	2/34 (5.9)	-1.8 (-33.0, 29.5)
Intolerance	1/10 (10.0)	7/22 (31.8)	21.8 (-15.6, 56.6)

E



	CS-free remission, n of N (%)		%-point difference (95% CI)
	Placebo	Vedolizumab	
Inadequate response	0/12 (0)	4/17 (23.5)	23.5 (-13.0, 56.4)
Loss of response	1/7 (14.3)	5/21 (23.8)	9.5 (-34.7, 51.8)
Intolerance	0/5 (0)	4/10 (40.0)	40.0 (-18.6, 85.3)

Figure 2. Maintenance endpoints in TNF-failure patients by type of failure. Forest plots show difference from placebo and 95% CIs for percentages of patients (*A*) in clinical remission, (*B*) with durable clinical response, (*C*) with mucosal healing, (*D*) with durable clinical remission, and (*E*) in corticosteroid-free remission at Week 52. Patients with more than one type of TNF antagonist failure were evaluated by each type of failure; thus the number of patients in the subgroups may total more than the number of enrolled patients. CI, confidence interval; CS, corticosteroid; TNF, tumor necrosis factor-α antagonist.

Table 3. Summary of Adverse Events Reported by TNF-Naive and TNF-Failure Patients (Maintenance Safety Population)

	TNF-naive patients[a]				TNF-failure patients[a]			
	Placebo[b] (n = 76)		Vedolizumab[c] (n = 309)		Placebo[b] (n = 63)		Vedolizumab[c] (n = 266)	
	Total PY[d] = 42.98 days		Total PY[d] = 236.42 days		Total PY[d] = 25.38 days		Total PY[d] = 172.04 days	
Event	Patients with event, n (%)	Patients with event, n/1000 PY	Patients with event, n (%)	Patients with event, n/1000 PY	Patients with event, n (%)	Patients with event, n/1000 PY	Patients with event, n (%)	Patients with event, n/1000 PY
Any adverse event	57 (75)	2832.2	228 (74)	2146.1	53 (84)	7283.0	233 (88)	4895.5
Any serious adverse event	12 (16)	310.1	28 (9)	121.8	7 (11)	297.3	44 (17)	274.1
Any serious infection[e]	3 (4)	72.3	4 (1)	17.0	2 (3)	80.3	8 (3)	47.2
Common adverse events (≥100 patients with event/1000 PY in any patient group shown)[f]								
Exacerbation of UC	16 (21)	394.6	36 (12)	156.9	11 (17)	457.5	54 (20)	335.2
Nasopharyngitis	3 (4)	70.4	26 (8)	114.9	8 (13)	333.2	46 (17)	309.8
Headache	3 (4)	72.1	33 (11)	152.8	10 (16)	448.5	40 (15)	267.8
Arthralgia	3 (4)	72.7	22 (7)	97.1	5 (8)	208.9	28 (11)	174.8
Upper respiratory tract infection	5 (7)	120.2	24 (8)	106.7	3 (5)	118.2	26 (10)	161.1
Fatigue	0	0.0	9 (3)	38.8	5 (8)	212.2	20 (8)	123.8
Nausea	6 (8)	145.5	16 (5)	70.0	7 (11)	310.1	20 (8)	121.9
Cough	5 (7)	124.0	14 (5)	61.2	2 (3)	79.4	18 (7)	111.2
Oropharyngeal pain	1 (1)	23.5	7 (2)	30.2	2 (3)	80.9	17 (6)	104.1
Bronchitis	1 (1)	23.3	7 (2)	30.0	4 (6)	172.8	17 (6)	102.9
Pyrexia	1 (1)	23.2	8 (3)	34.4	4 (6)	163.8	15 (6)	90.7
Vomiting	2 (3)	47.2	11 (4)	47.6	4 (6)	164.0	14 (5)	83.7
Abdominal pain	3 (4)	72.3	20 (6)	87.5	6 (10)	263.2	14 (5)	83.0
Back pain	3 (4)	72.1	10 (3)	43.0	3 (5)	124.4	12 (5)	72.0
Edema peripheral	1 (1)	23.7	3 (<1)	12.8	5 (8)	220.9	12 (5)	71.8
Anemia	6 (8)	146.4	23 (7)	102.2	6 (10)	256.3	12 (5)	71.6
Neutrophil count increased	1 (1)	23.2	3 (<1)	12.8	3 (5)	119.3	2 (<1)	11.7
Amnesia	1 (1)	23.4	0	0.0	3 (5)	123.2	0	0.0

CRF, case report form; ITT, intent-to-treat; IVRS, interactive voice response system; PY, person-year; TNF, tumor necrosis factor-α antagonist; UC, ulcerative colitis.

[a]TNF-naive patients were classified by data captured on the IVRS at screening and enrollment. Prior TNF failure was defined by data recorded on the CRF at Week 0. Patients without prior exposure on the IVRS, but who had prior TNF antagonist failure on the CRF, were included in both TNF-naive and TNF-failure populations.

[b]Patients received placebo during both the induction and maintenance phases (non-ITT).

[c]Patients received vedolizumab during both the induction and maintenance phases (non-ITT and ITT combined).

[d]PYs of exposure up to the first occurrence of each adverse event were calculated from the date of event onset minus the date of first dose plus 1 day. For patients who did not experience the event, PYs of exposure were calculated as the date of last dose plus 16 × 7 days minus the date of first dose plus 1 day or as the date of last dose minus the date of first dose plus 1 day if the patient continued in the open-label extension study (ClinTrials.gov, NCT00790933). Thus, the total PYs of exposure for each preferred term could be different because the number of PYs was truncated after a patient experienced the event of interest.

[e]Includes those reported under the "Infections and infestations" system organ class.

[f]Ranked from highest to lowest incidence in vedolizumab-treated TNF-failure patients.

concentrations) is potentially valuable in managing patients with poor response to a TNF antagonist,[25] very little data are available on the value of switching between drug classes based on the results of therapeutic drug monitoring.[26] Randomized trials should be performed comparing vedolizumab to the use of a second TNF antagonist in TNF antagonist failure patients with adequate serum drug concentrations.

Development of ADAs was low in both the TNF antagonist-naive and previously exposed populations (1% vs 1%). Although no association was demonstrated in either group between use of concomitant immunosuppression and efficacy, patients receiving these medications were numerically less likely to develop ADAs.[27] Likewise, although no meaningful differences in trough drug levels were observed between the subgroups, patients who developed ADAs had reduced vedolizumab drug concentrations.[27] Collectively, these observations indicate that the combined use of immunosuppression may be advantageous; however, results from a well-designed purpose built trial, analogous to the SONIC l trial,[28] are need before conclusions regarding this question can be drawn.

Our study has some limitations. Specifically, the results are based on exploratory and post hoc analyses of subpopulations from the GEMINI 1 study. Although subgroup comparisons should generally be interpreted cautiously, especially with the small numbers of patients within the subtypes of TNF antagonist failure, the relatively large number of TNF-naive and TNF-failure patients evaluated in total, the prospectively defined outcome measures, and the demonstration of analogous

findings with other biologics[3] support the validity of these conclusions for the 2 groups overall, which have important clinical implications. Physicians should be aware that failure of a TNF antagonist is a predictor of poor prognosis[29,30] and recognize the need to optimize subsequent induction therapy in these patients. Recently, multiple publications have emphasized the importance of this concept in detail, and include such strategies as coadministration of corticosteroids and immunosuppressives,[31–33] treating to a specific objectively defined target (eg, endoscopic healing),[34] use of therapeutic drug monitoring,[25,35,36] and ensuring an adequate duration of therapy.[37,38] These specific strategies should be evaluated in future vedolizumab studies.

Although it is alluring to compare these results with those obtained in previous pivotal trials of TNF antagonists, we would caution against using such an approach to determine relative efficacy given the confounding effects of differences in patient populations, outcome definitions, and, notably, trial design. A direct comparison of vedolizumab with adalimumab is currently underway (ClinicalTrials.gov, NCT02497469). The results of such studies will be critical in informing payors regarding the relative value of these agents.

Overall, the results of the present study are consistent with those reported previously[15] and indicate that vedolizumab could be considered as a viable first-line option for patients with UC who are TNF antagonist treatment naive, as well as safe and efficacious induction and maintenance therapy for patients with prior TNF antagonist treatment failure.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2016.08.044.

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Conflicts of interest
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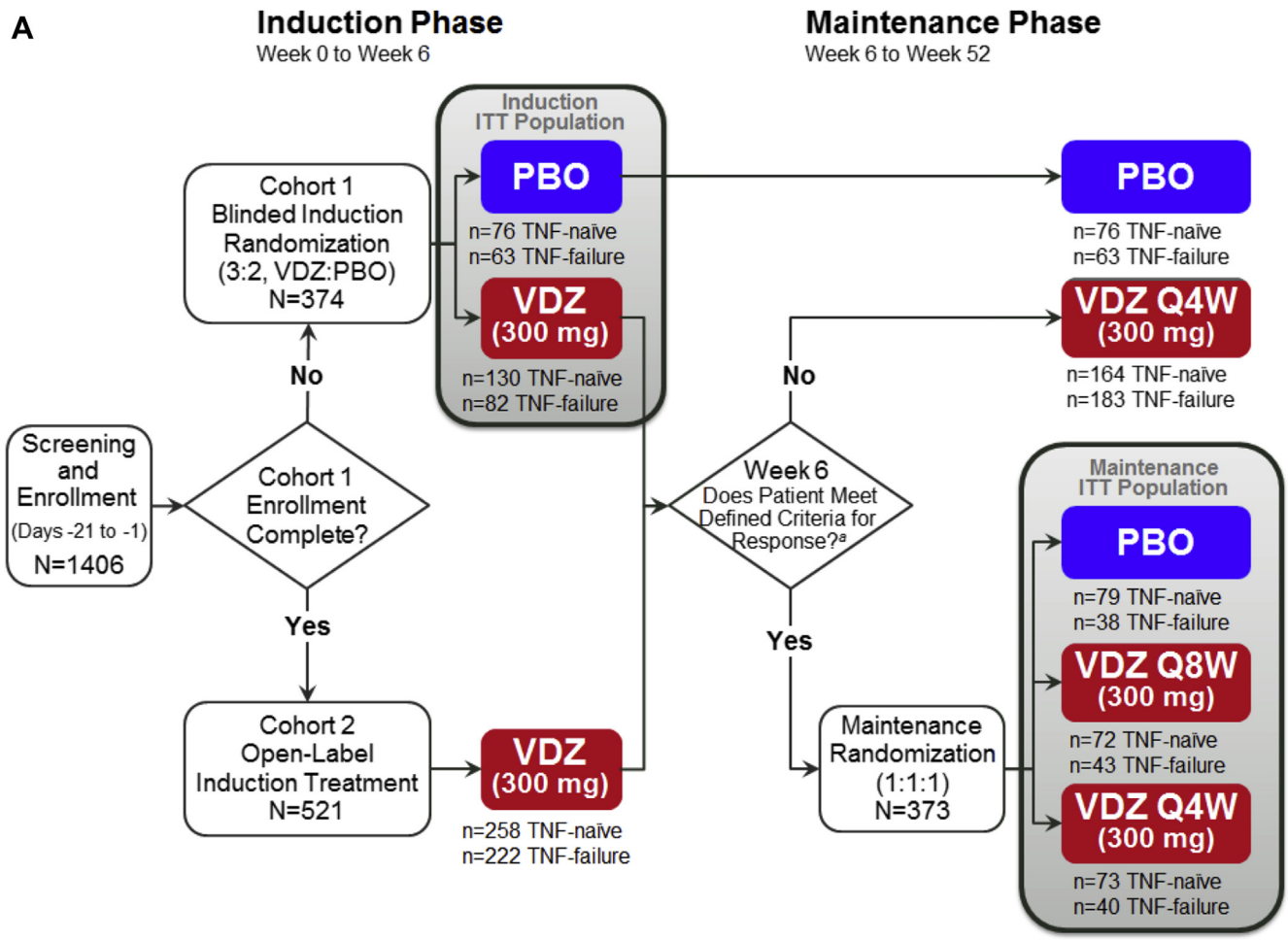
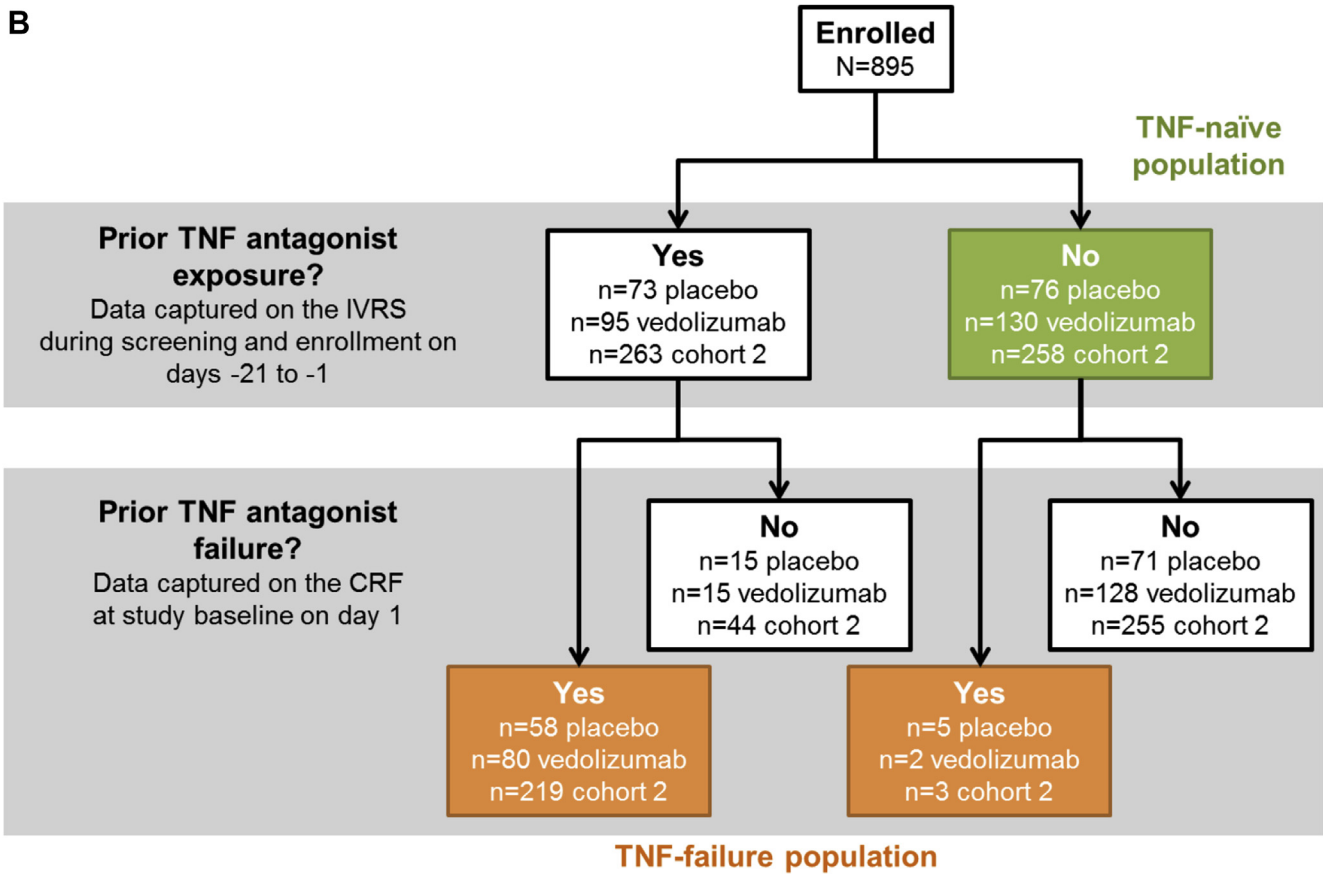


Supplementary Figure 1. (*A*) GEMINI 1 study design and (*B*) patient populations. During the induction phase, patients received double-blind vedolizumab or placebo or open-label vedolizumab at Weeks 0 and 2. Beginning at Week 6, patients who had a response to vedolizumab received double-blind placebo or vedolizumab every 8 or every 4 weeks for the duration of the maintenance phase. Patients who did not have a response at Week 6 could receive vedolizumab every 4 weeks and those who received placebo during maintenance continued to receive placebo during the maintenance phase. Data for prior TNF antagonist use were obtained from responses on the IVRS during screening and enrollment. Patients with prior TNF antagonist failure were identified by data on the CRF at the baseline (Week 0) visit. Patients with prior exposure to a TNF antagonist according to the IVRS and without prior failure according to the CRF were excluded from the analyses. [a]Response was defined as a reduction in complete Mayo score of $\geq$3 points and $\geq$30% from baseline, with an accompanying decrease in the rectal bleeding subscore of $\geq$1 point or absolute rectal bleeding subscore of $\leq$1. CRF, case report form; ITT, intent-to-treat; IVRS, interactive voice response system; PBO, placebo; Q4W, every 4 weeks; Q8W, every 8 weeks; TNF, tumor necrosis factor-α antagonist; VDZ, vedolizumab.



Supplementary Figure 1. (*continued*).

Supplementary Table 1. Patient Demographics and Baseline Disease Characteristics (Maintenance ITT Population)

Characteristic	TNF-naive patients[a]			TNF-failure patients[a]		
	Placebo (n = 79)	Vedolizumab Q8W (n = 72)	Vedolizumab Q4W (n = 73)	Placebo (n = 38)	Vedolizumab Q8W (n = 43)	Vedolizumab Q4W (n = 40)
Age, *y*, mean ± SD	39.5 ± 14.2	41.0 ± 13.8	38.3 ± 12.6	41.6 ± 13.4	41.3 ± 10.9	39.9 ± 18.1
Male sex, n (%)	45 (57)	39 (54)	39 (53)	21 (55)	24 (56)	21 (53)
Weight, *kg*, mean ± SD	71.3 ± 18.3	76.1 ± 19.0	70.3 ± 16.9	81.2 ± 23.8	79.1 ± 18.1	72.7 ± 17.4
BMI, kg/m^2, mean ± SD	24.9 ± 5.5	26.4 ± 6.3	24.1 ± 4.9	27.4 ± 7.0	27.0 ± 6.3	24.8 ± 4.6
Current smoker, n (%)	5 (6)	4 (6)	5 (7)	3 (8)	2 (5)	3 (8)
Disease duration, *y*, mean ± SD	6.4 ± 5.6	5.8 ± 4.8	7.0 ± 6.2	9.8 ± 8.4	6.8 ± 4.5	8.1 ± 7.4
Mayo Clinic score, mean ± SD	8.4 ± 1.7	8.3 ± 1.8	8.2 ± 1.8	8.2 ± 1.7	8.5 ± 1.9	8.4 ± 1.6
fCal, $\mu g/g$, mean ± SD	2474 ± 3441	1463 ± 2205	1709 ± 2931	1342 ± 1595	2428 ± 3805	1392 ± 2345
Disease localization, n (%)						
Proctosigmoiditis	8 (10)	13 (18)	10 (14)	1 (3)	5 (12)	3 (8)
Left-sided colitis	36 (46)	35 (49)	27 (37)	15 (39)	10 (23)	14 (35)
Extensive colitis	7 (9)	9 (13)	11 (15)	5 (13)	6 (14)	2 (5)
Pancolitis	28 (35)	15 (21)	25 (34)	17 (45)	22 (51)	21 (53)
Concomitant medications, n (%)						
CS only	28 (35)	27 (38)	29 (40)	16 (42)	21 (49)	11 (28)
IS only	19 (24)	18 (25)	14 (19)	6 (16)	2 (5)	5 (13)
CS and IS	15 (19)	12 (17)	15 (21)	7 (18)	5 (12)	8 (20)
No CS and IS	17 (22)	15 (21)	15 (21)	9 (24)	15 (35)	16 (40)
Prednisone-equivalent dose, *mg*, median (min, max)	20.0 (2.5–30.0)	20.0 (2.5–50.0)	17.5 (0.6–40.0)	15.0 (5.0–30.0)	20.0 (2.5–156.3)	15.0 (5.0–30.0)
Type of TNF failure, n (%)[b]						
Inadequate response	N/A	N/A	N/A	19 (50)	16 (37)	17 (43)
Loss of response	N/A	N/A	N/A	13 (34)	16 (37)	15 (38)
Intolerance	N/A	N/A	N/A	6 (16)	11 (26)	8 (20)

BMI, body mass index; CRF, case report form; CS, corticosteroid; fCal, fecal calprotectin; IS, immunosuppressant; ITT, intent-to-treat; IVRS, interactive voice response system; N/A, not applicable; Q4W, every 4 weeks; Q8W, every 8 weeks; SD, standard deviation; TNF, tumor necrosis factor-α antagonist.

[a]TNF-naive patients were classified by data captured on the IVRS at screening and enrollment. Prior TNF failure was defined by data recorded on the CRF at Week 0.

[b]Each patient was counted only once according to his or her worst outcome. Inadequate response was considered worse than lost response; lost response was considered worse than intolerance.

Supplementary Table 2. Outcome Measures at Week 52 (Maintenance ITT Population)

Outcome	TNF-naive[a]							TNF-failure[a]						
	Patients, n (%)			%-Point difference (95% CI)[b]		RR (95% CI)[b]		Patients, n (%)			%-Point difference (95% CI)[b]		RR (95% CI)[b]	
Week 52	Placebo n = 79	Q8W n = 72	Q4W n = 73	Q8W vs Placebo	Q4W vs Placebo	Q8W vs Placebo	Q4W vs Placebo	Placebo n = 38	Q8W n = 43	Q4W n = 40	Q8W vs Placebo	Q4W vs Placebo	Q8W vs Placebo	Q4W vs Placebo
Clinical remission[c]	15 (19.0)	33 (45.8)	35 (47.9)	26.6 (11.8 to 41.4)	28.4 (13.7 to 43.1)	2.4 (1.4 to 4.1)	2.5 (1.5 to 4.2)	2 (5.3)	16 (37.2)	14 (35.0)	27.8 (10.6 to 45.0)	31.3 (13.2 to 49.3)	6.3 (1.5 to 27.0)	6.9 (1.7 to 27.7)
Durable clinical response[d]	21 (26.6)	47 (65.3)	41 (56.2)	38.2 (22.6 to 53.8)	29.2 (13.7 to 44.7)	2.4 (1.6 to 3.6)	2.1 (1.4 to 3.2)	6 (15.8)	20 (46.5)	17 (42.5)	26.8 (7.4 to 46.2)	25.9 (5.8 to 45.9)	2.7 (1.2 to 5.9)	2.5 (1.1 to 5.7)
Mucosal healing[e]	19 (24.1)	43 (59.7)	44 (60.3)	35.4 (19.8 to 51.1)	35.5 (19.9 to 51.0)	2.5 (1.6 to 3.9)	2.5 (1.6 to 3.8)	3 (7.9)	18 (41.9)	19 (47.5)	29.8 (11.6 to 48.1)	39.3 (19.3 to 59.3)	4.8 (1.5 to 15.2)	5.8 (1.9 to 17.9)
Durable clinical remission[f]	10 (12.7)	16 (22.2)	21 (28.8)	9.2 (-2.7 to 21.0)	16.1 (3.3 to 28.8)	1.7 (0.8 to 3.6)	2.3 (1.1 to 4.6)	1 (2.6)	9 (20.9)	5 (12.5)	15.0 (1.2 to 28.7)	12.2 (-1.3 to 25.7)	6.0 (0.8 to 43.9)	4.8 (0.7 to 34.4)
	n = 43	n = 39	n = 44					n = 23	n = 26	n = 19				
Corticosteroid-free remission[g]	8 (18.6)	14 (35.9)	23 (52.3)	17.0 (-2.0 to 36.0)	33.7 (13.8 to 53.6)	1.9 (0.9 to 4.1)	2.8 (1.4 to 5.6)	1 (4.3)	6 (23.1)	6 (31.6)	15.7 (-3.1 to 34.5)	34.1 (5.4 to 62.8)	4.8 (0.5 to 43.4)	6.8 (0.9 to 50.2)

CI, confidence interval; ITT, intent-to-treat; Q4W, every 4 weeks; Q8W, every 8 weeks; RR, risk ratio; TNF, tumor necrosis factor-α antagonist.

[a]TNF-naive patients were classified by data captured on the IVRS at screening and enrollment. Prior TNF failure was defined by data recorded on the CRF at Week 0. Patients without prior exposure on the IVRS, but who had prior TNF antagonist failure on the CRF, were included in both TNF-naive and TNF-failure populations.

[b]Adjusted based on the Cochran-Mantel-Haenszel chi-square test, with stratification according to (1) concomitant use of oral corticosteroids (yes/no), (2) previous exposure to TNF antagonist and/or concomitant immunomodulator use (yes/no), and (3) enrollment in Cohort 1 or Cohort 2 in the induction phase.

[c]Defined as complete Mayo score of $\leq$2 points and no individual subscore $>$1 point.

[d]Defined as reduction in complete Mayo score of $\geq$3 points and $\geq$30% from baseline with an accompanying decrease in rectal bleeding subscore of $\geq$1 point or absolute rectal bleeding subscore of $\leq$1 point (clinical response) at both Weeks 6 and 52.

[e]Defined as Mayo endoscopic subscore of $\leq$1.

[f]Defined as clinical remission at both Weeks 6 and 52.

[g]Defined as patients using oral corticosteroids at baseline who have discontinued corticosteroids and are in clinical remission at Week 52.

Supplementary Table 3. Summary of Adverse Events Reported by TNF-Naive and TNF-Failure Patients During Induction Therapy

	TNF-naive patients[a]		TNF-failure patients[a]	
	Placebo (n = 76)	Vedolizumab (n = 388)	Placebo (n = 63)	Vedolizumab (n = 304)
Event	Patients, n (%)			
Any adverse event	29 (38)	149 (38)	39 (62)	164 (54)
Any serious adverse event	8 (11)	11 (3)	3 (5)	12 (4)
Any serious infection[b]	2 (3)	2 (<1)	2 (3)	2 (<1)
Common adverse events (≥3% of patients in the vedolizumab group)[c]				
Headache	1 (1)	26 (7)	6 (10)	27 (9)
Nasopharyngitis	1 (1)	9 (2)	4 (6)	17 (6)
Fatigue	0	5 (1)	3 (5)	12 (4)
Exacerbation of UC	6 (8)	8 (2)	3 (5)	11 (4)
Arthralgia	0	8 (2)	2 (3)	11 (4)
Nausea	2 (3)	10 (3)	3 (5)	9 (3)
Pyrexia	0	4 (1)	1 (2)	9 (3)
Cough	1 (1)	8 (2)	1 (2)	8 (3)
Upper respiratory tract infection	1 (1)	10 (3)	1 (2)	6 (2)
Anemia	3 (4)	12 (3)	3 (5)	2 (<1)

CRF, case report form; IVRS, interactive voice response system; TNF, tumor necrosis factor-α antagonist; UC, ulcerative colitis.

[a]TNF-naive patients were classified by data captured on the IVRS at screening and enrollment. Prior TNF failure was defined by data recorded on the CRF at Week 0. Patients without prior exposure on the IVRS, but who had prior TNF antagonist failure on the CRF, were included in both TNF-naive and TNF-failure populations.

[b]Includes those reported under the "Infections and infestations" system organ class.

[c]Ranked from highest to lowest incidence in vedolizumab-treated TNF-failure patients.