Vedolizumab as Induction and Maintenance Therapy for Crohn's Disease in Patients Naïve to or Who Have Failed Tumor Necrosis Factor Antagonist Therapy

Bruce E. Sands, MD, MS, William J. Sandborn, MD,† Gert Van Assche, MD, PhD,‡ Milan Lukas, MD, PhD,§ Jing Xu, PhD,‖ Alexandra James,¶ Brihad Abhyankar, MS, FRCS, MBA, FFPM,¶ and Karen Lasch, MD***

Background: Vedolizumab is a gut-selective $\alpha_4\beta_7$ integrin antagonist for the treatment of moderately to severely active Crohn's disease (CD). Aims of this study were to characterize the efficacy and safety of vedolizumab induction and maintenance therapy in patients who were naïve to tumor necrosis factor-alpha (TNF-α) antagonist therapy (TNF-naïve) or who had discontinued TNF-α antagonist therapy because of inadequate response (i.e., primary nonresponse), loss of response, or intolerance (collectively classified as the TNF-failure population).

Methods: Post hoc analyses of the efficacy data for 516 TNF-naïve and 960 TNF-failure patients from the GEMINI 2 and GEMINI 3 trials were evaluated at weeks 6, 10, and 52 and included clinical remission (CD Activity Index [CDAI] score ≤150), enhanced clinical response (≥100-point decrease from baseline in CDAI score), durable clinical remission (remission at ≥80% of visits), and corticosteroid-free remission. Adverse events were summarized for the TNF-naïve and TNF-failure subgroups by treatment received.

Results: Among patients who responded to vedolizumab induction at week 6, 48.9% of TNF-naïve and 27.7% of TNF-failure patients were in remission with vedolizumab at week 52 (versus 26.8% and 12.8% with placebo). Clinical efficacy was similar between the different types of TNF-α antagonist failure or the number of prior TNF-α antagonists failed. Safety profiles were similar in both subpopulations.

Conclusions: Vedolizumab had increased efficacy over placebo in CD patients irrespective of TNF-α antagonist treatment history. Overall, rates of response and remission were numerically higher in patients receiving vedolizumab as a first biologic than in patients who had experienced TNF failure.

(Inflamm Bowel Dis 2017;23:97–106)

Key Words: vedolizumab, treatment failure, treatment naïve, Crohn's disease, TNF antagonist

Crohn's disease (CD) is a chronic, relapsing inflammatory bowel disease that involves any portion of the gastrointestinal tract although the ileum and colon are the most commonly affected sites.[1,2] The primary goal of therapy for CD is to induce and maintain clinical remission, with the optimal outcome of maintaining steroid-free clinical remission and reducing the need for hospitalizations and surgery.[3,4] Although pharmacologic treatments exist for CD, there remains a significant medical need for more effective treatment options for induction and maintenance of remission. Current therapies for CD include corticosteroids, immunosuppressives (e.g., azathioprine, mercaptopurine, methotrexate), and biologics, which includes the tumor necrosis factor-alpha (TNF-α) antagonists infliximab, adalimumab, and certolizumab pegol, and the $\alpha_4\beta_7$ integrin antagonist vedolizumab.[1–3]

TNF-α antagonists have considerably improved the rates of remission in CD patients and decreased hospitalization and the need for surgery.[4,5] Although the addition of TNF-α antagonists to the CD treatment armamentarium has greatly improved outcomes, almost two-thirds of patients do not attain remission with TNF-α antagonist therapy.[6–8] Further, treatment failure of the first TNF-α antagonist is associated with a lower clinical response to subsequent TNF-α antagonists, limiting available treatment options for patients with CD.[9,10] The use of TNF-α antagonists is also restricted because of safety concerns arising from the systemic effects of immunosuppression, which can result in the reactivation of tuberculosis; bacterial, viral, fungal, and opportunistic infections; and malignancies.[11]

Vedolizumab is a humanized immunoglobulin G_1 monoclonal antibody targeting $\alpha_4\beta_7$ integrin that is approved for the

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.ibdjournal.org).

Received for publication September 13, 2016; Accepted September 22, 2016.

From the *The Dr Henry D. Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, New York; †Division of Gastroenterology, University of California San Diego, La Jolla, California; ‡Division of Gastroenterology, University Hospitals Leuven, Leuven, Belgium; §IBD Clinical and Research Centre, ISCARE Lighthouse Clinical Centre, Charles University, Prague, Czech Republic; ‖Takeda Pharmaceuticals International Co., Cambridge, Massachusetts; ¶Takeda Development Centre Europe Ltd., London, United Kingdom; and **Takeda Pharmaceuticals International, Inc., Deerfield, Illinois.

Author disclosures are available in the Acknowledgments.

Address correspondence to: Bruce E. Sands, MD, MS, The Dr Henry D. Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, Annenberg Building, Floor 5, 1468 Madison Avenue, New York, NY, 10029 (e-mail: bruce.sands@mssm.edu).

DOI 10.1097/MIB.0000000000000979

Published online 7 December 2016.

treatment of moderately to severely active CD and ulcerative colitis.[12,13] By specifically binding to the $\alpha_4\beta_7$ integrin, vedolizumab selectively inhibits adhesion of gut-homing leukocytes to the mucosal addressin cell adhesion molecule 1 (MAdCAM-1).[14] Preclinical and healthy volunteer studies suggest that inhibition of the $\alpha_4\beta_7$–MAdCAM-1 pathway reduces gastrointestinal inflammation without inhibiting systemic immunity or affecting leukocyte trafficking to the central nervous system.[15–18] The efficacy, safety, and tolerability of vedolizumab induction and maintenance therapies in CD were established in the pivotal GEMINI 2 and GEMINI 3 studies.[19,20] The objectives of the present analyses were to characterize the efficacy and safety of vedolizumab induction and maintenance therapy in patients according to their prior TNF-α antagonist treatment history.

MATERIALS AND METHODS

Study Design and Patient Stratification

The results presented here are based on prespecified and post hoc exploratory analyses of the phase 3, randomized, placebo-controlled GEMINI 2 (ClinicalTrials.gov No., NCT00783692) and GEMINI 3 (ClinicalTrials.gov No., NCT01224171) trials (see Fig. 1, Supplemental Digital Content 1, http://links.lww.com/IBD/B401), which were reported in detail elsewhere.[19,20] Briefly, both studies had similar inclusion criteria and enrolled patients with clinical and endoscopic evidence of moderately to severely active CD. Baseline CD Activity Index (CDAI) scores of 220 to 450 were required of GEMINI 2 patients and scores of 220 to 400 of GEMINI 3 patients. In addition, patients must have had ≥1 of the following: serum C-reactive protein (CRP) concentration >2.87 mg/L, documentation of ulceration by colonoscopy, or fecal calprotectin concentration >250 μg/g together with imaging (computed tomography enterography, magnetic resonance enterography, contrast-enhanced small bowel radiography, or wireless capsule endoscopy) revealing Crohn's ulcerations.

During GEMINI 2, patients were randomized to induction treatment for 6 weeks with intravenous vedolizumab or placebo at weeks 0 and 2 (see Fig. 1, Supplemental Digital Content 1, http://links.lww.com/IBD/B401); these patients composed the induction intent-to-treat (ITT) population (Cohort 1).[19] A second cohort of patients received open-label vedolizumab at weeks 0 and 2 (Cohort 2) to fulfill sample size requirements for the maintenance trial. Thereafter, vedolizumab-treated patients from both cohorts who had a clinical response (≥70-point decrease from baseline CDAI score) at week 6 were randomized in a blinded fashion to receive vedolizumab dosed every 8 weeks or every 4 weeks or placebo beginning at week 6 and until week 52 (maintenance ITT population). Patients who had not responded to 2 doses of vedolizumab at week 6 continued on vedolizumab every 4 weeks during the maintenance phase of GEMINI 2 (maintenance non-ITT population). Patients who received placebo during the double-blind induction study (Cohort 1) continued on placebo during the maintenance phase of the study. GEMINI 3 was a 10-week induction trial during which patients were randomized to receive vedolizumab or placebo at weeks 0, 2, and 6 (see Fig. 1, Supplemental Digital Content 1, http://links.lww.com/IBD/B401).[20]

Patients from both GEMINI studies were stratified by prior TNF-α antagonist treatment history according to those who had no prior exposure to TNF-α antagonist therapy (TNF-naïve) or who had failed prior TNF-α antagonist therapy (TNF-failure) and pooled to allow for a more robust evaluation of induction efficacy. In GEMINI 2 and GEMINI 3, prior TNF-α antagonist exposure was defined according to data from the interactive voice response system (IVRS) at screening and enrollment. Prior TNF-α antagonist failure was also determined from the IVRS at screening and enrollment in GEMINI 3, but in GEMINI 2, prior failure was defined by data collected on the case report form (CRF) at baseline (week 0). Consequently, 9 patients in the GEMINI 2 induction ITT population (3 placebo; 6 vedolizumab) had prior failure recorded on the CRF without exposure to a TNF-α antagonist according to the IVRS. To compensate for this, in the pooled GEMINI 2 and GEMINI 3 induction population, TNF-naïve patients were classified by TNF-α antagonist exposure defined according to the IVRS, excluding GEMINI 2 patients with prior TNF-α antagonist failure recorded on the CRF at baseline, and TNF-failure patients were classified by prior TNF-α antagonist failure defined from data recorded on the CRF at baseline for GEMINI 2 patients and from the IVRS at screening for GEMINI 3 patients. Thus, the number of TNF-failure and TNF-naïve patients in the combined induction population does not equal the total number enrolled because 17 patients (5 placebo; 12 vedolizumab) who were exposed to TNF-α antagonist therapy without documentation of treatment failure were excluded.

Failure of prior TNF-α antagonist therapy was predefined in the original study protocols as either an inadequate response—or primary nonresponse—to treatment with a TNF-α antagonist (i.e., signs and symptoms of persistently active disease despite at least one 4-week induction regimen of infliximab [5 mg/kg intravenously, 2 doses ≥2 weeks apart], adalimumab [one 80 mg subcutaneous dose followed by one 40 mg dose ≥2 weeks apart], or certolizumab pegol [400 mg subcutaneous, 2 doses ≥2 weeks apart]), a loss of response—or secondary nonresponse—to a TNF-α antagonist (i.e., recurrence of symptoms during maintenance dosing after prior clinical benefit), or intolerance of a TNF-α antagonist (i.e., treatment-related toxicity). Within the TNF-failure population, patients were evaluated by the type of failure—inadequate response, loss of response, or intolerance—and by the number of TNF-α antagonists failed. In the present analyses, patients could be included in more than 1 type of failure subgroup.

Efficacy Analyses

The GEMINI 2 induction ITT population and the GEMINI 3 population were pooled in the present analyses for the inclusion of a larger patient population. Induction treatment endpoints included clinical remission (CDAI score of ≤150) and enhanced clinical response (≥100-point decrease from baseline in the CDAI score [CDAI-100 response]) at week 6 and week 10. A clinical

response of ≥70-point decrease from baseline in the CDAI score (CDAI-70 response) was also evaluated. For week 10 analyses, the vedolizumab group included GEMINI 3 patients and GEMINI 2 vedolizumab induction ITT patients who continued with maintenance vedolizumab treatment irrespective of week 6 response status (i.e., maintenance ITT and non-ITT vedolizumab); thus, all patients in the combined induction vedolizumab population at week 10 were dosed at weeks 0, 2, and 6 (see Fig. 1, Supplemental Digital Content 1, http://links.lww.com/IBD/B401). The placebo group at week 10 included GEMINI 3 patients and GEMINI 2 placebo patients from Cohort 1. Patients from either Cohort 1 or Cohort 2 of GEMINI 2 who had responded to vedolizumab treatment at week 6 and were randomized to placebo for the maintenance phase of GEMINI 2 were excluded from the week 10 analysis.

Maintenance treatment endpoints were evaluated in the GEMINI 2 population at week 52 and included clinical remission, CDAI-100 response, corticosteroid-free remission (CDAI ≤150 without corticosteroid therapy among patients taking corticosteroids at baseline), and durable clinical remission (CDAI ≤150 at ≥80% of study visits, including the final visit). Because the vedolizumab every 8-week and every 4-week dosing groups had similar treatment outcomes in the total GEMINI 2 population,[19] the 2 groups were evaluated as a combined vedolizumab treatment group to increase the sample size of the subgroup analyses.

All efficacy outcomes were evaluated in the TNF-naïve and TNF-failure ITT populations. Comparisons between the vedolizumab and placebo treatment arms were made using descriptive statistics. Specifically, the absolute differences in percentages for vedolizumab and placebo were calculated for each of the dichotomous outcomes along with 95% confidence intervals (CIs); missing efficacy data were considered therapy failure. For week 6 and week 10 endpoints, when GEMINI 2 and GEMINI 3 populations are combined, adjusted 95% CIs were calculated by stratifying for baseline corticosteroid use, previous exposure to a TNF-α antagonist, or concomitant immunosuppressant use and study. For week 6 and week 52 endpoints for the GEMINI 2 population alone, unadjusted CIs were calculated. Percentage-point differences from placebo were considered significant if the 95% CI did not contain zero.[21]

Safety Evaluation

Safety of vedolizumab in TNF-naïve and TNF-failure populations was evaluated separately according to treatment arms. Safety analyses for the induction phase included all safety data collected from baseline through week 6 (GEMINI 2) or week 10 (GEMINI 3) for all patients who received study medications, including patients from Cohort 2 of GEMINI 2 (see Fig. 1, Supplemental Digital Content 1, http://links.lww.com/IBD/B401). The safety analyses for the maintenance phase are cumulative, including all safety data collected from baseline through the end of the study for GEMINI 2. Safety findings were based largely on the incidence, severity, and type of adverse events. An adverse event was defined as any untoward medical occurrence in a patient administered a study drug (vedolizumab or placebo) and was classified according to the *Medical Dictionary for Regulatory Activities*[22] version 14.

RESULTS

Patients

In the combined GEMINI 2 and GEMINI 3 population, 516 patients were TNF-naïve and prior TNF-α antagonist therapy had failed in 960 patients (see Fig. 1, Supplemental Digital Content 1, http://links.lww.com/IBD/B401). Patient demographics and clinical characteristics at baseline for the TNF-naïve and TNF-failure populations are shown according to the induction treatment groups (Table 1) and GEMINI 2 maintenance ITT treatment groups (see Table 1, Supplemental Digital Content 1, http://links.lww.com/IBD/B401). There were no notable differences between the ITT vedolizumab and placebo groups. No statistical comparisons were made between treatment groups or between TNF-naïve and TNF-failure populations. However, a descriptive summary of the range in baseline characteristics across the vedolizumab and placebo treatment groups shows that compared with TNF-naïve patients, TNF-failure patients generally had higher disease burden as illustrated by longer mean duration of disease (range: 10.7–11.4 years versus 5.3–7.0 years) and higher mean fecal calprotectin levels (range: 1083–1655 versus 958–1230 μg/g) at baseline. Further, a greater percentage of TNF-failure patients overall had surgery for CD (range: 48%–52%) and histories of fistulizing disease (range: 38%–46%) and extraintestinal manifestations (range: 83%–89%) than TNF-naïve patients (ranges: 18%–36%, 21%–35%, and 72%–77%, respectively). TNF-naïve patients overall had higher percentages of immunosuppressant users (alone [range: 21%–23%] or in addition to corticosteroid use [range: 22%–24%]) at baseline than TNF-failure patients (ranges: 13%–14% and 13%–15%, respectively). The pattern of baseline characteristics observed in the induction treatment groups was generally maintained after rerandomization in the maintenance trial (see Table 1, Supplemental Digital Content 1, http://links.lww.com/IBD/B401) except for history of extraintestinal manifestations, which appeared similar between TNF-naïve and TNF-failure patients.

Efficacy of Vedolizumab in the TNF-Naïve Population

Within the TNF-naïve population, percentages of patients in clinical remission were significantly higher with vedolizumab induction treatment than with placebo at week 6 (12.6% difference; 95% CI: 3.7, 21.4) and at week 10 (11.3% difference; 95% CI: 1.5–21.1) (Fig. 1A). Rates of clinical response, whether defined as CDAI-100 response (Fig. 1B) or CDAI-70 response (see Fig. 2, Supplemental Digital Content 1, http://links.lww.com/IBD/B401), were also significantly higher with vedolizumab induction than with placebo at both week 6 and week 10 in the TNF-naïve population.

Table 1. Patient Demographics and Baseline Disease Characteristics (Combined Induction Populations)

	TNF-naïve Patients (n = 516)[a]			TNF-failure Patients (n = 960)[b]		
	ITT Population		Cohort 2	ITT Population		Cohort 2
Characteristic	Placebo (n = 123)	Vedolizumab (n = 154)	Vedolizumab (n = 239)	Placebo (n = 227)	Vedolizumab (n = 263)	Vedolizumab (n = 470)
Age, mean ± SD, y	37 ± 12	36 ± 12	35 ± 12	38 ± 13	38 ± 12	36 ± 12
Male sex, n (%)	65 (53)	79 (51)	127 (53)	91 (40)	114 (43)	202 (43)
Weight, mean ± SD, kg	69 ± 19	66 ± 19	68 ± 18	71 ± 19	70 ± 18	72 ± 20
Current smoker, n (%)	27 (22)	46 (30)	69 (29)	65 (29)	69 (26)	131 (28)
Disease duration, mean ± SD, y	5.3 ± 5.5	7.0 ± 7.9	6.1 ± 6.9	11.3 ± 8.2	11.4 ± 8.3	10.7 ± 7.6
CDAI score, mean ± SD	305 ± 76	317 ± 65	312 ± 66	314 ± 61	324 ± 61	329 ± 67
CRP, mean ± SD, mg/L	19.3 ± 19.9	20.7 ± 27.5	17.8 ± 24.6	21.4 ± 27.1	21.7 ± 23.9	22.0 ± 29.2
fCal, mean ± SD, μg/g	1230 ± 1853	1225 ± 1883	958 ± 1168	1534 ± 2436	1655 ± 2540	1083 ± 1600
Disease localization, n (%)						
Ileum only	22 (18)	34 (22)	50 (21)	28 (12)	33 (13)	67 (14)
Colon only	38 (31)	38 (25)	61 (26)	54 (24)	71 (27)	138 (29)
Ileum and colon	63 (51)	82 (53)	128 (54)	145 (64)	159 (60)	265 (56)
Prior surgery for CD, n (%)	22 (18)	56 (36)	58 (24)	119 (52)	127 (48)	238 (51)
History of fistulizing disease, n (%)	26 (21)	54 (35)	55 (23)	104 (46)	100 (38)	192 (41)
Draining fistulae, n (%)	18 (15)	26 (17)	26 (11)	29 (13)	33 (13)	71 (15)
History of EIMs, n (%)	89 (72)	114 (74)	184 (77)	203 (89)	218 (83)	404 (86)
EIMs, n (%)	75 (61)	95 (62)	137 (57)	157 (69)	145 (55)	300 (64)
Concomitant medications, n (%)						
CS only	31 (25)	42 (27)	78 (33)	85 (37)	94 (36)	178 (38)
IS only	28 (23)	32 (21)	49 (21)	30 (13)	35 (13)	65 (14)
CS and IS	28 (23)	34 (22)	57 (24)	32 (14)	40 (15)	62 (13)
No CS and IS	36 (29)	46 (30)	55 (23)	80 (35)	94 (36)	165 (35)
Prednisone-equivalent dose, median (min, max), mg	20.0 (5.0, 35.0)	20.0 (5.0, 30.0)	20.0 (5.0, 280.0)	20.0 (0.6, 250.0)	17.5 (2.5, 40.0)	20.0 (2.5, 280.0)

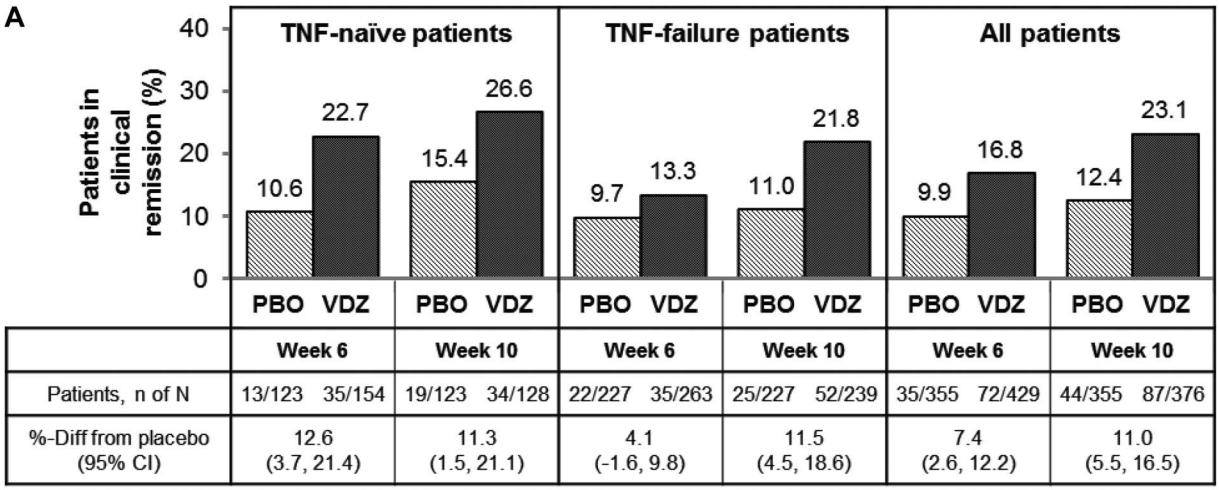
[a]TNF exposure was defined according to data captured on the interactive voice response system (IVRS) at screening and enrollment, excluding GEMINI 2 patients with prior TNF failure recorded on the case report form (CRF) at baseline (week 0).
[b]Prior TNF failure was defined from data recorded on the CRF at baseline for GEMINI 2 patients and from the IVRS at screening for GEMINI 3 patients.
CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; CS, corticosteroid; EIM, extraintestinal manifestation; fCal, fecal calprotectin; IS, immunosuppressant; ITT, intent-to-treat; SD, standard deviation; TNF, tumor necrosis factor.

At week 52, percentages of TNF-naïve patients meeting all efficacy endpoints were higher with vedolizumab maintenance treatment than with placebo (Fig. 2). Significant differences from placebo were observed in the percentage of TNF-naïve patients who achieved clinical remission with vedolizumab at week 52 (22.1% difference; 95% CI: 8.9–35.4) (Fig. 2A) and in those who achieved CDAI-100 response (18.9% difference; 95% CI: 4.9–32.9) (Fig. 2B).

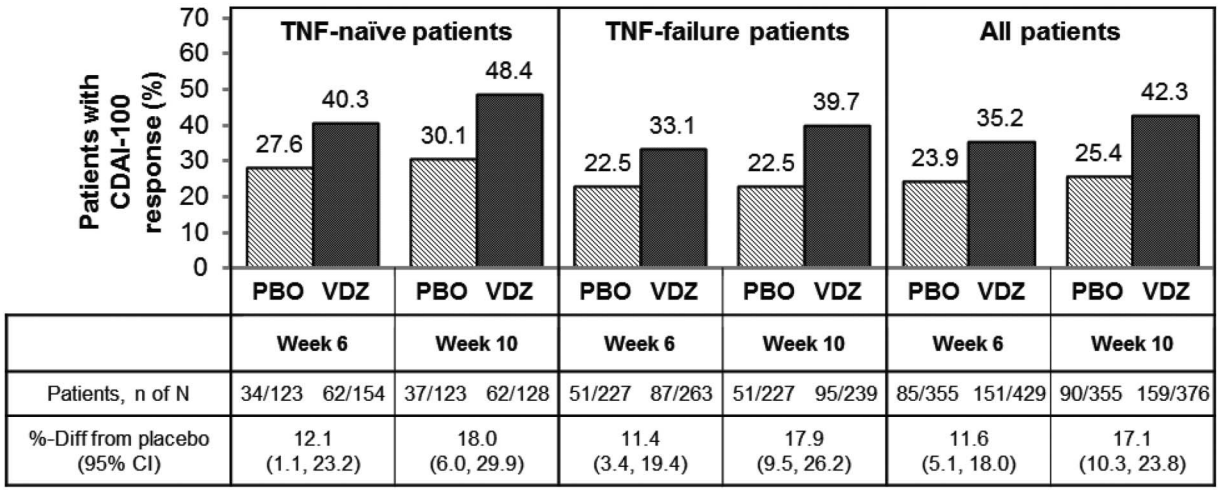
Combining the GEMINI 2 and GEMINI 3 populations allowed for a larger sample size to be included in the induction subgroup analyses. When evaluating the GEMINI 2 TNF-naïve population alone, clinical remission and CDAI-100 response rates were higher with vedolizumab at week 6 than with placebo, but not significantly (see Table 2, Supplemental Digital Content 1, http://links.lww.com/IBD/B401). Similarly, combining the every 8-week and every 4-week dosing groups increased the sample size for the maintenance efficacy analyses. Efficacy outcomes evaluated in the every 8-week and every 4-week dosing groups separately are provided in Table 2 (Supplemental Digital Content 1, http://links.lww.com/IBD/B401).

Efficacy of Vedolizumab in the TNF-Failure Population

Vedolizumab induction treatment resulted in significantly greater percentages of TNF-failure patients in clinical remission and with CDAI-100 response than treatment with placebo (Fig. 1). For TNF-failure patients in remission, the treatment difference from placebo was not significant at week 6 (4.1%



	Week 6	Week 10	Week 6	Week 10	Week 6	Week 10
Patients, n of N	13/123 35/154	19/123 34/128	22/227 35/263	25/227 52/239	35/355 72/429	44/355 87/376
%-Diff from placebo (95% CI)	12.6 (3.7, 21.4)	11.3 (1.5, 21.1)	4.1 (-1.6, 9.8)	11.5 (4.5, 18.6)	7.4 (2.6, 12.2)	11.0 (5.5, 16.5)



	Week 6	Week 10	Week 6	Week 10	Week 6	Week 10
Patients, n of N	34/123 62/154	37/123 62/128	51/227 87/263	51/227 95/239	85/355 151/429	90/355 159/376
%-Diff from placebo (95% CI)	12.1 (1.1, 23.2)	18.0 (6.0, 29.9)	11.4 (3.4, 19.4)	17.9 (9.5, 26.2)	11.6 (5.1, 18.0)	17.1 (10.3, 23.8)

FIGURE 1. Clinical efficacy of induction therapy at weeks 6 and 10 by TNF antagonist treatment history. Percentages of patients in (A) clinical remission, defined by CDAI score ≤150 and with (B) enhanced clinical response, defined by a change from baseline score of ≥100 points (CDAI-100 response). CDAI, Crohn's Disease Activity Index; CI, confidence interval; diff, difference; PBO, placebo; TNF, tumor necrosis factor; VDZ, vedolizumab.

difference; 95% CI: −1.6, 9.8) but reached significance at week 10 (11.5% difference; 95% CI: 4.5–18.6) (Fig. 1A). Differences from placebo in percentages of patients achieving CDAI-100 response were significant at week 6, with greater differences from placebo achieved at week 10 (Fig. 1B). Percentages of patients with response overall were higher when the cutoff for defining a response in CDAI score was 70 points (see Fig. 2, Supplemental Digital Content 1, http://links.lww.com/IBD/B401).

Trends favoring vedolizumab induction were observed across all 3 measures of efficacy—clinical remission (Fig. 3A, B), CDAI-100 response (Fig. 3C, D), and CDAI-70 response (see Fig. 2, Supplemental Digital Content 1, http://links.lww.com/IBD/B401)—at both weeks 6 and 10, irrespective of the type of failure or the number of prior TNF-α antagonists failed. Although there was some variability in the absolute treatment difference between the subgroups, vedolizumab was consistently favored at week 10, with significant differences from placebo achieved for all TNF-failure subgroups with clinical remission, excluding those with 1 prior failure (Fig. 3B). Significant differences from placebo were also observed at week 10 for all TNF-failure subgroups with CDAI-100 response (Fig. 3D). Clinical response rates at week 6 were not significantly different from placebo in patients with failure of ≥2 TNF-α antagonists or prior intolerance to TNF-α antagonist therapy (Fig. 3C and see Fig. 2B, Supplemental Digital Content 1, http://links.lww.com/IBD/B401).

Vedolizumab maintenance treatment among those with response at week 6 resulted in greater percentages of TNF-failure patients in remission than treatment with placebo (27.7% and 12.8%, respectively; 14.9% difference; 95% CI: 4.7–25.0), but the treatment difference was numerically lower than in TNF-naïve patients (Fig. 2A). Percentages of TNF-failure patients with a CDAI-100 response (Fig. 2B), corticosteroid-free remission (Fig. 2C), and durable clinical remission (Fig. 2D) were also higher with vedolizumab treatment than with placebo. The number of prior TNF-α antagonists failed did

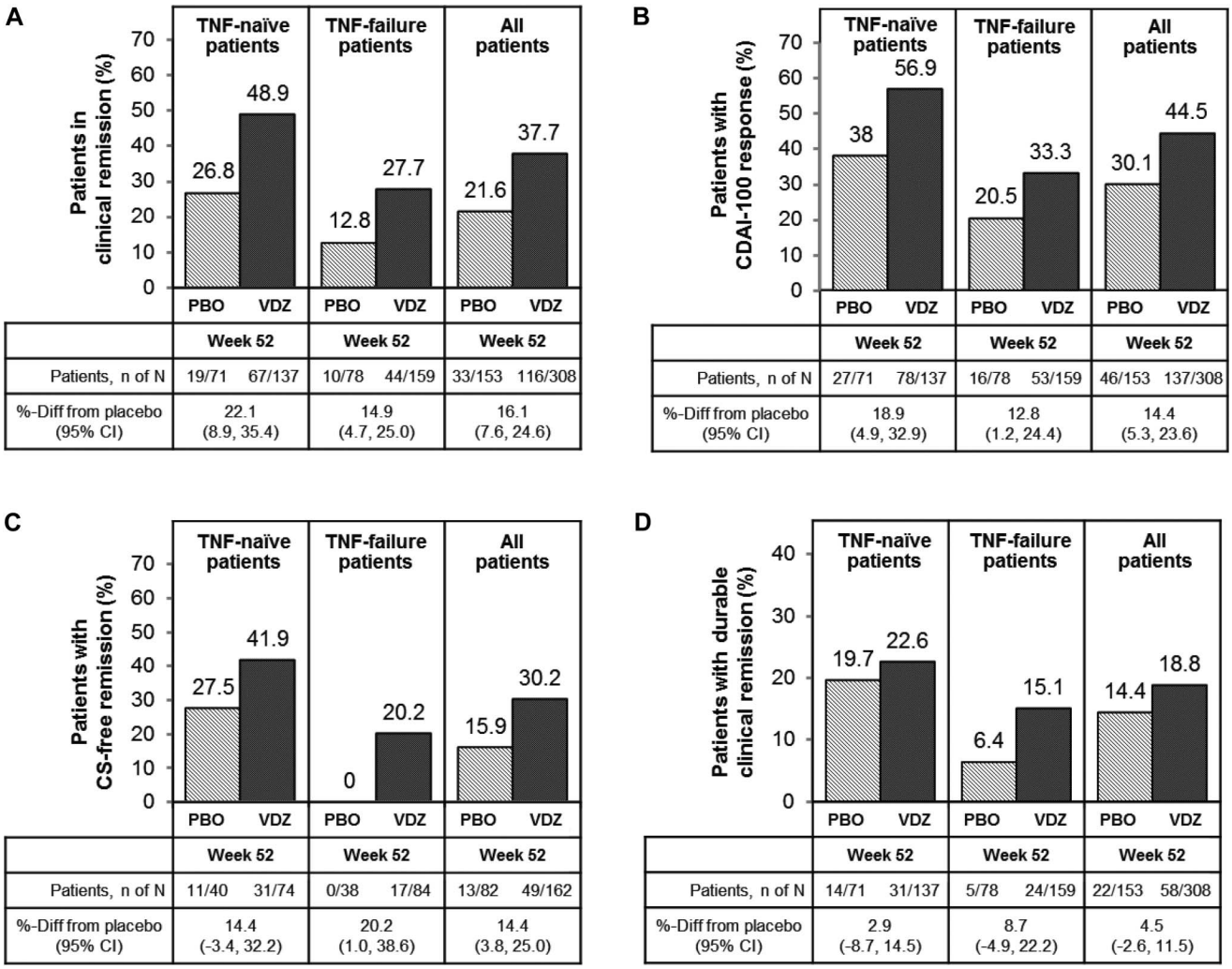


FIGURE 2. Clinical efficacy of maintenance therapy at week 52 by TNF antagonist treatment history. A, Percentages of patients in clinical remission, defined by a CDAI score ≤150. B, Percentages of patients with enhanced clinical response, defined by a change from baseline score of ≥100 points (CDAI-100 response). C, Percentages of patients with corticosteroid-free remission, defined as clinical remission without corticosteroid therapy among patients on corticosteroids at baseline. D, Percentages of patients with durable clinical remission, defined as clinical remission at ≥80% of study visits, including the final visit. CDAI, Crohn's Disease Activity Index; CI, confidence interval; CS, corticosteroid; diff, difference; PBO, placebo; TNF, tumor necrosis factor; VDZ, vedolizumab.

not affect the efficacy of vedolizumab maintenance therapy (Fig. 4); statistically significant differences from placebo were observed for patients with ≥2 prior failures who were in clinical remission (13.9% difference; 95% CI: 1.7, 26.2) and with CDAI-100 response (17.5% difference; 95% CI: 4.1–31.0) (Fig. 4A, B). Over 30% of patients with 1 prior failure and 25% of patients with ≥2 prior failures were in clinical remission at week 52 with vedolizumab treatment (versus 16% and 11%, respectively, with placebo).

Safety

In general, no clinically important differences in adverse events were observed between vedolizumab and placebo treatment groups in the TNF-naïve and TNF-failure populations (Table 2). In the pooled induction population, including patients who received open-label vedolizumab during GEMINI 2 (Cohort 2), adverse events were experienced by 43% of vedolizumab-exposed and 50% of placebo-exposed TNF-naïve patients and 64% of vedolizumab-exposed and 65% of placebo-exposed TNF-failure patients (see Table 3, Supplemental Digital Content 1, http://links.lww.com/IBD/B401). During the 52-week GEMINI 2 study, 80% of vedolizumab-exposed and 76% of placebo-exposed TNF-naïve patients and 90% of vedolizumab-exposed and 83% of placebo-exposed TNF-failure patients experienced an adverse event (Table 2). The most common adverse event with vedolizumab exposure in both TNF-naïve and TNF-failure patient populations was exacerbation of disease, which occurred in 14% of TNF-naïve patients and 23% of TNF-failure patients. Arthralgia, nasopharyngitis, nausea, pyrexia, and headache each occurred

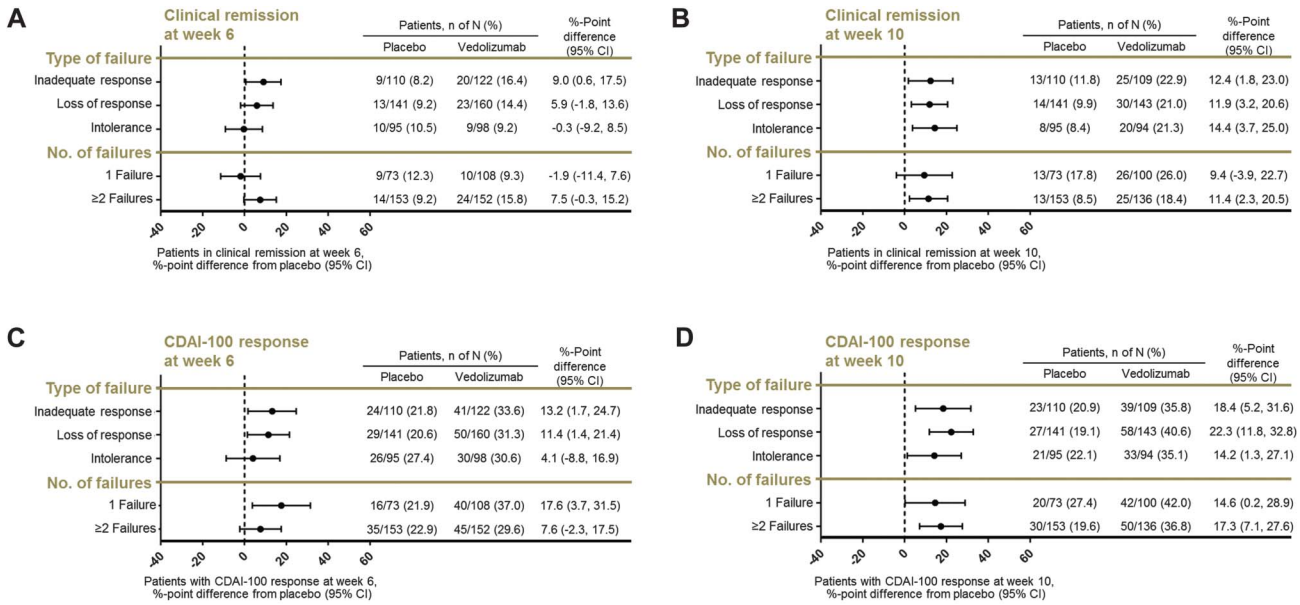


FIGURE 3. Clinical efficacy of induction therapy at weeks 6 and 10 by type of TNF antagonist failure and number of prior TNF antagonists failed. Patients may have had >1 type of failure. A and B, Percentages of patients in clinical remission, defined by CDAI score ≤150, at weeks 6 and 10, respectively. C and D, Percentages of patients with enhanced clinical response, defined by a change from baseline score of ≥100 points (CDAI-100 response), at weeks 6 and 10, respectively. Forest plots show the percent difference from placebo with 95% CI. CDAI, Crohn's Disease Activity Index; CI, confidence interval; TNF, tumor necrosis factor.

in ≥10% of vedolizumab-exposed patients in either population (Table 2). More individual events occurred in ≥5% of TNF-failure patients (i.e., nausea, fatigue, back pain, urinary tract infection, dizziness, bronchitis, diarrhea, and sinusitis) than in patients who were TNF-naïve (Table 2); however, no statistical comparisons were performed. Overall, 11% of vedolizumab-exposed patients from each population discontinued from the 52-week GEMINI 2 study versus 4% of TNF-naïve patients and 14% of TNF-failure patients exposed to placebo (Table 2).

Serious adverse events with vedolizumab exposure occurred in 24% of patients from each population. Of note, serious infections occurred in 6% of vedolizumab-exposed and 3% of placebo-exposed TNF-naïve patients and 5% of vedolizumab-exposed and 3% of placebo-exposed TNF-failure patients, corresponding to <30 patients in any treatment group (Table 2).

No deaths occurred during GEMINI 3.[20] Four vedolizumab-exposed patients died during GEMINI 2: 1 death was due to exacerbation of CD and sepsis (TNF-naïve), 1 from septic shock (TNF-naive), 1 from intentional overdose (TNF-failure), and 1 from myocarditis (TNF-failure). One patient who was TNF-naïve and randomized to placebo died because of bronchopneumonia. Both cases of sepsis occurred in patients with significant comorbidities and a complicated hospital course that contributed to the deaths. Detailed accounts of their deaths have been described previously.[19]

DISCUSSION

The efficacy and safety of vedolizumab induction and maintenance therapy in TNF-naïve and TNF-failure subgroups were evaluated here in a pooled analysis of patients with moderately to severely active CD from the GEMINI 2 and GEMINI 3 phase 3 clinical trials. In both TNF-naïve and TNF-failure populations, vedolizumab was more efficacious than placebo in achieving clinical remission. In TNF-naïve patients, the effects of vedolizumab induction on clinical remission were evident at week 6 and week 10, with both being significantly different from placebo. By contrast, in TNF-failure patients, the effects of vedolizumab induction on clinical remission did not become evident until week 10. Remission rates remained higher than placebo with vedolizumab maintenance through week 52 in both populations, illustrating the potential value of vedolizumab as a first-line biologic and as a treatment alternative in those who are TNF-α antagonist experienced. Compared with placebo, vedolizumab generally showed similar efficacy irrespective of the type of prior TNF-α antagonist failure—whether inadequate response, loss of response, or intolerance. There were no consistent differences in the efficacy of vedolizumab with the number of prior TNF-α antagonists failed. These findings are of particular clinical relevance because studies have shown that overall response and remission rates may be diminished when switching to a second or third TNF-α antagonist, especially in primary nonresponders, where disease activity may be driven via a TNF-α independent pathway.[6,10,23,24] When a treatment switch is warranted, a drug with a different mechanism of action may be preferred.[24] Empiric switching—or cycling—through multiple TNF-α antagonists may result in suboptimal clinical and economic outcomes.[25] However, the exclusion from the maintenance trial of those patients who may have responded at week 10 or later—for example,

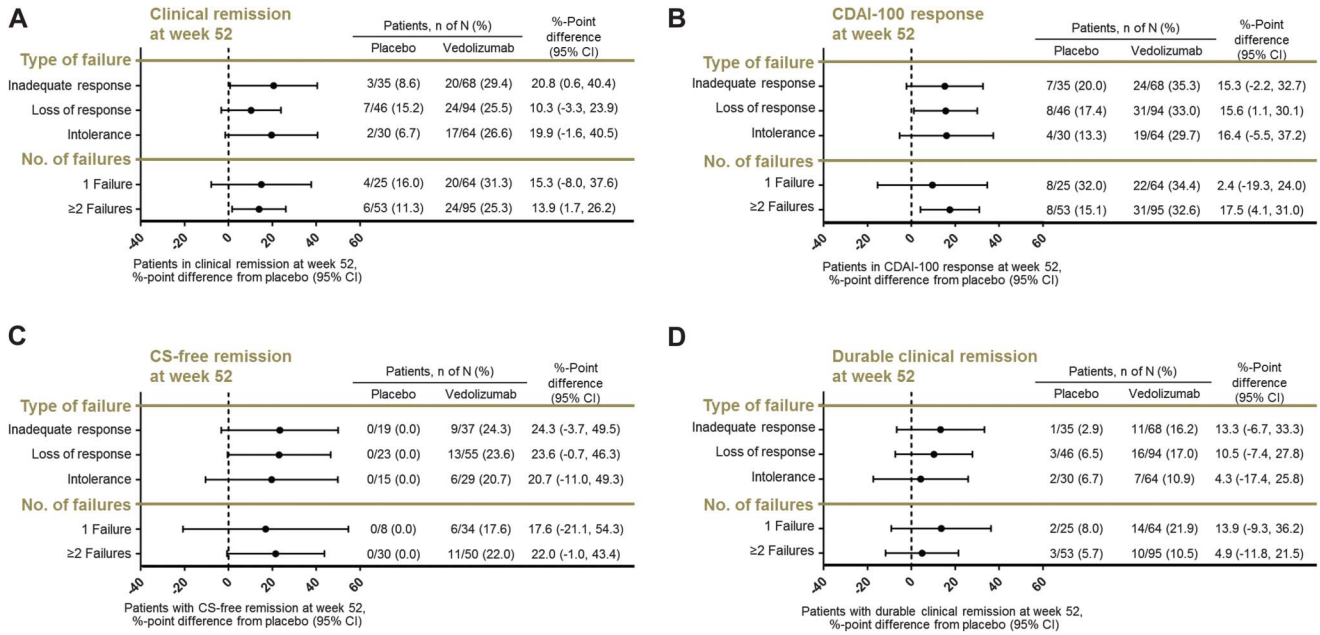


FIGURE 4. Clinical efficacy of maintenance therapy at week 52 by type of TNF antagonist failure and number of TNF antagonists failed. Forest plots show the percent difference from placebo and 95% CIs for patients with (A) clinical remission, defined by a CDAI score ≤150; (B) enhanced clinical response, defined by a change from baseline score of ≥100 points (CDAI-100 response); (C) corticosteroid-free remission, defined as clinical remission without corticosteroid therapy among patients on corticosteroids at baseline; and (D) durable clinical remission, defined as clinical remission at ≥80% of study visits, including the final visit. CDAI, Crohn's Disease Activity Index; CI, confidence interval; CS, corticosteroid; TNF, tumor necrosis factor antagonist.

patients with failure of ≥2 TNF-α antagonists—should be considered when interpreting these data.

The definition of TNF-α antagonist failure used in these analyses was prespecified in the study protocols and may not be consistent with how treatment failure is now classified in clinical practice. In an era when monitoring serum drug concentrations and antidrug antibodies can optimize treatment response,[26] some patients who we categorized in the TNF-failure population may not truly have had their therapy fail by current standards. Further, although intolerable side effects would preclude successful treatment, intolerance itself does not necessarily represent failed efficacy. Nonetheless, the TNF-failure patients in this study collectively represent a highly treatment-experienced population with clinical features—including evidence of active inflammation—that could explain, at least in part, the slower inductive efficacy. For example, compared with TNF-naïve patients, those with prior TNF-α antagonist treatment failure had longer duration of disease and more complicated disease, including prior surgery and histories of fistulas and extraintestinal manifestations. The additional vedolizumab dose at week 6 or an incremental effect of time on the drug's ability to exert a therapeutic effect may have contributed to the greater efficacy observed at week 10 in this treatment-experienced patient population. The mechanism of action of vedolizumab may contribute to a more gradual onset of efficacy in CD patients than other biologics, such as TNF-α antagonists. Specifically, vedolizumab interferes with the binding and adhesion of gut-homing leukocytes by antagonizing the interaction of $\alpha_4\beta_7$ integrin MAdCAM-1 on the mucosal endothelium.[14] In this manner, vedolizumab inhibits lymphocyte migration to the site of inflammation to prevent disease exacerbation and may not directly reduce preexisting inflammation of CD. The efficacy of vedolizumab may thus not be apparent until the natural resolution of such inflammation. Although the lower percentage-point difference from placebo observed in the TNF-failure population in remission at week 6 compared with the TNF-naïve population may seem, from Figure 3, to be driven by patients with intolerance to prior TNF-α antagonist therapy, that patients could have more than 1 type of prior failure and belong to more than one subgroup should be taken into consideration.

Taken together, these efficacy and safety data suggest that induction and maintenance treatments with vedolizumab provide clinical benefit to both TNF-naïve and TNF-failure patients. Patients who were TNF-naïve may experience treatment benefits earlier than those who had failed prior TNF-α antagonist therapy and achieve higher overall rates of response and remission. As previously discussed, limited options are available to patients with CD who do not benefit from TNF-α antagonist therapy. In these exploratory analyses, we demonstrate that the novel biological vedolizumab is effective in TNF-naïve and TNF-failure patients with moderately to severely active CD, without the associated adverse events that often accompany systemic immunosuppressant therapies. Although the present analyses are limited by the post hoc analyses of data from trials not designed to investigate these subpopulations and the small patient numbers within the

Table 2. Summary of Adverse Events Reported by TNF-naïve and TNF-failure Patients (GEMINI 2 Safety Population)

	TNF-naïve Patients		TNF-failure Patients	
Event	Placebo[a] (n = 76)	Vedolizumab[b] (n = 279)	Placebo[a] (n = 70)	Vedolizumab[b] (n = 497)
	Patients, n (%)			
Any adverse event	58 (76)	223 (80)	58 (83)	448 (90)
Any serious adverse event	6 (8)	66 (24)	16 (23)	119 (24)
Any serious infection[c]	2 (3)	16 (6)	2 (3)	26 (5)
Any adverse event leading to discontinuation	3 (4)	32 (11)	10 (14)	53 (11)
Common adverse events (≥5% of patients in the vedolizumab group)[d]				
Exacerbation of CD	7 (9)	40 (14)	28 (40)	114 (23)
Arthralgia	9 (12)	28 (10)	9 (13)	77 (15)
Nasopharyngitis	6 (8)	28 (10)	3 (4)	68 (14)
Nausea	4 (5)	12 (4)	8 (11)	72 (14)
Pyrexia	9 (12)	31 (11)	8 (11)	67 (13)
Headache	9 (12)	30 (11)	9 (13)	64 (13)
Abdominal pain	10 (13)	26 (9)	11 (16)	45 (9)
Fatigue	2 (3)	8 (3)	3 (4)	42 (8)
Upper respiratory tract infection	4 (5)	17 (6)	7 (10)	34 (7)
Vomiting	3 (4)	13 (5)	6 (9)	32 (6)
Back pain	1 (1)	6 (2)	4 (6)	29 (6)
Urinary tract infection	0	10 (4)	3 (4)	25 (5)
Dizziness	4 (5)	5 (2)	3 (4)	23 (5)
Bronchitis	3 (4)	6 (2)	2 (3)	23 (5)
Diarrhea	3 (4)	5 (2)	2 (3)	23 (5)
Sinusitis	1 (1)	4 (1)	0	23 (5)
Anemia	7 (9)	14 (5)	2 (3)	16 (3)

[a]Patients received placebo during both the induction and maintenance phases (non-ITT).
[b]Patients received vedolizumab during both the induction and maintenance phases (non-ITT and ITT combined).
[c]Includes those reported under the "Infections and infestations" system organ class.
[d]Ranked from highest to lowest incidence in vedolizumab-treated TNF-failed patients.
CD, Crohn's disease; ITT, intent-to-treat; TNF, tumor necrosis factor.

TNF-failure subgroups, trends favoring vedolizumab were consistently observed. Vedolizumab therefore provides an additional treatment option for patients irrespective of prior TNF-α antagonist treatment history.

ACKNOWLEDGMENTS

The clinical studies were funded by Millennium Pharmaceuticals, Inc (d/b/a Takeda Pharmaceuticals International Co.). Medical writing assistance was provided by inVentiv Medical Communications and funded by Takeda Pharmaceuticals International, Inc. Publication management support was provided by Caterina Hatzifoti, PhD, of Takeda Pharmaceuticals International.

B. E. Sands has served as a consultant for AbbVie, Amgen, AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Celgene, GlaxoSmithKline Inc., Immune Pharmaceuticals, Janssen Biotech, Luitpold Pharmaceuticals, Pfizer Inc., Prometheus Laboratories, PureTech Ventures, LLC, Receptos, Takeda Pharmaceuticals International Company, and Topivert Pharma; and has received financial support for research from Prometheus Laboratories Inc., Pfizer Inc., Janssen Biotech, Bristol-Myers Squibb, AbbVie, MedImmune, and Takeda. W. J. Sandborn has received financial support for research from Janssen, AbbVie, Pfizer, Amgen, Genentech; has received lecture fees from AbbVie, Takeda; and has served as a consultant to Janssen, AbbVie, Pfizer, Amgen, Genentech, Takeda. G. Van Assche has served as a consultant for AbbVie, Takeda, Janssen, BMS, Robarts Clinical Trials; and has received lecture fees from Janssen, Aptalis, Ferring, Warner Chillcott, AbbVie. J. Xu is an employee of Takeda Pharmaceuticals International Co., Cambridge, MA. A. James is an employee of Takeda Development Centre Europe Ltd., London, United Kingdom. B. Abhyankar is an employee of Takeda Develop-

ment Centre Europe Ltd., London, United Kingdom. K. Lasch is an employee of Takeda Pharmaceuticals U.S.A., Inc., Deerfield, IL. The remaining author has no conflict of interest to disclose.

REFERENCES

1. Lichtenstein GR, Hanauer SB, Sandborn WJ; Practice Parameters Committee of American College of Gastroenterology. Management of Crohn's disease in adults. *Am J Gastroenterol.* 2009;104:465–483.
2. Baumgart DC, Sandborn WJ. Crohn's disease. *Lancet*. 2012;380: 1590–1605.
3. Dignass A, Van Assche G, Lindsay JO, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: current management. *J Crohns Colitis.* 2010;4:28–62.
4. Sandborn WJ. Current directions in IBD therapy: what goals are feasible with biological modifiers? *Gastroenterology*. 2008;135:1442–1447.
5. Feagan BG, Sandborn WJ, Lazar A, et al. Adalimumab therapy is associated with reduced risk of hospitalization in patients with ulcerative colitis. *Gastroenterology*. 2014;146:110–118.
6. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology*. 2007;132:52–65.
7. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet*. 2002;359: 1541–1549.
8. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med.* 2005;353:2462–2476.
9. Sandborn WJ. Clinical perspectives in Crohn's disease. Moving forward with anti-TNF-alpha therapy: current needs and future treatments. *Rev Gastroenterol Disord.* 2007;7(suppl 2):S23–S35.
10. Sandborn WJ, Rutgeerts P, Enns R, et al. Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. *Ann Intern Med.* 2007;146:829–838.
11. McLean LP, Cross RK. Adverse events in IBD: to stop or continue immune suppressant and biologic treatment. *Expert Rev Gastroenterol Hepatol.* 2014;8:223–240.
12. Takeda Entyvio (vedolizumab) [package insert]. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; 2014.
13. Takeda Entyvio. *Entyvio (Vedolizumab): Summary of Product Characteristics*. Taastrup, Denmark: Takeda Pharma A/S; 2014.
14. Soler D, Chapman T, Yang LL, et al. The binding specificity and selective antagonism of vedolizumab, an anti-$\alpha_4\beta_7$ integrin therapeutic antibody in development for inflammatory bowel diseases. *J Pharmacol Exp Ther.* 2009;330:864–875.
15. Fedyk ER, Wyant T, Yang LL, et al. Exclusive antagonism of the $\alpha_4\beta_7$ integrin by vedolizumab confirms the gut-selectivity of this pathway in primates. *Inflamm Bowel Dis.* 2012;18:2107–2119.
16. Haanstra KG, Hofman SO, Lopes Estevao DM, et al. Antagonizing the anti-$\alpha_4\beta_1$ integrin, but not $\alpha_4\beta_7$, inhibits leukocytic infiltration of the central nervous system in rhesus monkey experimental autoimmune encephalomyelitis. *J Immunol.* 2013;190:1961–1973.
17. Hesterberg PE, Winsor-Hines D, Briskin MJ, et al. Rapid resolution of chronic colitis in the cotton-top tamarin with an antibody to a gut-homing integrin alpha 4 beta 7. *Gastroenterology*. 1996;111:1373–1380.
18. Milch C, Wyant T, Xu J, et al. Vedolizumab, a monoclonal antibody to the gut homing $\alpha_4\beta_7$ integrin, does not affect cerebrospinal fluid T-lymphocyte immunophenotype. *J Neuroimmunol.* 2013;264:123–126.
19. Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med.* 2013;369: 711–721.
20. Sands BE, Feagan BG, Rutgeerts P, et al. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. *Gastroenterology*. 2014; 147:618–627.
21. du Prel JB, Hommel G, Rohrig B, et al. Confidence interval or p-value?: part 4 of a series on evaluation of scientific publications. *Dtsch Arztebl Int.* 2009;106:335–339.
22. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). *Drug Saf.* 1999;20:109–117.
23. Leal RF, Planell N, Kajekar R, et al. Identification of inflammatory mediators in patients with Crohn's disease unresponsive to anti-TNFα therapy. *Gut*. 2015;64:233–242.
24. Panaccione R, Ghosh S. Optimal use of biologics in the management of Crohn's disease. *Therap Adv Gastroenterol.* 2010;3:179–189.
25. Rubin DT, Mody R, Davis KL, et al. Real-world assessment of therapy changes, suboptimal treatment and associated costs in patients with ulcerative colitis or Crohn's disease. *Aliment Pharmacol Ther*. 2014; 39:1143–1155.
26. Colombel JF, Feagan BG, Sandborn WJ, et al. Therapeutic drug monitoring of biologics for inflammatory bowel disease. *Inflamm Bowel Dis.* 2012;18:349–358.