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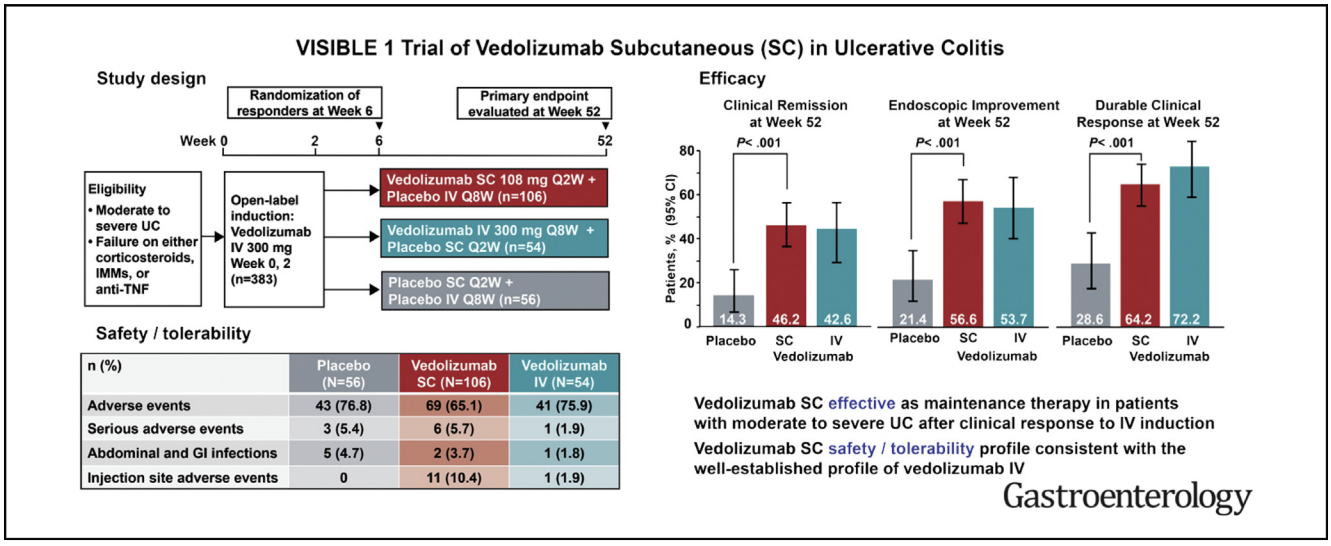
CLINICAL AT

Efficacy and Safety of Vedolizumab Subcutaneous Formulation in a Randomized Trial of Patients With Ulcerative Colitis

William J. Sandborn,[1] Filip Baert,[2] Silvio Danese,[3] Željko Krznarić,[4] Taku Kobayashi,[5] Xiaopan Yao,[6] Jingjing Chen,[6] Maria Rosario,[6] Siddharth Bhatia,[7] Krisztina Kisfalvi,[6] Geert D'Haens,[8] and Séverine Vermeire[9]

[1]Division of Gastroenterology, University of California-San Diego, La Jolla, California; [2]Department of Gastroenterology, AZ Delta, Roeselare, Belgium; [3]Gastrointestinal Immunopathology, Humanitas University, Italy; [4]Division of Gastroenterology and Hepatology, University Hospital Centre Zagreb, Zagreb, Croatia; [5]Center for Advanced IBD Research and Treatment, Kitasato University Kitasato Institute Hospital, Tokyo, Japan; [6]Takeda Development Center Americas Inc, Cambridge, Massachusetts; [7]Takeda International, London, UK; [8]Department of Gastroenterology, Academic Medical Centre, Amsterdam, The Netherlands; and [9]Department of Clinical and Experimental Medicine, University Hospitals Leuven, Leuven, Belgium



BACKGROUND & AIMS: Maintenance treatment with vedolizumab, a monoclonal antibody that inhibits the gut-selective $\alpha^4\beta^7$ integrin, is administered intravenously. Some patients might prefer a subcutaneous formulation of vedolizumab for maintenance treatment. Subcutaneous vedolizumab was investigated as maintenance treatment in patients with moderately to severely active ulcerative colitis. **METHODS:** We performed a phase 3, double-blind, double-dummy trial at 141 sites in 29 countries from December 18, 2015 through August 21, 2018. Patients with moderately to severely active ulcerative colitis received open-label treatment with intravenous vedolizumab 300 mg at weeks 0 and 2. At week 6, patients with clinical response were randomly assigned maintenance treatment with subcutaneous vedolizumab 108 mg every 2 weeks, intravenous vedolizumab 300 mg every 8 weeks, or placebo. The primary end point was clinical remission at week 52, which was defined as a total Mayo score of $\leq$2 and no subscore $>$1. **RESULTS:** Among the randomized 216 patients, clinical remission at week 52 was achieved by 46.2%, 42.6%, and 14.3% of patients in the subcutaneous vedolizumab, intravenous vedolizumab, and placebo groups, respectively (subcutaneous vedolizumab vs placebo: Δ32.3%; 95% confidence interval, 19.7%–45.0%; $P < .001$). The subcutaneous vedolizumab group also had greater endoscopic improvement and durable clinical response at week 52 compared with placebo (both $P < .001$). The incidence of injection-site reactions was more frequent in patients given subcutaneous vedolizumab (10.4%) than intravenous vedolizumab (1.9%) or placebo (0%); these were not treatment limiting, most were mild, and none resulted in discontinuation. Subcutaneous and intravenous vedolizumab safety profiles were otherwise similar. **CONCLUSIONS:** Subcutaneous vedolizumab is effective as maintenance therapy in patients with moderately to severely active ulcerative colitis who had a clinical response to intravenous vedolizumab induction therapy. It has a favorable safety and tolerability profile. ClinicalTrials.gov ID: NCT02611830; EudraCT 2015-000480-14.

Keywords: VISIBLE 1; UC; Inflammatory Bowel Disease; Long-Term Therapy.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Some patients might prefer subcutaneous administration of vedolizumab for maintenance treatment of ulcerative colitis (UC) instead of the current intravenous administration. We performed a phase 3 trial to evaluate subcutaneous vedolizumab as maintenance therapy in patients with moderately to severely active UC.

NEW FINDINGS

Subcutaneous vedolizumab was effective as maintenance therapy, with a favorable safety profile in patients with moderately to severely active UC who had a clinical response to intravenous vedolizumab induction therapy.

LIMITATIONS

The study was powered to assess the primary endpoint of clinical remission after 52 weeks, but was not sufficient to assess some secondary endpoints.

IMPACT

Patients with moderately to severely active UC can use either intravenous or subcutaneous vedolizumab for maintenance therapy without losing efficacy or experiencing additional safety issues.

Ulcerative colitis (UC) is a chronic disease of the colon and rectum that can result in structural bowel damage, loss of function, and disability.[1] If not treated effectively, UC can decrease patient quality of life, with patients often reporting symptoms of fatigue, depression, and anxiety, in addition to the typical diarrhea with blood and mucus discharge.[2,3]

Initial management of UC with conventional therapy includes the use of mesalamine and corticosteroids and/or immunomodulators.[4] Both oral mesalamine and immunomodulators are used for maintenance of conventional treatment effects.[5,6] Biologic treatments, such as vedolizumab and tumor necrosis factor antagonists (anti-TNFs), are indicated for patients failing conventional maintenance therapy.[7–9] The currently available biologic treatments for UC are administered as either intravenous (IV) or subcutaneous (SC) injections. For chronic diseases such as UC that require long-term maintenance treatment, some patients may prefer self-administered SC dosing to IV dosing as a less time-intensive and more convenient treatment option.[10–14]

Vedolizumab is a humanized monoclonal antibody that inhibits the gut-selective $\alpha_4\beta_7$ integrin on the surface of a subset of leukocytes, preventing their trafficking into the gastrointestinal tract.[15] An IV formulation of vedolizumab can be used as a first- or second-line biologic and is indicated for adult patients with moderately to severely active UC and Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to either conventional therapy or an anti-TNF.[7,16] The safety and efficacy of vedolizumab IV is well-established for both induction and maintenance treatment of UC.[17,18]

A new formulation for SC administration of vedolizumab has been developed to offer this option to patients who may prefer the convenience of SC therapy. Here, we report the primary efficacy and safety results from the phase 3 VISIBLE 1 trial, which evaluated the efficacy and safety of maintenance therapy with vedolizumab SC vs placebo in patients with UC after induction therapy with vedolizumab IV.

Methods

Study Population

Eligible patients were 18–80 years of age with moderately to severely active UC for ≥6 months, confirmed with histopathology. Moderately to severely active disease was defined as a total Mayo score[19] of 6–12 (with a centrally read endoscopic subscore ≥2). Patients were required to have evidence of UC extending proximal to the rectum (≥15 cm of involved colon) and an inadequate response to, loss of response to, or intolerance to at least 1 other treatment that was either a corticosteroid, immunomodulator, or anti-TNF.

Patients with an abdominal abscess, toxic megacolon, subtotal or total colectomy, unresected adenomatous colonic polyps, colonic mucosal dysplasia, or prior exposure to any anti-integrin therapies (eg, vedolizumab, natalizumab, efalizumab, etrolizumab, and AMG 181), anti-MAdCAM-1 antibodies, or rituximab were ineligible. Exposure to any biologics within 60 days or 5 half-lives of screening (whichever was longer) or exposure to any nonbiologic therapies, such as cyclosporine, tacrolimus, thalidomide, methotrexate, or tofacitinib, within 30 days or 5 half-lives of screening (whichever was longer) was also not permitted. Concomitant treatment with oral mesalamine (provided the dose was stable for the 2 weeks before the first dose of study drug), azathioprine (provided the dose was stable for the 8 weeks before first dose of study drug), 6-mercaptopurine (provided the dose was stable for the 8 weeks before first dose of study drug), or oral corticosteroids (stable dose of prednisone ≤30 mg/d or budesonide ≤9 mg/d, or equivalent; provided the dose was stable for the 4 weeks before first dose of study drug if just initiated, or for the 2 weeks prior if being tapered) was allowed. After clinical response at week 6, corticosteroid tapering was mandatory, with prednisone doses >10 mg/d (or equivalent) reduced at a rate of 5 mg/wk until a 10 mg/d dose was reached, and prednisone doses ≤10 mg/d (or equivalent) reduced at a rate of 2.5 mg/wk until discontinuation. Patients who could not tolerate corticosteroid tapering without experiencing a recurrence of clinical symptoms were allowed to increase their corticosteroid dose back up to their baseline (week 0) dose,

Abbreviations used in this paper: **AE, adverse event; AVA, anti-vedolizumab antibody; $C_{avg,ss}$, average serum concentration at steady state; CI, confidence interval; $C_{trough,ss}$, trough concentrations at steady state; EQ-5D, EuroQoL-5D; ISR, injection-site reaction; IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; PK, pharmacokinetic; SC, subcutaneous; TNF, tumor necrosis factor; UC, ulcerative colitis.**

Most current article

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with the condition that tapering be reinitiated within 2 weeks. Patients who consistently could not be tapered were withdrawn from the study.

Study Design

VISIBLE 1 (ClinicalTrials.gov ID: NCT02611830; EudraCT 2015-000480-14) was a phase 3, randomized, placebo-controlled, double-blind, double-dummy trial conducted at 141 sites in 29 countries between December 18, 2015, and August 21, 2018 (see Supplementary Figure 1 for study design). The investigator or investigator's designee accessed an interactive web response system at screening to register a patient and obtain a patient identification number to identify the patient throughout the study. After a 28-day screening period, patients with moderately to severely active UC received open-label induction treatment with 300 mg vedolizumab IV at weeks 0 and 2. At week 6, patients were assessed for clinical response, defined as a reduction in total Mayo score of $\geq$3 points and $\geq$30% from baseline (week 0) with an accompanying decrease in rectal bleeding subscore of $\geq$1 point or absolute rectal bleeding subscore of $\leq$1. The Mayo endoscopic subscore (a component of the Mayo score) was assessed by a central reader. Patients with a clinical response at week 6 were randomized to maintenance treatment with vedolizumab SC (108 mg vedolizumab SC every 2 weeks along with IV placebo every 8 weeks), vedolizumab IV (300 mg every 8 weeks along with SC placebo every 2 weeks), or placebo (SC placebo every 2 weeks and IV placebo every 8 weeks) in a 2:1:1 ratio, with stratification by concomitant corticosteroid use, clinical remission status at week 6, and previous anti-TNF failure or concomitant immunomodulator use. Vedolizumab SC dose selection for this study was based on the determination of bioavailability for the SC formulation compared with IV. Vedolizumab SC dosing at 108 mg every 2 weeks was calculated to provide generally comparable drug exposure to that achieved with vedolizumab IV 300 mg every 8 weeks based on average serum vedolizumab concentrations at steady state ($C_{avg,ss}$). A previous population pharmacokinetic (PK) model was used to perform the simulations.[20] The medication identification number of the investigational drug was dispensed as provided by the interactive web response system.

Patients who did not achieve a clinical response at week 6 received a third open-label 300-mg vedolizumab IV dose at week 6 and were re-assessed for clinical response, defined as a reduction in partial Mayo score of $\geq$2 points and $\geq$25% from baseline with an accompanying decrease in rectal bleeding subscore of $\geq$1 point or absolute rectal bleeding subscore of $\leq$1, at week 14. Those achieving a clinical response at week 14 had the option to enroll in an open-label extension study (ClinicalTrials.gov ID: NCT02620046; EudraCT 2015-000482-31), and those who did not respond at week 14 were discontinued. All patients provided written informed consent before participation, and the study was conducted and reported according to the protocol (available in the Supplementary Materials).

Study Assessments

During induction treatment, patient visits were at weeks 0, 2, and 6. During maintenance treatment, patient visits were at weeks 7, 8, and 14; then every 8 weeks until week 46; then at weeks 50, 51, and 52. A final safety follow-up visit occurred at week 68. Flexible sigmoidoscopies were performed and colonic tissue samples were collected at screening, week 6, and week 52. Total Mayo scores, including the endoscopic subscores, were assessed at weeks 0, 6, and 52. Partial Mayo scores (stool frequency, rectal bleeding, and physician rating of disease activity) were assessed at weeks 2 and 14, and then every 8 weeks until week 46, and also at week 50. Safety was assessed at each study visit through the final safety follow-up visit at week 68. Pharmacokinetics and vedolizumab serum concentrations were assessed using a previously described, validated drug-tolerant, sandwich enzyme-linked immunosorbent assay.[20] Blood samples for PK analyses were obtained within 30 minutes before dosing at study visits on weeks 0, 6, 8, 14, 22, 30, 38, 46, and 50, and at any time during study visits at weeks 7, 51, and 52. Immunogenicity was assessed in serum samples collected at weeks 0, 6, 8, 14, 22, 30, 38, 46, and 52 using an electrochemiluminescence assay with a drug tolerance of $\geq$50 μg/mL. Fecal calprotectin was measured via enzyme-linked immunosorbent assay at screening and at weeks 0, 6, 30, and 52.

Study End Points

Efficacy. Patients who achieved clinical response at week 6 after induction treatment at weeks 0 and 2 were randomized into the maintenance phase of the study where they were assessed for all primary and secondary clinical end points at week 52. The primary efficacy end point was the proportion of patients in clinical remission, defined as a total Mayo score of $\leq$2 and no individual subscore $>$1 at week 52. Secondary efficacy end points at week 52, in ranked order, were the proportion of patients with endoscopic improvement (termed *mucosal healing* in the study protocol) assessed as Mayo endoscopic subscore $\leq$1 (normal/inactive disease or mild disease), durable clinical response (clinical response at weeks 6 and 52), durable clinical remission (clinical remission at weeks 6 and 52), and corticosteroid-free remission (discontinuation of oral corticosteroids, followed by clinical remission at week 52, assessed in patients using oral corticosteroids at baseline). Exploratory efficacy end points included corticosteroid-free status, corticosteroid dose, clinical remission at study visits, alternative definitions of clinical remission based on modified Mayo scores, fecal calprotectin as an inflammatory biomarker, and histology using Geboes score and Robarts Histopathology Index.

Patient-reported outcomes. Inflammatory Bowel Disease Questionnaire total score and subscores, EuroQoL-5D (EQ-5D) utility scores, EQ-5D visual analog scale score, and Work Productivity and Activity Impairment–Ulcerative Colitis instrument scores were assessed.

Safety/tolerability. Adverse events (AEs), defined as any AE regardless of relationship to study drug, were captured during study visits and from any spontaneous reports at any time during the study, and were coded using the MedDRA (Medical Dictionary for Regulatory Activities).

Pharmacokinetics and immunogenicity. Vedolizumab PK exposure (as $C_{avg,ss}$) and anti-vedolizumab antibody (AVA) development rates were evaluated. Positive AVA status was defined as having at least 1 positive AVA result from predose through week 52. Persistently positive AVA status was defined as having an AVA-positive serum sample at 2 or more consecutive visits.

Statistical Analyses

The efficacy of vedolizumab SC vs placebo was evaluated in the patients who were randomized into the maintenance phase of the study and received at least 1 dose of study drug. Formal statistical comparisons were performed only for primary and secondary efficacy end points with the vedolizumab SC vs placebo groups. The vedolizumab IV reference group was included to allow for within-study exploratory comparisons of efficacy end points between the vedolizumab IV group and the placebo group (nominal *P* values presented) and descriptive comparisons between vedolizumab SC and IV formulations.

Efficacy data were analyzed in the full analysis set (all randomized patients who received ≥1 dose of study drug) according to treatment allocation. AEs were analyzed in the safety analysis set (all randomized patients who received ≥1 dose of study SC drug [placebo or vedolizumab]) according to actual treatment received. PK data were analyzed in the PK-evaluable population (all randomized patients who received at least 1 dose of study SC drug [placebo or vedolizumab] and had sufficient blood sampling to allow for PK evaluation).

Statistical comparisons between vedolizumab SC and placebo were performed with a 2-sided test at significance level of .05 using a hierarchical approach to control the overall type I error rate. The primary end point was tested first, with subsequent secondary end points tested only if statistical significance was achieved with the primary end point and dependent on the significance of the preceding secondary end point in the following order: endoscopic improvement, durable clinical response, durable clinical remission, and corticosteroid-free remission. Other comparisons were considered exploratory, and nominal *P* values were presented.

The proportions of patients achieving each efficacy end point were compared between treatments using the Cochran-Mantel-Haenszel test, adjusted for study randomization stratification factors (concomitant use of corticosteroids, clinical remission status at week 6, and previous anti-TNF failure or concomitant immunomodulator use), or Fisher's exact test if the number of remitters in either vedolizumab SC or placebo group was ≤5.

For dichotomous (ie, proportion-based) end points, any patient with missing information for determination of endpoint status was considered as a nonresponder in the analysis. Missing data for continuous end points were imputed using the last available post-baseline observation carried forward method.

Incidence rates were analyzed for the safety end points (AEs) and immunogenicity (AVAs). Population PK modeling methodology, described previously,[20] was used to estimate median $C_{avg,ss}$ and median trough concentrations at steady state ($C_{trough,ss}$) with 90% confidence intervals (CIs) based on pooled PK data from the GEMINI and VISIBLE clinical trial programs, including the current study.[21] Briefly, vedolizumab $C_{trough,ss}$ and $C_{avg,ss}$ were simulated using the population PK model developed from the vedolizumab IV program as updated with VISIBLE 1 data. For this analysis, complete observed covariate sets were resampled from vedolizumab SC and vedolizumab IV patient populations at week 46.[21] All 1000 posterior samples from the final population PK model were used to simulate 1000 patients per arm (ie, regimen × study) at the resampled covariates.[21]

Assuming a clinical remission rate of 42% for vedolizumab SC vs 16% for placebo at week 52 after maintenance treatment, a sample size of 94 patients in the vedolizumab SC group and 47 patients in the placebo group was determined to provide 90% power to detect a treatment difference at a 2-sided significance level of .05. Anticipating that 47% of patients would achieve clinical response at week 6 after induction treatment and would enter the maintenance phase, it was determined that an enrollment of 400 patients was needed to ensure a randomized sample size of 188 patients (94 for vedolizumab SC and 47 for placebo, plus another 47 for vedolizumab IV reference arm) during maintenance.

Study Oversight

This study was overseen by the sponsor, Takeda Development Center, and conducted by contracted clinical investigators. Medical and clinical monitoring were conducted by the sponsor and its designated representatives. A Data Safety Monitoring Board independent from the sponsor regularly reviewed unblinded safety data. An Independent Adjudication Committee was established to review and adjudicate potential progressive multifocal leukoencephalopathy events. The clinical study protocol and all applicable protocol amendments, the investigator's brochure, a sample informed consent form, and other study-related documents were reviewed and approved by the local or central institutional review boards of all study sites. This study was conducted in compliance with the informed consent regulations stated in the Declaration of Helsinki, International Conference on Harmonisation Guidelines for Good Clinical Practice, and all applicable local laws and regulations.

All authors had access to the study data and reviewed and approved the final manuscript.

Results

Study Population

In total, 383 patients were enrolled and treated in the open-label induction phase, with 353 (92.2%) completing vedolizumab IV (300 mg) induction treatment (Figure 1). At week 6, 215 patients responded to vedolizumab IV induction (56.1%), 5 of whom were not randomized (Supplementary Table 1). Six patients who did not achieve clinical response were randomized in error, for a total of 216 enrolled patients (56.4%) randomized (210 with clinical response, 6 randomized in error) to receive placebo (n = 56), vedolizumab SC (n = 106), or vedolizumab IV (n = 54) during the maintenance phase. There were no clinically important differences in demographic or baseline characteristics, or in medication history among the 3 maintenance treatment groups, and the majority of patients had severe disease (defined as total Mayo score 9–12) (Table 1). During the maintenance phase, 139 of 216 randomized patients (64.4%) completed treatment: 21 patients (37.5%) in the placebo group, 77 (72.6%) in the vedolizumab SC group, and 41 (75.9%) in the vedolizumab IV group. The main reason for discontinuation in the maintenance phase was lack of efficacy, with 28, 18, and 6 patients on placebo, vedolizumab SC, and vedolizumab IV, respectively,

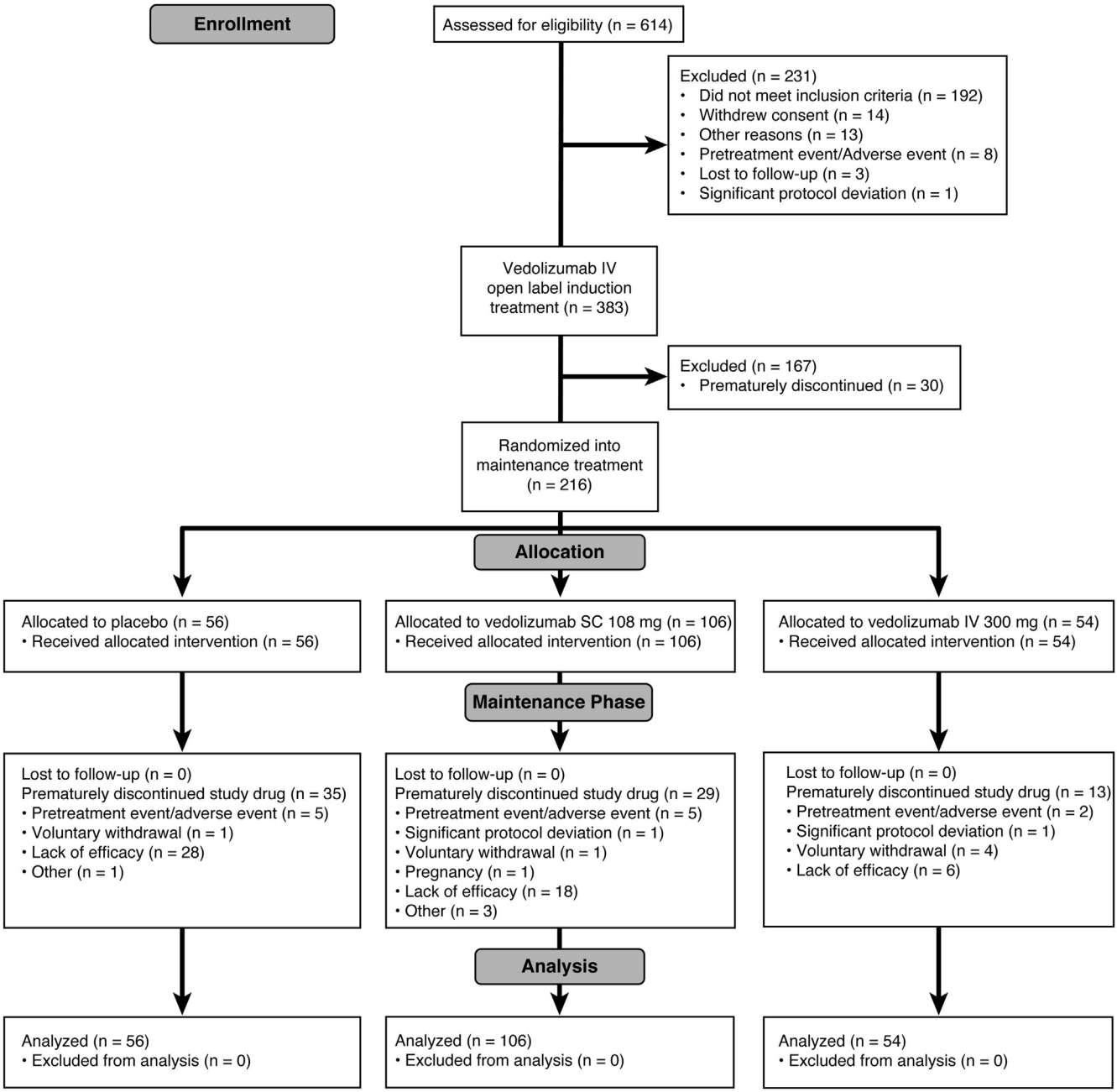

Figure 1. Patient disposition.

discontinuing for this reason. Other reasons for discontinuation included pretreatment AEs, voluntary withdrawal, and "other" (Figure 1).

Efficacy

Patients receiving vedolizumab SC maintenance treatment were more likely to show clinical remission at week 52 compared with placebo, with 49 of 106 patients (46.2%) on vedolizumab SC showing clinical remission vs 8 of 56 (14.3%) of the placebo group (Δ32.3%; 95% CI, 19.7%–45.0%; $P < .001$) (Figure 2). Greater rates of clinical remission occurred with vedolizumab SC compared with placebo among both anti-TNF naïve and anti-TNF failure patients (Figure 2). The treatment effects on rates of clinical remission at week 52 across subgroups based on baseline patient and disease characteristics are presented in Supplementary Figure 2.

Patients treated with vedolizumab SC experienced significantly greater rates of endoscopic improvement and durable clinical response compared with those treated with placebo (both, $P < .001$) (Table 2). The proportion of patients in endoscopic remission (Mayo endoscopic subscore = 0) at week 52 was 29.2% with vedolizumab SC and 12.5% with placebo (Supplementary Table 2). Rates of durable clinical remission as a proportion of the full study population were numerically greater in the

Table 1. Demographic and Baseline Characteristics and Medication History of Patients Who Received Maintenance Treatment

Characteristic	Placebo (n = 56)	Vedolizumab SC (n = 106)	Vedolizumab IV (n = 54)
Age, *y*, mean (SD)	39.4 (11.7)	38.1 (13.1)	41.6 (14.1)
Sex, *male*, n (%)	34 (60.7)	65 (61.3)	31 (57.4)
Race, *white*, n (%)	42 (75.0)	92 (86.8)	47 (87.0)
Body weight, *kg*, mean (SD)	74.0 (20.9)	71.6 (17.2)	77.0 (16.9)
Current smoker, *yes*, n (%)	0	11 (10.4)	10 (18.5)
Duration of UC, *y*, mean (SD)	7.4 (7.1)	8.0 (6.2)	8.2 (5.9)
Mayo score, n (%)			
Mild (total Mayo score, <6)	0	0	0
Moderate (total Mayo score, 6–8)	20 (35.7)	46 (43.4)	17 (31.5)
Severe (total Mayo score, 9–12)	36 (64.3)	60 (56.6)	37 (68.5)
Mayo score, median (minimum–maximum)			
Baseline	9.0 (6–11)	9.0 (6–12)	9.0 (6–12)
Wk 6	4.0 (0–7)	3.5 (0–8)	4.0 (0–7)
Albumin, *g/L*, median (minimum–maximum)			
Baseline	43.0 (35-49)	42.5 (33-53)	43.0 (35-49)
Week 6	44.0 (36-51)	45.0 (35-53)	45.0 (36-49)
Fecal calprotectin, n (%)			
≤250 μg/g	5 (8.9)	9 (8.5)	2 (3.7)
>250 to ≤500 μg/g	7 (12.5)	6 (5.7)	4 (7.4)
>500 μg/g	44 (78.6)	87 (82.1)	46 (85.2)
Fecal calprotectin, *μg/g*, median (minimum–maximum)			
Baseline	1554 (30–13,620)	1735 (42–15,696)	1589 (130–28,490)
Week 6	917 (14–43,503)	431 (10–76,800)	505 (20–5043)
Disease localization, n (%)			
Proctosigmoiditis	7 (12.5)	15 (14.2)	7 (13.0)
Left-sided colitis	24 (42.9)	46 (43.4)	21 (38.9)
Extensive colitis	4 (7.1)	7 (6.6)	7 (13.0)
Pancolitis	21 (37.5)	37 (34.9)	19 (35.2)
Prior use of immunomodulators (only), *yes*, n (%)[a]	1 (1.8)	6 (5.7)	1 (1.9)
Prior use of oral corticosteroids (only), *yes*, n (%)[a]	22 (39.3)	28 (26.4)	21 (38.9)
Prior use of oral corticosteroids and immunosuppressants, *yes*, n (%)[a]	32 (57.1)	71 (67.0)	32 (59.3)
Concomitant use of oral corticosteroids at wk 0, *yes*, n (%)[b]	24 (42.9)	45 (42.5)	21 (38.9)
Concomitant oral corticosteroid use, *mg*, median (minimum–maximum) [n]	20.0 (10.0–20.0) [24]	20.0 (11.3–25.0) [45]	20.0 (10.0–20.0) [21]
Prior anti-TNF use, *yes*, n (%)[a]	20 (35.7)	40 (37.7)	24 (44.4)
Extraintestinal manifestation, *yes*, n (%)[a]	5 (8.9)	13 (12.3)	7 (13.0)

[a]Data were collected using electronic case report forms.
[b]Data on corticosteroid use were collected using an interactive web response system at the time of patient randomization.

vedolizumab SC arm (16 of 106 [15.1%]) than in the placebo arm (3 of 56 [5.4%]), although the results did not meet statistical significance ($P = .076$) (Table 2). Rates of durable clinical remission at week 52 among patients who achieved clinical remission at week 6 (47 patients on vedolizumab SC, 24 patients on vedolizumab IV, and 25 on placebo) were 14 (29.8%) on vedolizumab SC, 8 (33.3%) on vedolizumab IV, and 3 (12%) on placebo. The proportion of patients with corticosteroid-free clinical remission at week 52 was numerically greater with vedolizumab SC (13 of 45 [28.9%]) than placebo (2 of 24 [8.3%]) (Table 2). Among patients who had corticosteroid-free clinical remission at week 52, there were 12 (26.7%) treated with vedolizumab SC who had been corticosteroid-free for the prior 180 days compared with 2 (8.3%) on placebo (Supplementary Table 3). The mean (SE) corticosteroid dose was 4.6 (1.59) mg/d for vedolizumab SC and 5.5 (2.52) mg/d for placebo at week 52 (Supplementary Table 3).

Efficacy with vedolizumab SC vs placebo was observed based on clinical remission at ≥80% of study visits, including week 52 and on clinical remission according to alternate definitions of clinical remission using a modified Mayo score (Supplementary Tables 4 and 5). Patients receiving vedolizumab SC retained their improvements in partial Mayo scores in the maintenance phase, with scores improving further over time, while patients receiving placebo showed worsening over time (Supplementary Figure 3). Fecal calprotectin concentrations and histologic end points with vedolizumab SC vs placebo also showed improvements (Supplementary Tables 6 and 7).

In all patients, Inflammatory Bowel Disease Questionnaire and EQ-5D visual analog scale patient-reported outcome instrument scores increased by week 6 after

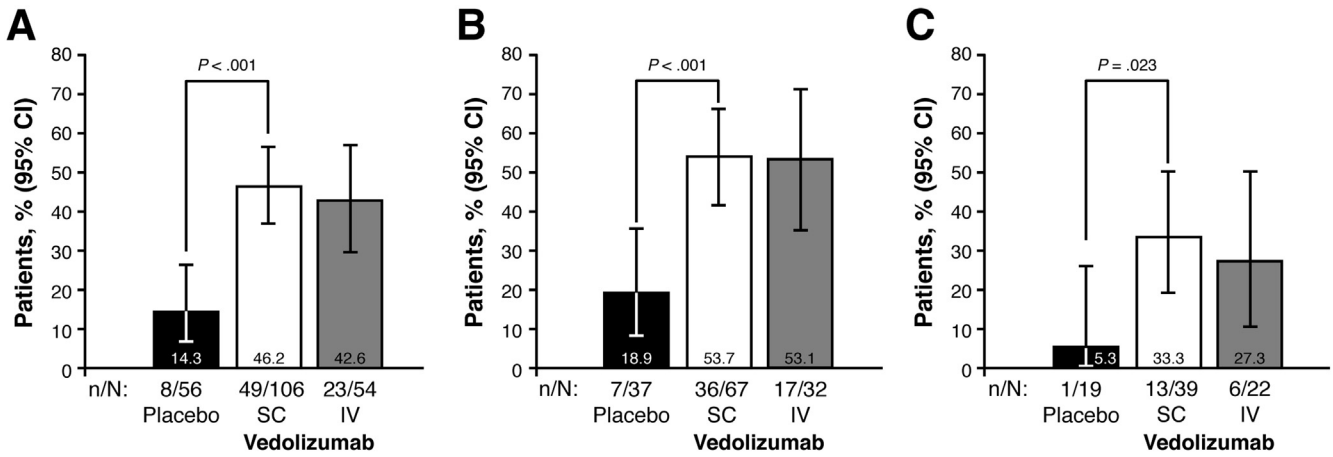

Figure 2. Clinical remission at week 52 (full analysis set) in (*A*) overall treatment groups, n = 216; (*B*) in anti-TNF–naïve patients, n = 136; and (*C*) in patients with prior anti-TNF treatment, n = 80. Clinical remission: Total Mayo score of ≤2 and no individual subscore >1.

open-label vedolizumab IV induction at weeks 0 and 2. During maintenance treatment, Inflammatory Bowel Disease Questionnaire and EQ-5D visual analog scale scores gradually decreased for patients on placebo, while patients on vedolizumab SC and IV maintained the improvement in scores they had achieved after induction treatment (Supplementary Figures 4–6, Supplementary Table 8).

Table 2. Primary and Secondary Efficacy End Points, Week 52, Full Analysis Set[a] (n = 216)

52-wk end point	Placebo[b] (n = 56)	Vedolizumab SC (108 mg) Q2W[c] (n = 106)	Vedolizumab IV (300 mg) Q8W[d] (n = 54)	Vedolizumab SC vs placebo, *P* value[e]
Primary end point				
Clinical remission,[f] % (95% CI)[g]	14.3 (6.4–26.2)	46.2 (36.5–56.2)	42.6 (29.2–56.8)	<.001
Secondary efficacy end points				
Endoscopic improvement,[h] % (95% CI)[g]	21.4 (11.6–34.4)	56.6 (46.6–66.2)	53.7 (39.6–67.4)	<.001
Durable clinical response,[i] % (95% CI)[g]	28.6 (17.3–42.2)	64.2 (54.3–73.2)	72.2 (58.4–83.5)	<.001
Durable clinical remission,[j] % (95% CI)[g]	5.4 (1.1–14.9)	15.1 (8.9–23.4)	16.7 (7.9–29.3)	.076
Corticosteroid-free remission,[k] % (95% CI)[g]	8.3 (1.0–27.0)	28.9 (16.4–44.3)	28.6 (11.3–52.2)	.067[l]

NOTE. All patients received open-label vedolizumab IV induction treatment (300 mg vedolizumab IV at wk 0 and wk 2). Patients who achieved clinical response were randomized into treatments for the maintenance phase. Clinical response was defined as a reduction in total Mayo score of ≥3 points and ≥30% from baseline (wk 0) with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1. Statistical tests were performed only between placebo and vedolizumab SC arms. Maintenance treatment was initiated at wk 6 after the open-label induction phase. The last IV injection (vedolizumab or placebo) was administered at wk 46, and the last SC injection (vedolizumab or placebo) was administered at wk 50.

Q2W, every 2 wk; Q8W, every 8 wk.

[a]The full analysis set included all randomized patients who received at least 1 dose of study drug (vedolizumab SC or placebo SC). Patients who received induction IV treatment only and were not randomized into the maintenance phase were not included in the full analysis set.

[b]Placebo IV Q8W and placebo SC Q2W.

[c]Vedolizumab SC Q2W and placebo IV Q8W.

[d]Vedolizumab IV Q8W and placebo SC Q2W.

[e]*P* values for clinical remission, endoscopic improvement, and durable clinical response were obtained using a Cochran-Mantel Haenszel test stratified by randomization strata, and those for durable clinical remission and corticosteroid-free remission were obtained using Fisher's exact test.

[f]Clinical remission was defined as a total Mayo score of ≤2 and no individual subscore >1.

[g]The 95% CIs were calculated using the Clopper-Pearson method.

[h]Endoscopic improvement was defined as Mayo endoscopic subscore of ≤1.

[i]Durable clinical response was defined as clinical response at wk 6 and wk 52.

[j]Durable clinical remission was defined as clinical remission at wk 6 and wk 52.

[k]Corticosteroid-free remission was defined as patients using oral corticosteroids at baseline (wk 0) who had discontinued oral corticosteroids and were in clinical remission at wk 52. Placebo: n = 24, vedolizumab SC: n = 45, vedolizumab IV: n = 21.

[l]Nominal *P* value.

Table 3. Overview of Adverse Events (Safety Analysis Set[a])

Variable	Placebo (n = 56)	Vedolizumab SC, 108 mg (n = 106)	Vedolizumab IV, 300 mg (n = 54)
AEs, n (%)	43 (76.8)	69 (65.1)	41 (75.9)
Related	10 (17.9)	28 (26.4)	9 (16.7)
Not related	33 (58.9)	41 (38.7)	32 (59.3)
Mild	18 (32.1)	27 (25.5)	17 (31.5)
Moderate	22 (39.3)	36 (34.0)	23 (42.6)
Severe	3 (5.4)	6 (5.7)	1 (1.9)
Leading to discontinuation	5 (8.9)	5 (4.7)	2 (3.7)
Serious AEs, n (%)	6 (10.7)	10 (9.4)	7 (13.0)
Related	0	1 (0.9)	1 (1.9)
Not related	6 (10.7)	9 (8.5)	6 (11.1)
Leading to discontinuation	1 (1.8)	1 (0.9)	2 (3.7)
Deaths, n	0	0	0

[a]The safety analysis set included all patients who were randomized to the maintenance phase and received at least 1 dose of study drug.

Efficacy and patient-reported outcome end points were all generally similar between patients on vedolizumab SC or vedolizumab IV throughout the study (Table 2, Supplementary Tables 2–8, Figure 2, and Supplementary Figures 3 and 4).

Safety/Tolerability

Overall safety findings were similar between vedolizumab SC and IV (Table 3). The most common AE was worsening of UC disease activity, with higher proportions of patients experiencing this AE in the placebo group (32.1%) than in either the vedolizumab SC (14.2%) or vedolizumab IV (11.1%) groups (Table 4). Other common AEs were nasopharyngitis, anemia, and upper respiratory tract infection (Table 4).

Among infections, abdominal and gastrointestinal infections were observed in 5 patients (4.7%) in the vedolizumab SC group, 2 patients (3.7%) in the vedolizumab IV group, and 1 patient (1.8%) in the placebo group (Supplementary Table 9). Two infections in the vedolizumab SC group were considered serious (1 anal abscess and 1 peritonitis), but were not deemed treatment-related and did not lead to discontinuation. There were no *Clostridium difficile* infections.

Table 4. Most Frequent (≥5% in Any Treatment Group) Adverse Events by System Organ Class (Safety Analysis Set[a])

Variable	Placebo (n = 56), n (%)	Vedolizumab SC 108 mg (n = 106), n (%)	Vedolizumab IV 300 mg (n = 54), n (%)
Patients with any most frequent AEs	32 (57.1)	43 (40.6)	31 (57.4)
Blood and lymphatic system disorders	2 (3.6)	6 (5.7)	5 (9.3)
Anemia	2 (3.6)	6 (5.7)	5 (9.3)
Gastrointestinal disorders	18 (32.1)	15 (14.2)	6 (11.1)
Colitis ulcerative	18 (32.1)	15 (14.2)	6 (11.1)
Infections and infestations	14 (25.0)	21 (19.8)	15 (27.8)
Nasopharyngitis	11 (19.6)	11 (10.4)	10 (18.5)
Upper respiratory tract infection	1 (1.8)	10 (9.4)	2 (3.7)
Sinusitis	3 (5.4)	1 (0.9)	0
Urinary tract infection	2 (3.6)	0	4 (7.4)
Investigations	1 (1.8)	2 (1.9)	5 (9.3)
Alanine aminotransferase increased	0	1 (0.9)	3 (5.6)
Blood creatine phosphokinase increased	1 (1.8)	1 (0.9)	3 (5.6)
Musculoskeletal and connective tissue disorders	1 (1.8)	6 (5.7)	4 (7.4)
Arthralgia	1 (1.8)	6 (5.7)	4 (7.4)
Nervous system disorders	6 (10.7)	9 (8.5)	0
Headache	6 (10.7)	9 (8.5)	0
Psychiatric disorders	0	1 (0.9)	3 (5.6)
Insomnia	0	1 (0.9)	3 (5.6)
Skin and subcutaneous tissue disorders	1 (1.8)	1 (0.9)	3 (5.6)
Rash	1 (1.8)	1 (0.9)	3 (5.6)

[a]The safety analysis set included all patients who were randomized to the maintenance phase and received at least 1 dose of study drug.

Injection-site reactions (ISRs; mainly rash, swelling, erythema, and pruritus) occurred in 11 patients (10.4%) receiving vedolizumab SC, 1 patient (1.9%) receiving vedolizumab IV (plus matching SC placebo), and 0 patients receiving placebo (Supplementary Table 10). Almost all ISRs were reported as mild in intensity and none were reported as a serious AE. Most of the patients who experienced ISRs (8 of 11) experienced 1 to 4 ISRs after vedolizumab SC injections (2 patients experienced 1 ISR, 4 patients experienced 2 ISRs each, 1 patient experienced 3 ISRs, and 1 patient experienced 4 ISRs). Although the number of patients with ISRs was limited, the likelihood of experiencing an ISR trended down over time with increasing injection experience. ISRs did not lead to discontinuation of, or changes to, the study medication dose, or treatment unblinding.

No serious cases were reported for the AEs of special interest: hypersensitivity (including ISRs or infusion-related AEs), malignancies, and liver injury. There were no cases of progressive multifocal leukoencephalopathy and no deaths.

Pharmacokinetics and Immunogenicity

The median serum vedolizumab $C_{trough,ss}$ in our initial PK modeling was estimated to be higher for vedolizumab SC at 34.6 μg/mL (90% CI, 15.5–72.8 μg/mL) than for vedolizumab IV at 11.1 μg/mL (90% CI, 2.1–34.2 μg/mL) (Supplementary Figure 7). These findings were consistent with the observed values across study visits (Supplementary Figure 8). Median serum vedolizumab $C_{avg,ss}$ was estimated as 39.8 μg/mL (90% CI, 20.8–75.4 μg/mL) vedolizumab SC and 32.2 μg/mL (90% CI, 16.5–60.7 μg/mL) for vedolizumab IV (Supplementary Figure 7). The proportion of patients receiving vedolizumab SC for maintenance who achieved clinical remission at week 52 increased with increasing vedolizumab exposure from 50% (quartile 1) to 83% (quartile 4). Similarly, the proportion of patients with endoscopic improvement at week 52 increased with increasing exposure from 50% (quartile 1) to 89% (quartile 4) (Supplementary Figure 9).

Anti-vedolizumab antibodies were detected in 6% of patients (6 of 106) receiving vedolizumab SC and 6% (3 of 54) receiving vedolizumab IV. Among AVA-positive patients on vedolizumab SC, 4 patients (4%) were persistently positive and 3 (3%) developed neutralizing antibodies. Among AVA-positive patients on vedolizumab IV, all 3 were persistently positive and developed neutralizing antibodies. The proportion of AVA-positive patients was higher among patients who received vedolizumab in the induction phase and were randomized to placebo for the maintenance phase, with 17 of 56 (30%) of patients overall; of those, 14 were persistently positive and 12 had neutralizing antibodies. The presence of AVAs in patients who received vedolizumab SC or vedolizumab IV maintenance treatment resulted in lower PK exposure and reduced treatment efficacy. However, there was no discernable relationship between AVA status and safety issues relating to ISRs or hypersensitivity reactions (Supplementary Table 11).

Discussion

The VISIBLE 1 trial demonstrated that vedolizumab SC is effective, generally safe, and well-tolerated as maintenance treatment after vedolizumab IV induction in patients with UC. The trial met its primary end point, demonstrating that clinical remission at week 52 was significantly greater for vedolizumab SC vs placebo. The trial also met its first 2 prespecified secondary efficacy end points, with significantly greater endoscopic improvement and durable clinical response for vedolizumab SC vs placebo. The efficacy end points of durable remission and corticosteroid-free remission with vedolizumab SC showed results that were numerically favorable over placebo, but differences did not reach statistical significance. In general, the efficacy endpoint rates for patients treated with either vedolizumab SC or IV maintenance were highly consistent with those reported from the GEMINI 1 pivotal trial for vedolizumab IV.[17] Overall, the new SC formulation showed comparable efficacy to that of the currently available IV formulation across all end points, including analyses in patient subgroups who were anti-TNF–naïve or who had prior anti-TNF failure. Similar efficacy results with vedolizumab IV were seen when GEMINI 1 study results were analyzed based on prior treatment with an anti-TNF.[17]

The safety/tolerability of vedolizumab SC in UC was generally favorable, with no treatment-limiting safety issues. Most AEs were mild to moderate in intensity, and the rate of discontinuations due to AEs was low and largely attributable to disease worsening or exacerbation. The number of patients who reported infections was similar in each group (35.7%, 36.8%, and 37.0% in the placebo, vedolizumab SC, and vedolizumab IV groups, respectively). There were also no serious cases reported for AEs of special interest (hypersensitivity, ISRs, and liver injury), and no cases of progressive multifocal leukoencephalopathy or death. An ISR rate of 10.4% for vedolizumab SC is in line with other SC treatments in inflammatory bowel disease, which ranged from 3% to 20% in other reports.[9,22,23] The ISRs observed in the study were reported as nonserious AEs, mostly mild in intensity, not treatment limiting, and mostly manageable without any treatment. Importantly, ISRs did not lead to discontinuation of, or changes to, the study medication dose. In addition, there were no cases of severe hypersensitivity or anaphylaxis. Besides the rate of ISRs, there were no other apparent differences observed between the safety profiles of vedolizumab SC and IV. The safety/tolerability profile of vedolizumab in this study was comparable with GEMINI 1 and the integrated safety data on IV dosing,[17,24] with the exception of ISRs observed that were due to the SC administration route.

The predicted vedolizumab PK exposure achieved with the new SC formulation (vedolizumab SC 108 mg every 2 weeks) was comparable with that of the IV formulation (vedolizumab IV 300 mg every 8 weeks). These results support vedolizumab SC 108 mg every 2 weeks as an appropriate treatment option for UC maintenance therapy in place of vedolizumab IV 300 mg every 8 weeks. Immunogenicity rates were in alignment with what was reported

for the GEMINI studies and were relatively low for the 2 active maintenance treatment arms (6%).[25,26] Although this rate appears high, the rate of AVAs for patients who received placebo during the maintenance phase (30%) was in line with previous findings from the GEMINI trials, as assessed using the electrochemiluminescence assay,[26] and was within the range of immunogenicity rates observed with other biologics.[27,28]

Patient-reported health-related quality of life improved with vedolizumab IV during induction, and these improvements were subsequently maintained with vedolizumab SC and IV, but not with placebo, throughout the maintenance treatment phase. Patient-reported outcome findings were consistent with efficacy and safety/tolerability end-point results, suggesting that they may translate into perceived beneficial effects on quality of life. These findings were consistent with previously reported improvements in these health-related quality of life measures in patients with UC treated with vedolizumab IV.[29]

The route of drug administration can be an important determinant of a patient's treatment experience, particularly for chronic diseases such as UC. Intravenous administration of a biologic treatment requires the patient to set time aside and travel to a treatment center for an infusion. In addition, the greater use of a health care facility increases the direct costs of care.[30,31] Some studies show that even with the option of self-injection, some patients may still prefer an IV route of administration for the reassurance provided by the opportunity for interacting with a health care professional or because they are averse to self-injection.[10,12,32] The availability of both an SC and IV injection of vedolizumab will enable patients to choose the route of administration for maintenance treatment.

A limitation of the study is the sample size, which was smaller than the previous GEMINI pivotal study for vedolizumab IV in UC.[17] This limitation may have contributed to the findings of numerically greater but not statistically significant differences between treatment arms for some secondary end points, such as durable clinical remission and corticosteroid-free clinical remission.

In conclusion, the new vedolizumab SC formulation, administered at 108 mg every 2 weeks, was effective and generally safe as maintenance therapy for patients with moderately to severely active UC who responded to therapy with vedolizumab IV 300 mg at weeks 0 and 2. Vedolizumab SC will provide patients with an additional option for maintaining clinical response to vedolizumab.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2019.08.027.

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Author names in bold designate shared co-first authorship.

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Reprint requests
Address requests for reprints to: William J. Sandborn, MD, Division of Gastroenterology, University of California-San Diego, La Jolla, 9500 Gilman Drive, MC 0956, La Jolla, California 92093-0956. e-mail: wsandborn@ucsd.edu.

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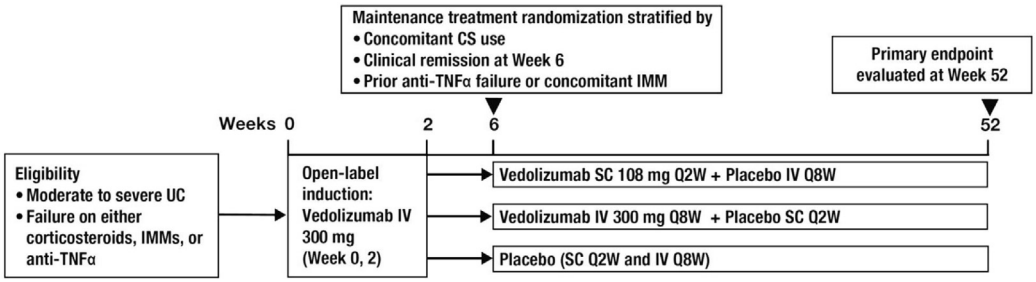
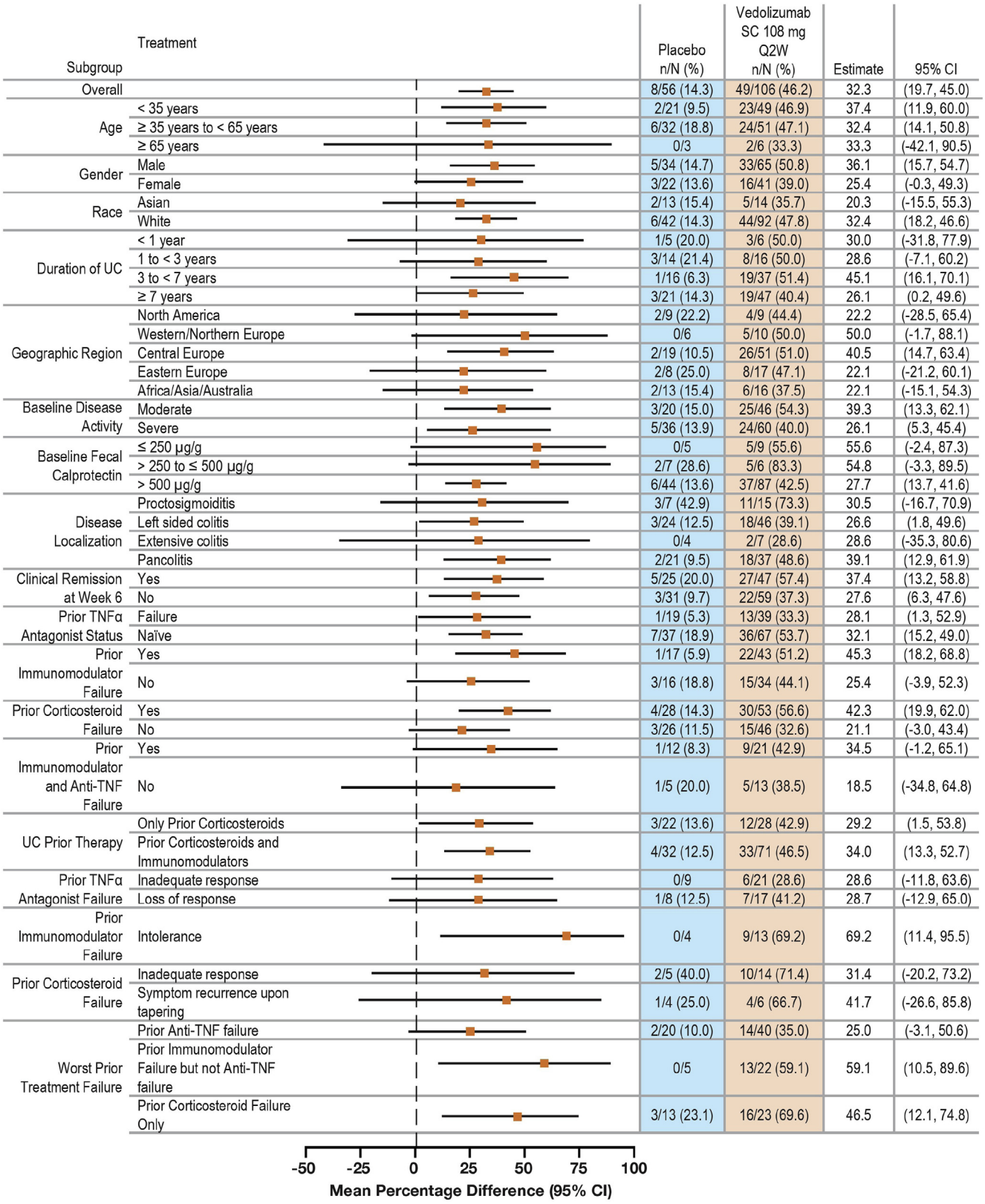
Supplementary Material

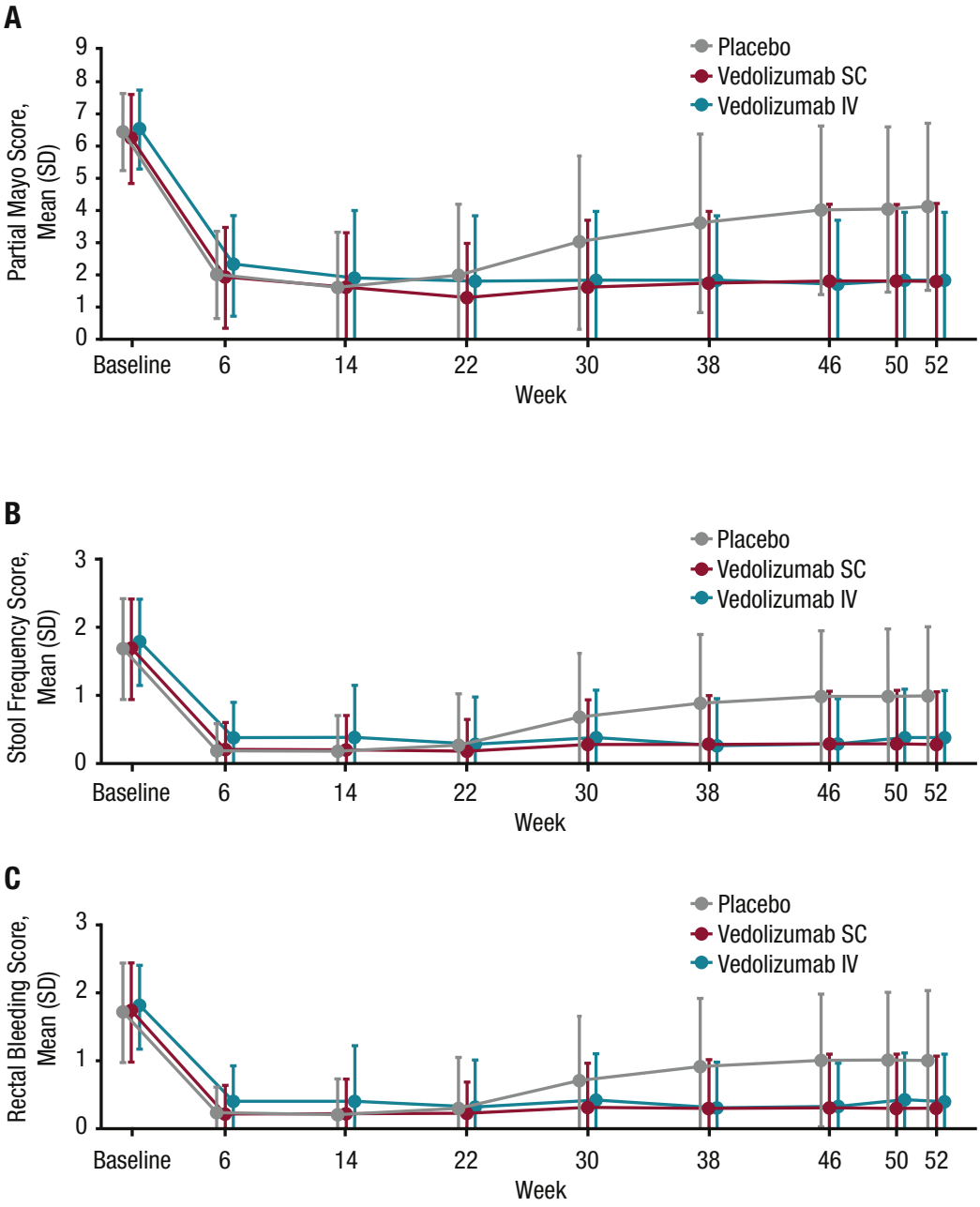


Supplementary Figure 1. Study design. VISIBLE 1 was a phase 3, randomized, placebo-controlled trial. After a 28-day screening period, eligible patients with moderately to severely active UC received open-label treatment with 300 mg vedolizumab IV at weeks 0 and 2. At week 6, patients were assessed for clinical response, defined as a reduction in total Mayo score of $\geq$3 points and $\geq$30% from baseline (week 0) with an accompanying decrease in rectal bleeding subscore of $\geq$1 point or absolute rectal bleeding subscore of $\leq$1. Patients with a clinical response at week 6 were randomized to double-blind, double-dummy maintenance treatment with vedolizumab SC (108 mg vedolizumab SC every 2 weeks [Q2W] along with IV placebo every 8 weeks [Q8W]), vedolizumab IV (300 mg Q8W along with SC placebo Q2W), or placebo (SC placebo Q2W and IV placebo Q8W) in a 2:1:1 ratio, with stratification by concomitant corticosteroid (CS) use, clinical remission at week 6, and previous anti-TNF failure or concomitant immunomodulator (IMM) use.

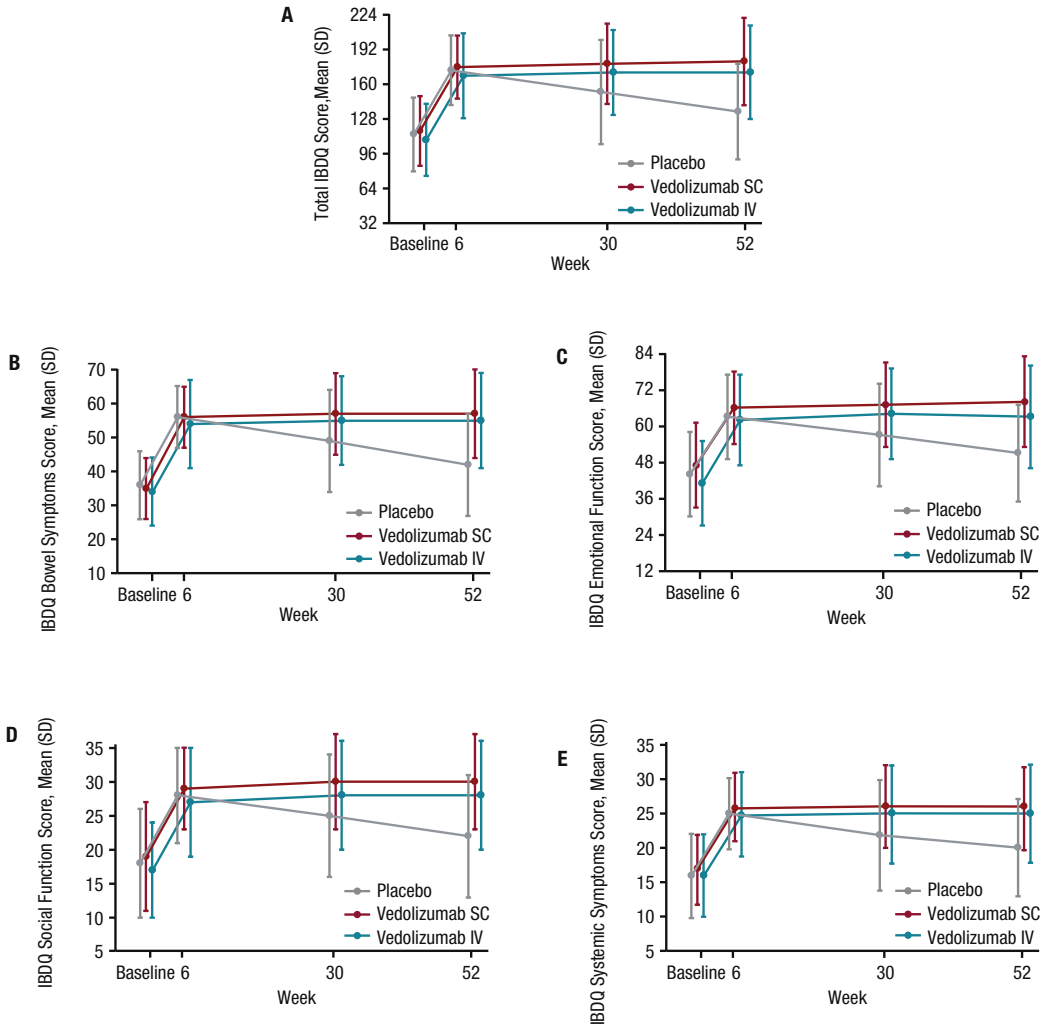


Subgroup	Treatment	Placebo n/N (%)	Vedolizumab SC 108 mg Q2W n/N (%)	Estimate	95% CI
Overall		8/56 (14.3)	49/106 (46.2)	32.3	(19.7, 45.0)
Age	< 35 years	2/21 (9.5)	23/49 (46.9)	37.4	(11.9, 60.0)
	≥ 35 years to < 65 years	6/32 (18.8)	24/51 (47.1)	32.4	(14.1, 50.8)
	≥ 65 years	0/3	2/6 (33.3)	33.3	(-42.1, 90.5)
Gender	Male	5/34 (14.7)	33/65 (50.8)	36.1	(15.7, 54.7)
	Female	3/22 (13.6)	16/41 (39.0)	25.4	(-0.3, 49.3)
Race	Asian	2/13 (15.4)	5/14 (35.7)	20.3	(-15.5, 55.3)
	White	6/42 (14.3)	44/92 (47.8)	32.4	(18.2, 46.6)
Duration of UC	< 1 year	1/5 (20.0)	3/6 (50.0)	30.0	(-31.8, 77.9)
	1 to < 3 years	3/14 (21.4)	8/16 (50.0)	28.6	(-7.1, 60.2)
	3 to < 7 years	1/16 (6.3)	19/37 (51.4)	45.1	(16.1, 70.1)
	≥ 7 years	3/21 (14.3)	19/47 (40.4)	26.1	(0.2, 49.6)
Geographic Region	North America	2/9 (22.2)	4/9 (44.4)	22.2	(-28.5, 65.4)
	Western/Northern Europe	0/6	5/10 (50.0)	50.0	(-1.7, 88.1)
	Central Europe	2/19 (10.5)	26/51 (51.0)	40.5	(14.7, 63.4)
	Eastern Europe	2/8 (25.0)	8/17 (47.1)	22.1	(-21.2, 60.1)
	Africa/Asia/Australia	2/13 (15.4)	6/16 (37.5)	22.1	(-15.1, 54.3)
Baseline Disease Activity	Moderate	3/20 (15.0)	25/46 (54.3)	39.3	(13.3, 62.1)
	Severe	5/36 (13.9)	24/60 (40.0)	26.1	(5.3, 45.4)
Baseline Fecal Calprotectin	≤ 250 µg/g	0/5	5/9 (55.6)	55.6	(-2.4, 87.3)
	> 250 to ≤ 500 µg/g	2/7 (28.6)	5/6 (83.3)	54.8	(-3.3, 89.5)
	> 500 µg/g	6/44 (13.6)	37/87 (42.5)	27.7	(13.7, 41.6)
Disease Localization	Proctosigmoiditis	3/7 (42.9)	11/15 (73.3)	30.5	(-16.7, 70.9)
	Left sided colitis	3/24 (12.5)	18/46 (39.1)	26.6	(1.8, 49.6)
	Extensive colitis	0/4	2/7 (28.6)	28.6	(-35.3, 80.6)
	Pancolitis	2/21 (9.5)	18/37 (48.6)	39.1	(12.9, 61.9)
Clinical Remission at Week 6	Yes	5/25 (20.0)	27/47 (57.4)	37.4	(13.2, 58.8)
	No	3/31 (9.7)	22/59 (37.3)	27.6	(6.3, 47.6)
Prior TNFα Antagonist Status	Failure	1/19 (5.3)	13/39 (33.3)	28.1	(1.3, 52.9)
	Naïve	7/37 (18.9)	36/67 (53.7)	32.1	(15.2, 49.0)
Prior Immunomodulator Failure	Yes	1/17 (5.9)	22/43 (51.2)	45.3	(18.2, 68.8)
	No	3/16 (18.8)	15/34 (44.1)	25.4	(-3.9, 52.3)
Prior Corticosteroid Failure	Yes	4/28 (14.3)	30/53 (56.6)	42.3	(19.9, 62.0)
	No	3/26 (11.5)	15/46 (32.6)	21.1	(-3.0, 43.4)
Prior Immunomodulator and Anti-TNF Failure	Yes	1/12 (8.3)	9/21 (42.9)	34.5	(-1.2, 65.1)
	No	1/5 (20.0)	5/13 (38.5)	18.5	(-34.8, 64.8)
UC Prior Therapy	Only Prior Corticosteroids	3/22 (13.6)	12/28 (42.9)	29.2	(1.5, 53.8)
	Prior Corticosteroids and Immunomodulators	4/32 (12.5)	33/71 (46.5)	34.0	(13.3, 52.7)
Prior TNFα Antagonist Failure	Inadequate response	0/9	6/21 (28.6)	28.6	(-11.8, 63.6)
	Loss of response	1/8 (12.5)	7/17 (41.2)	28.7	(-12.9, 65.0)
Prior Immunomodulator Failure	Intolerance	0/4	9/13 (69.2)	69.2	(11.4, 95.5)
Prior Corticosteroid Failure	Inadequate response	2/5 (40.0)	10/14 (71.4)	31.4	(-20.2, 73.2)
	Symptom recurrence upon tapering	1/4 (25.0)	4/6 (66.7)	41.7	(-26.6, 85.8)
Worst Prior Treatment Failure	Prior Anti-TNF failure	2/20 (10.0)	14/40 (35.0)	25.0	(-3.1, 50.6)
	Prior Immunomodulator Failure but not Anti-TNF failure	0/5	13/22 (59.1)	59.1	(10.5, 89.6)
	Prior Corticosteroid Failure Only	3/13 (23.1)	16/23 (69.6)	46.5	(12.1, 74.8)

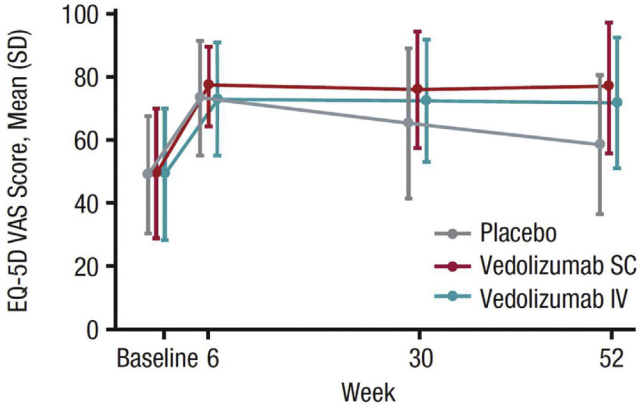
Supplementary Figure 2. Clinical remission at week 52 by subgroups based on key patient and disease characteristics (full analysis set). The full analysis set included all randomized patients who received at least 1 dose of study drug. Patients who only received vedolizumab IV induction treatment and were not randomized into the maintenance phase were not included in the full analysis set. Q2W, every 2 weeks; TNF, tumor necrosis factor; UC, ulcerative colitis.



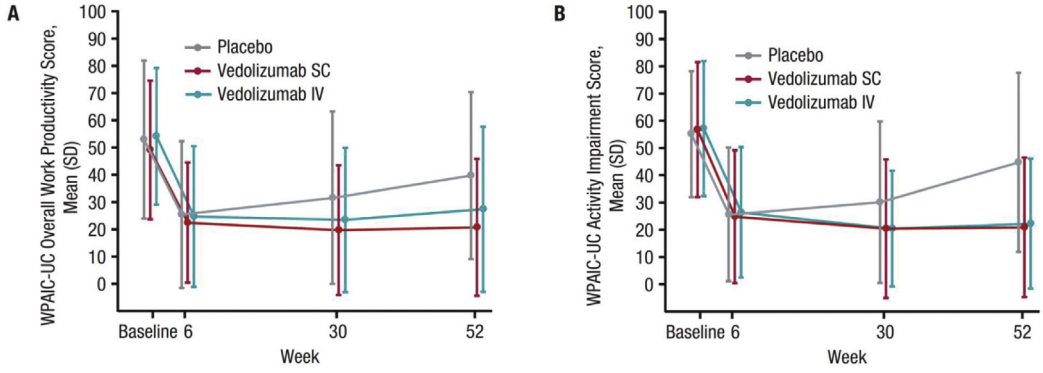
Supplementary Figure 3. Partial Mayo scores and symptom scores by study visit (full analysis set, last observation carried forward). The full analysis set included all randomized patients who received at least 1 dose of study drug. Patients who only received vedolizumab IV induction treatment and were not randomized into the maintenance phase were not included in the full analysis set. (*A*) The partial Mayo score is composed of the 3 noninvasive symptom score components of the total Mayo score: (*B*) stool frequency, (*C*) rectal bleeding, and physician's global assessment (not shown). The maximum total score is 9 points, whereas each component can score up to 3 points.



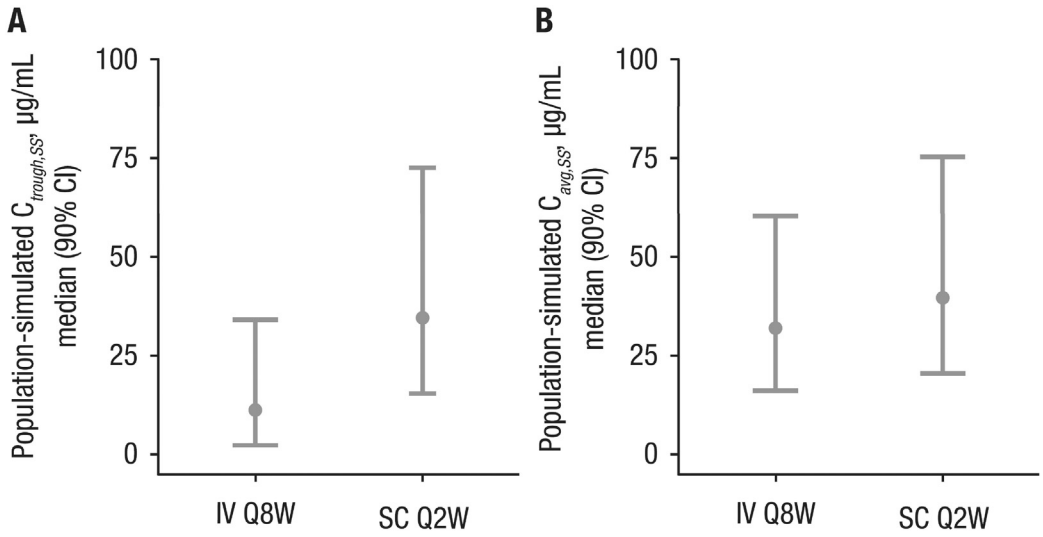
Supplementary Figure 4. The Inflammatory Bowel Disease Questionnaire (IBDQ) includes 32 questions on 4 domains of health-related quality of life: bowel symptoms (10 items), emotional function (12 items), social function (5 items), and systemic function (5 items). A total IBDQ score is calculated by summing the scores from each domain, with the total IBDQ score ranging from 32 to 224. (*A*) IBDQ total score by study visit. (*B*) IBDQ bowel symptoms domain score by study visit. (*C*) IBDQ emotional function domain score by study visit. (*D*) IBDQ social function domain score by study visit. (*E*) IBDQ systemic symptoms score by study visit. Data are from the full analysis set, last observation carried forward. The full analysis set included all randomized patients who received at least 1 dose of study drug. Patients who only received vedolizumab IV induction treatment and were not randomized into the maintenance phase were not included in the full analysis set.



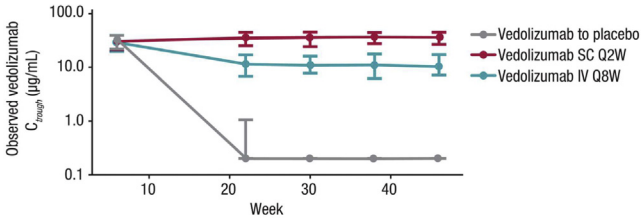
Supplementary Figure 5. The EuroQol-5D (EQ-5D) visual analog scale (VAS) score is a self-assessment of overall health using a 20-cm visual, vertical scale, with a score of 0 as the worst and 100 as the best possible health. Data are from the full analysis set, last observation carried forward. The full analysis set included all randomized patients who received at least 1 dose of study drug. Patients who only received vedolizumab IV induction treatment and were not randomized into the maintenance phase were not included in the full analysis set.



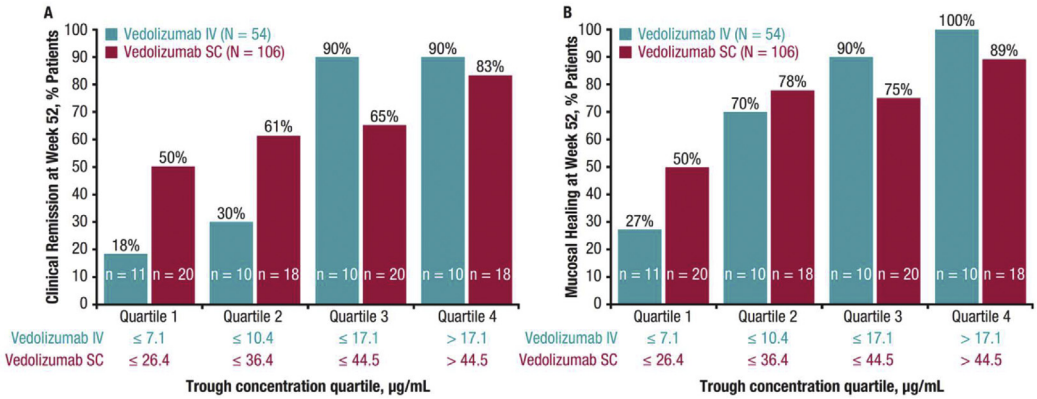
Supplementary Figure 6. The Work Productivity and Activity Impairment–Ulcerative Colitis (WPAI-UC) instrument consists of 4 metrics: absenteeism (the percentage of work time missed because of one's health in the past 7 days), presenteeism (the percentage of impairment experienced because of one's health while at work in the past 7 days), overall work productivity loss (an overall impairment estimate that is a combination of absenteeism and presenteeism), and activity impairment (the percentage of impairment in daily activities because of one's health in the past 7 days). Higher WPAI-UC percentages indicate greater impairment and less productivity (ie, worse outcomes). (*A*) WPAI-UC overall work productivity score by study visit. (*B*) WPAI-UC activity impairment score by study visit. Data are from the full analysis set, last observation carried forward. The full analysis set included all randomized patients who received at least 1 dose of study drug. Patients who only received vedolizumab IV induction treatment and were not randomized into the maintenance phase were not included in the full analysis set.



Supplementary Figure 7. Vedolizumab SC and vedolizumab IV model-predicted (*A*) trough concentrations at steady state ($C_{trough,ss}$) and (*B*) average serum concentration at steady state ($C_{avg,ss}$). Data are from the PK-evaluable population. The PK-evaluable population included all randomized patients who received at least 1 dose of study drug and had sufficient blood sampling to allow for evaluation. Q2W, every 2 weeks; Q8W, every 8 weeks.



Supplementary Figure 8. Observed median and interquartile range trough concentrations (C_{trough}) by study visit (PK-evaluable population), presented on a semi-log scale (y-axis). The PK-evaluable population included all randomized patients who received at least 1 dose of study drug and had sufficient blood sampling to allow for evaluation. Q2W, every 2 weeks; Q8W, every 8 weeks.



Supplementary Figure 9. Vedolizumab SC and IV (*A*) Clinical remission and (*B*) endoscopic improvement at week 52 by trough concentration quartiles. Data are from the PK-evaluable population. The PK-evaluable population included all randomized patients who received at least 1 dose of study drug and had sufficient blood sampling to allow for evaluation.

Supplementary Table 1. Clinical Response During Vedolizumab IV Induction at Weeks 6 and 14

Clinical response[a]	Wk 6 nonresponders who received third vedolizumab IV induction dose, n (%) (n = 139)	Patients randomized to maintenance treatment, n (%) (n = 216)[b]	All enrolled, n (%) (n = 383)
Wk 6[c]	0	210 (97.2)[d]	215 (56.1)
Wk 14[e]	110 (79.1)	NA	110 (28.7)[f]
Overall for induction treatment	110 (79.1)	210 (97.2)	325 (84.9)

NA, not applicable.
[a]Clinical response is defined as a reduction in total Mayo score of ≥3 points and ≥30% from baseline (wk 0) (or partial Mayo score of ≥2 points and ≥25% from baseline if the complete Mayo score was not performed at the visit) with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point.
[b]Six patients who did not achieve clinical response at wk 6 were randomized in error.
[c]Determined by complete Mayo score.
[d]Five patients with clinical response were not randomized.
[e]Determined by partial Mayo score.
[f]Twenty-four patients discontinued before receiving a third vedolizumab IV induction dose, 4 patients received a third vedolizumab IV induction dose although they were wk 6 responders.

Supplementary Table 2. Endoscopic Remission (Mayo Endoscopic Subscore = 0) at Week 52 (Full Analysis Set,[a] Nonresponder Imputation)

Endoscopic remission at wk 52[b]	Placebo (n = 56)	Vedolizumab SC (n = 106)	Vedolizumab IV (n = 54)
Yes, n (%)	7 (12.5)	31 (29.2)	15 (27.8)
No, n (%)	49 (87.5)	75 (70.8)	39 (72.2)
Treatment difference, vedolizumab vs placebo (95% CI)[c]	—	16.9 (5.2–28.6)	15.1 (0.8–29.4)
P value, vedolizumab vs placebo[d]	—	.014	.046

NOTE. This analysis was conducted post-hoc.
[a]The full analysis set included all randomized patients who received at least 1 dose of study drug. Patients who received vedolizumab IV induction treatment only and were not randomized into the maintenance phase were not included in the full analysis set.
[b]All patients with missing data for determination of end-point status are categorized as "no."
[c]The 95% CI of the treatment difference is based on the normal approximation method, or the exact method if the number of remissions in either treatment group is ≤5.
[d]The *P* values were obtained using a Cochran-Mantel-Haenszel test stratified by randomization stratum (concomitant use of corticosteroids, clinical remission status at wk 6, and previous anti-TNF failure or concomitant immunomodulator use) or Fisher's exact test if the number of remissions in either treatment group was ≤5.

Supplementary Table 3. Corticosteroid Use at Week 52 (Last Observation Carried Forward) and Corticosteroid-Free Clinical Remission at Week 52 With Corticosteroid-Free for 90 and 180 Days (Full Analysis Set,[a] Nonresponder Imputation)

	Placebo (N=24)	Vedolizumab SC (N=45)	Vedolizumab IV (N=21)
Corticosteroid use, *mg/d*[b]			
Wk 52, mean (SE)	5.5 (2.5)	4.6 (1.6)	4.0 (1.8)
Adjusted change from baseline, mean (SE)[c]	−12.7 (2.4)	−13.4 (1.5)	−14.2 (2.2)
95% CI[d]	−17.6 to −7.9	−16.5 to −10.4	−18.5 to −9.9
Difference in adjusted change from baseline vs placebo, mean (SE)[c]	—	−0.7 (2.9)	−1.5 (3.3)
95% CI[d]	—	−6.4 to 5.0	−8.0 to 5.0
Corticosteroid-free clinical remission and corticosteroid-free for 90 d			
n (%)	2 (8.3)	12 (26.7)	6 (28.6)
95% CI[e]	1.0 to 27.0	14.6 to 41.9	11.3 to 52.2
Difference from placebo	—	18.3	20.2
95% CI[f]	—	−6.7 to 41.6	−9.8 to 47.8
P value[g]	—	.115	.121
Corticosteroid-free clinical remission and corticosteroid-free for 180 d			
n (%)	2 (8.3)	12 (26.7)	6 (28.6)
95% CI[e]	1.0 to 27.0	14.6 to 41.9	11.3 to 52.2
Difference from placebo	—	18.3	20.2
95% CI[f]	—	−6.7 to 41.6	−9.8 to 47.8
P value[g]	—	.115	.121

[a]The full analysis set included all randomized patients who received at least 1 dose of study drug. Patients who received vedolizumab IV induction treatment only and were not randomized into the maintenance phase were not included in the full analysis set.
[b]Corticosteroid use was defined as use of prednisone or equivalent.
[c]Adjusted means and SEs are based on an analysis of covariance model with treatment as factor and baseline corticosteroid use as a covariate.
[d]CIs are based on an analysis of covariance model with treatment as factor and baseline corticosteroid use as a covariate.
[e]The 95% CIs of the percentage are based on the Clopper-Pearson method.
[f]The 95% CIs of the difference are based on the normal approximation method or the exact method if the number of clinical remissions in each treatment group was ≤5.
[g]The *P* values were obtained using a Cochran-Mantel-Haenszel test stratified by randomization stratum (concomitant use of corticosteroids, clinical remission status at wk 6, and previous anti-TNF failure or concomitant immunomodulator use) or Fisher's exact test if the number of remissions in either treatment group was ≤5.

Supplementary Table 4. Clinical Remission at ≥80% of Study Visits Including Week 52 (Full Analysis Set[a])

Variable	Placebo (n = 56)	Vedolizumab SC (n = 106)	Vedolizumab IV (n = 54)
Clinical remission,[b] n (%)	10 (17.9)	59 (55.7)	25 (46.3)
95% CI[c]	8.9–30.4	45.7–65.3	32.6–60.4
Difference from placebo	—	37.8	28.2
95% CI[d]	—	24.9–50.8	12.1–44.3
P value[e]	—	<.001	.001

NOTE. All patients with missing data for determination of end-point status were categorized as nonresponders.
[a]The full analysis set included all randomized patients who received at least 1 dose of study drug. Patients who received vedolizumab IV induction treatment only and were not randomized into the maintenance phase were not included in the full analysis set.
[b]Clinical remission by partial Mayo score is defined as a partial Mayo score of ≤2 points and no individual subscore >1 point.
[c]The 95% CIs of the clinical remission rate were based on the Clopper-Pearson method.
[d]The 95% CI of the difference was based on the normal approximation method, or the exact method if the number of clinical remissions in each treatment group was ≤5.
[e]The *P* values were obtained using a Cochran-Mantel-Haenszel test stratified by randomization stratum (concomitant use of corticosteroids, clinical remission status at wk 6, and previous anti-TNF failure or concomitant immunomodulator use) or Fisher's exact test if the number of remissions in either treatment group was ≤5.

Supplementary Table 5. Clinical Remission Based on Modified Mayo Score at Week 52 (Full Analysis Set[a])

		Alternate clinical remission definition		
Treatment group	Statistic	Definition 1[b]	Definition 2[c]	Definition 3[d]
Placebo (n = 56)	Clinical remission, n (%)	6 (10.7)	8 (14.3)	8 (14.3)
	95% CI[e]	4.0–21.9	6.4–26.2	6.4–26.2
Vedolizumab SC (n = 106)	Clinical remission, n (%)	42 (39.6)	47 (44.3)	49 (46.2)
	95% CI[e]	30.3–49.6	34.7–54.3	36.5–56.2
	Difference from placebo	29.2	30.5	32.3
	95% CI[f]	17.0–41.4	17.9–43.2	19.7–45.0
	P value[g]	<.001	<.001	<.001
Vedolizumab IV (n = 54)	Clinical remission, n (%)	19 (35.2)	22 (40.7)	22 (40.7)
	95% CI[e]	22.7–49.4	27.6–55.0	27.6–55.0
	Difference from placebo	24.0	26.1	26.1
	95% CI[f]	8.9–39.0	10.3–41.8	10.3–41.8
	P value[g]	.003	.002	.002

NOTE. All patients with missing data for the determination of end-point status were categorized as nonresponders.
[a]The full analysis set included all randomized patients who received at least 1 dose of study drug. Patients who received vedolizumab IV induction treatment only and were not randomized into the maintenance phase were not included in the full analysis set.
[b]Clinical remission (alternate definition 1) was defined as stool frequency subscore = 0, rectal bleeding subscore = 0, and endoscopy subscore = 0 or 1 (modified so that a score of 1 did not include friability).
[c]Clinical remission (alternate definition 2) was defined as stool frequency subscore = 0 or 1 and a prespecified change of 1 or more from baseline and rectal bleeding subscore = 0 and endoscopy subscore = 0 or 1 (modified so that a score of 1 did not include friability).
[d]Either definition 1 or 2.
[e]The 95% CIs of the clinical remission rate were based on the Clopper-Pearson method.
[f]The 95% CI of the difference was based on the normal approximation method, or the exact method if the number of clinical remissions in each treatment group was ≤5.
[g]The *P* values were obtained using a Cochran-Mantel-Haenszel test stratified by randomization stratum (concomitant use of corticosteroids, clinical remission status at wk 6, and previous anti-TNF failure or concomitant immunomodulator use) or Fisher's exact test if the number of remissions in either treatment group was ≤5.

Supplementary Table 6. Observed Fecal Calprotectin by Study Visit (Full Analysis Set[a])

Study visit	Placebo (n = 56)	Vedolizumab SC (n = 106)	Vedolizumab IV (n = 54)
Baseline[b]			
n	56	102	52
≤250 μg/g	5 (8.9)	9 (8.8)	2 (3.8)
>250 to ≤500 μg/g	7 (12.5)	6 (5.9)	4 (7.7)
>500 μg/g	44 (78.6)	87 (85.3)	46 (88.5)
Week 6			
n	50	97	49
≤250 μg/g	15 (30.0)	39 (40.2)	16 (32.7)
>250 to ≤500 μg/g	4 (8.0)	13 (13.4)	8 (16.3)
>500 μg/g	31 (62.0)	45 (46.4)	25 (51.0)
Week 30			
n	46	90	38
≤250 μg/g	18 (39.1)	50 (55.6)	23 (60.5)
>250 to ≤500 μg/g	6 (13.0)	6 (6.7)	6 (15.8)
>500 μg/g	22 (47.8)	34 (37.8)	9 (23.7)
Week 52			
n	18	72	39
≤250 μg/g	8 (44.4)	50 (69.4)	27 (69.2)
>250 to ≤500 μg/g	0	7 (9.7)	3 (7.7)
>500 μg/g	10 (55.6)	15 (20.8)	9 (23.1)

NOTE. Values are n (%) unless indicated otherwise.
[a]The full analysis set included all randomized patients who received at least 1 dose of study drug. Patients who received vedolizumab IV induction treatment only and were not randomized into the maintenance phase were not included in the full analysis set.
[b]Baseline was defined as the last nonmissing measurement before or on the date of the first dose of study drug (study day 1).

Supplementary Table 7. Histologic Remission and Minimal Histologic Activity at Week 52 (Full Analysis Set[a])

Outcome	Placebo (n = 56)	Vedolizumab SC (n = 106)	Vedolizumab IV (n = 54)
Histologic remission (Geboes <2)			
n[b]	56	105	54
n (%)	1 (1.8)	0	1 (1.9)
95% CI[c]	0.0–9.6	—	0.0–9.9
Histologic remission (RHI <3)			
n[b]	56	105	54
n (%)	3 (5.4)	17 (16.2)	10 (18.5)
95% CI[c]	1.1–14.9	9.7–24.7	9.3–31.4
Minimal histologic activity (Geboes <3.2)			
n[b]	56	105	54
n (%)	4 (7.1)	14 (13.3)	6 (11.1)
95% CI[c]	2.0–17.3	7.5–21.4	4.2–22.6
Minimal histologic activity (RHI <5)			
n[b]	56	105	54
n (%)	5 (8.9)	19 (18.1)	13 (24.1)
95% CI[c]	3.0–19.6	11.3–26.8	13.5–37.6

NOTE. Patients who completed a visit but had missing numeric histology data due to bad orientation, insufficient tissue, no tissue on slide or only ulcer, or nonevaluable were excluded from the analyses post-hoc. The worst score across locations at a given time point was used in the analyses.
RHI, Robarts histopathology index.
[a]The full analysis set included all randomized patients who received at least 1 dose of study drug. Patients who received vedolizumab IV induction treatment only and were not randomized into the maintenance phase were not included in the full analysis set.
[b]Number of patients excluding those who completed the study visit but did not have valid non-missing numeric data. All patients with missing data for determination of end-point status are categorized as "no."
[c]The 95% CIs of the percentages are based on Clopper-Pearson method.

Supplementary Table 8. Difference in Least Squares Means for Vedolizumab vs Placebo Change From Baseline[a] to Week 52 in the Mean IBDQ Total Score, IBDQ Domain Scores, WPAI-UC Overall Work Productivity Score, and WPAI-UC Activity Impairment Score (Full Analysis Set,[b] Last Observation Carried Forward)

	Vedolizumab SC			Vedolizumab IV		
Outcome	LS mean difference vs placebo	95% CI[c]	*P* value[d]	LS mean difference vs placebo	95% CI[c]	*P* value[d]
IBDQ total score	43.9	30.6 to 57.1	<.001	37.1	21.9 to 52.4	<.001
IBDQ bowel symptoms domain score	14.9	10.6 to 19.2	<.001	12.8	7.8 to 17.7	<.001
IBDQ emotional function domain score	15.6	10.7 to 20.6	<.001	13.0	7.3 to 18.7	<.001
IBDQ social function domain score	7.5	5.0 to 10.0	<.001	6.4	3.5 to 9.2	<.001
EQ-5D VAS score	17.6	11.0 to 24.3	<.001	13.1	5.5 to 20.8	.001
WPAI-UC overall work productivity score	–18.8	–31.1 to –6.6	.003	–14.2	–27.9 to –0.6	.041
WPAI-UC activity impairment score	–24.4	–33.1 to –15.7	<.001	–23.2	–33.2 to –13.2	<.001

IBDQ, Inflammatory Bowel Disease Questionnaire; LS, least squares; WPAI-UC, Work Productivity and Activity Impairment–Ulcerative Colitis; VAS, visual analog scale.
[a]Baseline was defined as the last non-missing measurement prior to or on the date of the first dose of study drug (study day 1).
[b]The full analysis set included all randomized patients who received at least 1 dose of study drug. Patients who only received vedolizumab IV induction treatment and were not randomized into the maintenance phase were not included in the full analysis set.
[c]The 95% CI of the difference was based on the normal approximation method, or the exact method if the number of clinical remissions in each treatment group was ≤5.
[d]*P* values were obtained using an analysis of covariance model with treatment as a factor and baseline score as a covariate.

Supplementary Table 9. Gastrointestinal Infections (Safety Analysis Set)[a]

Variable	Placebo (n = 56), n (%)	Vedolizumab SC (n = 106), n (%)	Vedolizumab IV (n = 54), n (%)
Abdominal and gastrointestinal infections	1 (1.8)	5 (4.7)	2 (3.7)
Gastroenteritis	1 (1.8)	2 (1.9)	2 (3.7)
Anal abscess	0	2 (1.9)	0
Peritonitis	0	1 (0.9)	0
Campylobacter infection	0	0	1 (1.9)
Viral gastroenteritis	0	1 (0.9)	0
Gastrointestinal viral infection	0	1 (0.9)	0
Gastroenteritis rotavirus	1 (1.8)	0	0
Clostridium difficile	0	0	0

[a]The safety analysis set included all patients who were randomized to the maintenance phase and received at least 1 dose of study drug.

Supplementary Table 10. Injection-Site Reactions (Safety Analysis Set[a])

Variable	Placebo (n = 56), n (%)	Vedolizumab SC (n = 106), n (%)	Vedolizumab IV (n = 54), n (%)
Patients with any injection-site AEs	0	11 (10.4)	1 (1.9)
Injection-site reaction	0	5 (4.7)	0
Injection-site rash	0	2 (1.9)	0
Injection-site swelling	0	2 (1.9)	0
Injection-site bruising	0	1 (0.9)	0
Injection-site erythema	0	1 (0.9)	0
Injection-site hematoma	0	1 (0.9)	0
Injection-site pruritus	0	0	1 (1.9)
Pruritus	0	1 (0.9)	0
Erythema	0	1 (0.9)	0

[a]The safety analysis set included all patients who were randomized to the maintenance phase and received at least 1 dose of study drug.

Supplementary Table 11. Clinical Remission at Week 52, Injection-Site Reactions During Maintenance Treatment, and Hypersensitivity Reactions by Overall Anti-Vedolizumab Antibody Status (Safety Analysis Set[a])

Variable	Placebo (n = 56)	Vedolizumab SC (n = 106)	Vedolizumab IV (n = 54)
Clinical remission at wk 52			
Yes, n	8	49	23
AVA positive,[b] n (%)	2 (25.0)	0	0
No, n	48	57	31
AVA positive[b], n (%)	15 (31.3)	6 (10.5)	3 (9.7)
ISRs during maintenance[c]			
Yes, n	0	11	1
AVA positive[b], n (%)	0	1 (9.1)	1 (100)
No, n	56	94	52
AVA positive[b], n (%)	16 (28.6)	3 (3.2)	3 (5.8)
Hypersensitivity reactions			
Yes, n	2	16	7
AVA positive[b], n (%)	0	0	0
No, n	54	89	46
AVA positive, n (%)	16 (29.6)	4 (4.5)	3 (6.5)

[a]The safety analysis set included all patients who were randomized to the maintenance phase and received at least 1 dose of study drug.
[b]AVA positive was defined as a confirmed AVA-positive result at 1 or more visits.
[c]Randomized, double-blind, double-dummy, placebo-controlled maintenance treatment was administered between study wk 6 and wk 52.