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

William J. Sandborn, Filip Baert, Silvio Danese, Željko Krznarić, Taku Kobayashi, Xiaopan Yao, Jingjing Chen, Maria Rosario, Siddharth Bhatia, Krisztina Kisfalvi, Geert D'Haens, Séverine Vermeire

PII: S0016-5085(19)41247-X
DOI: https://doi.org/10.1053/j.gastro.2019.08.027
Reference: YGAST 62854

To appear in: *Gastroenterology*
Accepted Date: 15 August 2019

Please cite this article as: Sandborn WJ, Baert F, Danese S, Krznarić Ž, Kobayashi T, Yao X, Chen J, Rosario M, Bhatia S, Kisfalvi K, D'Haens G, Vermeire S, Efficacy and Safety of Vedolizumab Subcutaneous Formulation in a Randomized Trial of Patients With Ulcerative Colitis, *Gastroenterology* (2019), doi: https://doi.org/10.1053/j.gastro.2019.08.027.

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

Running head: Subcutaneous Vedolizumab for UC

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] Séverine Vermeire[9]

[1]Division of Gastroenterology, University of California San Diego, La Jolla, CA, USA
[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, MA, USA
[7]Takeda International UK Branch, London, UK
[8]Department of Gastroenterology, Academic Medical Centre, Amsterdam, Netherlands
[9]Department of Clinical and Experimental Medicine, University Hospitals Leuven, Leuven, Belgium

ACKNOWLEDGMENTS

This study was sponsored by Takeda. We thank the patients who participated in the trial, their caregivers, and the study investigators and members of the VISIBLE study team. Medical writing support was provided by Rezan Sahinkaya, PhD, of ProEd Communications, Inc., and funded by Takeda.

Grant support: None

Abbreviations: 5-ASA, 5-aminosalicylic acid; AE, adverse event; AVA, anti-vedolizumab antibody; $C_{avg,ss}$, average serum concentration at steady state; CI, confidence interval; ECL, electrochemiluminescence; ELISA, enzyme-linked immunosorbent assay; EQ-5D, Euro Quality of Life-5D; HRQOL, health-related quality of life; IBD, inflammatory bowel disease; IBDQ, Inflammatory Bowel Disease Questionnaire; ISR, injection-site reaction; ITT, intent-to-treat; IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; PK, pharmacokinetics; PML, progressive multifocal leukoencephalopathy; PRO, patient-reported outcome; Q2W, every 2 weeks; Q8W, every 8 weeks; SAE, serious adverse event; SC, subcutaneous; TNF, tumor necrosis factor; UC, ulcerative colitis; VAS, visual analog scale; WPAI-UC, Work Productivity and Activity Impairment–Ulcerative Colitis.

Correspondence:

Name: William J. Sandborn, MD

Address: Division of Gastroenterology
University of California San Diego, La Jolla
9500 Gilman Dr. MC 0956
La Jolla, CA, 92093-0956

Tel: 858-657-5331

E-mail: wsandborn@ucsd.edu

Disclosures:

William J. Sandborn	**Financial support for research:** Atlantic Healthcare Limited, Amgen, Genentech, Gilead Sciences, Abbvie, Janssen, Takeda, Lilly, Celgene/Receptos, Pfizer, Prometheus Laboratories; **Consulting fees:** Abbvie, Allergan, Amgen, Arena Pharmaceuticals, Avexegen Therapeutics, BeiGene, Boehringer Ingelheim, Celgene, Celltrion, Conatus, Cosmo, Escalier Biosciences, Ferring, Forbion, Genentech, Gilead Sciences, Gossamer Bio, Incyte, Janssen, Kyowa Kirin Pharmaceutical Research, Landos Biopharma, Lilly, Oppilan Pharma, Otsuka, Pfizer, Precision IBD, Progenity, Prometheus Laboratories, Reistone, Ritter Pharmaceuticals, Robarts Clinical Trials (owned by Health Academic

	Research Trust, HART), Series Therapeutics, Shire, Sienna Biopharmaceuticals, Sigmoid Biotechnologies, Sterna Biologicals, Sublimity Therapeutics, Takeda, Theravance Biopharma, Tigenix, Tillotts Pharma, UCB Pharma, Ventyx Biosciences, Vimalan Biosciences, Vivelix Pharmaceuticals; **Stock or stock options:** BeiGene, Escalier Biosciences, Gossamer Bio, Oppilan Pharma, Precision IBD, Progenity, Ritter Pharmaceuticals, Ventyx Biosciences, Vimalan Biosciences. **Spouse:** Opthotech - consultant, stock options; Progenity - consultant, stock; Oppilan Pharma - employee, stock options; Escalier Biosciences - employee, stock options; Precision IBD - employee, stock options; Ventyx Biosciences – employee, stock options; Vimalan Biosciences – employee, stock options.
Filip Baert	**Financial support for research:** AbbVie, Chiesi, Ipsen, MSD, Roche. **Consultancy:** AbbVie, Celgene, Falk, Ferring, Janssen, Mundipharma, MSD, Pfizer, Takeda, Vifor.
Silvio Danese	**Lecture fees:** AbbVie, Ferring, Hospira, Johnson & Johnson, Merck, MSD, Takeda, Mundipharma, Pfizer Inc, Tigenix, UCB Pharma, Vifor, Biogen, Celgene, Allergan, Celltrion, Sandoz, Boehringer Ingelheim; **Consultancy:** AbbVie, Ferring, Hospira, Johnson & Johnson, Merck, MSD, Takeda, Mundipharma, Pfizer Inc, Tigenix, UCB Pharma, Vifor, Biogen, Celgene, Allergan, Celltrion, Sandoz, Boehringer Ingelheim.
Željko Krznarić	**Lecture fees:** AbbVie, Hospira, Johnson & Johnson, MSD, Oktal Pharma.
Taku Kobayashi	**Financial support for research:** EA Pharma, Thermo Fisher Scientific, Alfresa Pharma, and Nippon Kayaku. **Lecture fees:** Mitsubishi Tanabe Pharma, Pfizer, Eisai, Kyorin Pharmaceutical, AbbVie, Janssen, JIMRO, Ajinomoto Pharma, EA Pharma, Astellas Pharma, Mochida Pharmaceutical, Asahi Kasei Medical, Takeda, Gilead Sciences, Celltrion, Nippon Kayaku, Alfresa Pharma. **Consultancy**: Janssen, Pfizer, Kyorin Pharmaceutical, Mochida Pharmaceutical, Takeda, Eli Lilly, Ferring Pharmaceutical, Nippon Kayaku, Thermo Fisher Scientific, Covidien Japan.
Xiaopan Yao	Employee of Takeda at the time the study was

	conducted.
Jingjing Chen	Employee of Takeda
Maria Rosario	Employee of Takeda
Siddharth Bhatia	Employee of Takeda
Krisztina Kisfalvi	Employee of Takeda
Geert D'Haens	**Lecture fees:** AbbVie, Biogen, Ferring, Johnson & Johnson, Merck Sharp Dohme, Mundipharma, Norgine, Pfizer, Samsung Bioepis, Shire, Millennium/Takeda, Tillotts and Vifor. **Consultancy:** AbbVie, Ablynx, Allergan, Amakem, Amgen, AM Pharma, Arena Pharmaceuticals, AstraZeneca, Avaxia, Biogen, Bristol Myers Squibb, Boehringer Ingelheim, Celgene/Receptos, Celltrion, Cosmo, Covidien/Medtronics, Echo Pharmaceuticals, Eli Lilly, Engene, Ferring, DrFALK Pharma, Galapagos, Genentech/Roche, Gilead, GlaxoSmithKline, Gossamerbio, Hospira/Pfizer, Immunic, Johnson & Johnson, Lycera, Medimetrics, Millennium/Takeda, Mitsubishi Pharma, Merck Sharp Dohme, Mundipharma, Nextbiotics, Novo Nordisk, Otsuka, Pfizer/Hospira, Photopill, Prometheus Laboratories/Nestle, Progenity, Protagonist, Robarts Clinical Trials, Salix, Samsung Bioepis, Sandoz, Seres/Nestle, Setpoint, Shire, Teva, Tigenix, Tillotts, Topivert, Versant and Vifor.
Séverine Vermeire	**Financial support for research:** MSD, AbbVie, Takeda, Pfizer, Johnson & Johnson; **Lecture fees**: MSD, AbbVie, Takeda, Ferring, Centocor, Hospira, Pfizer, Johnson & Johnson, Genentech/Roche; **Consultancy:** MSD, AbbVie, Takeda, Ferring, Centocor, Hospira, Pfizer, Johnson & Johnson, Genentech/Roche, Celgene, Mundipharma, Celltrion, SecondGenome, Prometheus, Gilead, Galapagos, ProDigest.

Writing Assistance: Medical writing support was provided by Rezan Sahinkaya, PhD, of ProEd Communications, Inc., and was funded by Takeda.

Role of the Study Sponsor: The trial was sponsored by Takeda. Personnel from the study sponsor designed the trial in conjunction with the principal investigators. Takeda analyzed the data, and with all authors jointly interpreted the results.

Role of Authors: All authors were study investigators. All authors were involved in interpreting the results. All authors contributed to the development of this manuscript content and provided their final approval for publication.

ABSTRACT

Background & Aims: Maintenance treatment with vedolizumab, a monoclonal antibody that inhibits the gut-selective α4β7 integrin, is administered intravenously. Some patients might prefer a subcutaneous formulation of vedolizumab for maintenance treatment. Vedolizumab SC was investigated as maintenance treatment in patients with moderately to severely active ulcerative colitis (UC).

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 UC 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 endpoint was clinical remission at week 52, defined as a total Mayo score of 2 or lower and no subscore greater than 1.

Results: Among 216 patients randomly assigned to groups, 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% CI, 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 UC who had a clinical response to intravenous vedolizumab induction therapy. It has a favorable safety and tolerability profile. ClinicalTrials.gov no: NCT02611830; EudraCT 2015-000480-14

KEY WORDS: VISIBLE 1; UC; IBD; long-term therapy

INTRODUCTION

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 effectively treated, 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 aminosalicylates and corticosteroids and/or immunomodulators.[4] Both oral 5-aminosalicylates (5-ASAs) 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 over 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 (vedolizumab IV) 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 (CD) who have had an inadequate response with, 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 the option for SC administration 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 versus placebo in patients with UC following induction therapy with vedolizumab IV.

METHODS

Study Population

Eligible patients were 18 to 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 to 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, 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 5-ASAs (provided the dose was stable for the 2 weeks prior to the first dose of study drug), azathioprine (provided the dose was stable for the 8 weeks prior to first dose of study drug), 6-mercaptopurine (provided the dose was stable for the 8 weeks prior to first dose of study drug), or oral corticosteroids (stable dose of prednisone ≤30 mg/day or budesonide ≤9 mg/day, or equivalent (provided the dose was stable for the 4 weeks prior to first dose of study drug if just initiated, or for the 2 weeks prior if being tapered) was allowed. Following clinical response at Week 6, corticosteroid tapering was mandatory, with prednisone doses >10 mg/day (or equivalent) reduced at a rate of 5 mg/week until a 10 mg/day dose was reached, and prednisone doses ≤10 mg/day (or equivalent) reduced at a rate of 2.5 mg/week 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, 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 (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 S1 for study design). The investigator or investigator's designee accessed an interactive web response system (IWRS) at screening to register a subject and obtain a subject identification number to identify the subject throughout the study. Following 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 ≥3 points and ≥30% from baseline (Week 0) with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤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 [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 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 Q2W was calculated to provide generally comparable drug exposure to that achieved with vedolizumab IV 300 mg Q8W 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 IWRS.

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 ≥2 and ≥25% from baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1, at Week 14. Those achieving a clinical response at Week 14 had the option to enroll in an open-label extension study (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 Supplemental 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 (ELISA).[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 (ECL) assay with a drug tolerance of ≥50 µg/mL. Fecal calprotectin was measured via ELISA at screening and at Weeks 0, 6, 30, and 52.

Study Endpoints

Efficacy

Patients who achieved clinical response at Week 6 following 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 outcomes at Week 52. The primary efficacy endpoint was the proportion of patients in clinical remission, defined as a total Mayo score of ≤2 and no individual subscore >1 at Week 52. Secondary efficacy endpoints 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 ≤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 endpoints 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 (RHI).

Patient-Reported Outcomes (PROs)

Inflammatory Bowel Disease Questionnaire (IBDQ) total score and subscores, Euro Quality of Life-5D (EQ-5D) utility scores, EQ-5D visual analog scale (VAS) score, and Work Productivity and Activity Impairment (WPAI-UC) 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 Medical Dictionary for Regulatory Activities (MedDRA).

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 endpoints with the vedolizumab SC vs placebo groups. The vedolizumab IV reference group was included to allow for within-study exploratory comparisons of efficacy endpoints 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 (FAS; all randomized patients who received ≥1 dose of study drug) according to treatment allocation. Adverse events 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. Pharmacokinetic 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 0.05 using a hierarchical approach to control the overall type I error rate. The primary endpoint was tested first, with subsequent secondary endpoints tested only if statistical significance was achieved with the primary endpoint and dependent on the significance of the preceding secondary endpoint 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 endpoint 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) endpoints, any patient with missing information for determination of endpoint status was considered as a nonresponder in the analysis. Missing data for continuous endpoints were imputed using the last available postbaseline observation carried forward method.

Incidence rates were analyzed for the safety endpoints (AEs) and immunogenicity (AVAs). Population PK modeling methodology, described previously,[20] was used to estimate median $C_{avg,ss}$ and median $C_{trough,ss}$ 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 1,000 posterior samples from the final population PK model were used to simulate 1,000 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 following 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 0.05. Anticipating that 47% of patients would achieve clinical response at Week 6 following 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 was 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

(PML) 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 S1). Six patients who did not achieve clinical response were randomized in error, for a total of 216 (56.4%) enrolled patients 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 between 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, 139/216 (64.4%) randomized patients completed treatment: 21 (37.5%) patients 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, discontinuing for this reason. Other reasons for discontinuation included pre-treatment 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 49/106 (46.2%) patients on vedolizumab SC showing clinical remission versus 8/56 (14.3%) of the placebo group (Δ32.3%; 95% CI, 19.7%-45.0%; $p<0.001$) (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 S2.

Patients treated with vedolizumab SC experienced significantly greater rates of endoscopic improvement and durable clinical response compared with those treated with placebo (p<0.001 for both; 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 S2). Rates of durable clinical remission as a proportion of the full study population were numerically greater in the vedolizumab SC arm (16/106 [15.1%]) than in the placebo arm (3/56 [5.4%]), although the results did not meet statistical significance (p=0.076; 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 (13/45 [28.9%]) than placebo (2/24 [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 S3). The mean (standard error [SE]) corticosteroid dose was 4.6 (1.59) mg/day for vedolizumab SC and 5.5 (2.52) mg/day for placebo at Week 52 (Supplementary Table S3).

Efficacy with vedolizumab SC versus 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 S4 and S5). 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 S3). Fecal calprotectin concentrations and histologic endpoints with vedolizumab SC versus placebo also showed improvements (Supplementary Tables S6 and S7).

In all patients, IBDQ, and EQ-5D VAS PRO instrument scores increased by Week 6 following open-label vedolizumab IV induction at Weeks 0 and 2. During maintenance treatment, IBDQ and EQ-5D VAS scores gradually decreased for patients on placebo, while patients on vedolizumab SC and IV maintained the improvement in scores they had achieved following induction treatment (Supplementary Figures S4-S6; Supplementary Table S8).

Efficacy and PRO endpoints were all generally similar between patients on vedolizumab SC or vedolizumab IV throughout the study (Table 2 and Supplementary Tables S2-S8, Figure 2 and Supplementary Figures S3-S4).

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 S9). 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.

Injection-site reactions (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 S10). Almost all ISRs were reported as mild in intensity and none were reported as a serious AE (SAE). Most of the patients who experienced ISRs (8 of 11) experienced 1 to 4 ISRs following 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. Injection-site reactions 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 PML and no deaths.

Pharmacokinetics and Immunogenicity

The median (90% CI) serum vedolizumab $C_{trough,ss}$ in our initial PK modeling was estimated to be higher for vedolizumab SC at 34.6 (15.5-72.8) µg/mL than for vedolizumab IV at 11.1 (2.1-34.2) µg/mL (Supplementary Figure S7). These findings were consistent with the observed values across study visits (Supplementary Figure S8). The median (90% CI) serum vedolizumab $C_{avg,ss}$

was estimated as 39.8 (20.8-75.4) µg/mL vedolizumab SC and 32.2 (16.5-60.7) µg/mL for vedolizumab IV (Supplementary Figure S7). 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 S9).

Anti-vedolizumab antibodies were detected in 6% of patients (6/106) receiving vedolizumab SC and 6% (3/54) 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 17/56 (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 S11).

DISCUSSION

The VISIBLE 1 trial demonstrated that vedolizumab SC is effective, generally safe, and well-tolerated as maintenance treatment following vedolizumab IV induction in patients with UC. The trial met its primary endpoint, 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 endpoints, with significantly greater endoscopic improvement and durable clinical response for vedolizumab SC vs placebo. The efficacy endpoints 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 endpoints, 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 PML or death. An ISR rate of 10.4% for vedolizumab SC is in line with other SC treatments in inflammatory bowel disease (IBD), 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 Q2W) was comparable with that of the IV formulation (vedolizumab IV 300 mg Q8W). These results support vedolizumab SC 108 mg Q2W as an appropriate treatment option for UC maintenance therapy in place of vedolizumab IV 300 mg Q8W. 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 ECL 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 are consistent with efficacy and safety/tolerability endpoint results, suggesting that they may translate into perceived beneficial effects on quality of life. These findings are 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 healthcare 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 healthcare 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 ulcerative colitis.[17] This limitation may have contributed to the findings of numerically greater but not statistically significant differences between treatment arms for some secondary endpoints such as durable clinical remission and corticosteroid-free clinical remission.

In conclusion, the new vedolizumab SC formulation, administered at 108 mg Q2W, 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.

REFERENCES

1. Ungaro R, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel JF. Ulcerative colitis. Lancet 2017;389:1756-1770.
2. Williet N, Sarter H, Gower-Rousseau C, Adrianjafy C, Olympie A, Buisson A, Beaugerie L, Peyrin-Biroulet L. Patient-reported outcomes in a French nationwide survey of inflammatory bowel disease patients. J Crohns Colitis 2017;11:165-174.
3. Cohen BL, Zoega H, Shah SA, Leleiko N, Lidofsky S, Bright R, Flowers N, Law M, Moniz H, Merrick M, Sands BE. Fatigue is highly associated with poor health-related quality of life, disability and depression in newly-diagnosed patients with inflammatory bowel disease, independent of disease activity. Aliment Pharmacol Ther 2014;39:811-22.
4. **Harbord M,** Eliakim R, Bettenworth D, Karmiris K, Katsanos K, Kopylov U, Kucharzik T, Molnar T, Raine T, Sebastian S, de Sousa HT, **Dignass A, Carbonnel F,** European Crohn's and Colitis Organisation. Third European Evidence-based Consensus on

Diagnosis and Management of Ulcerative Colitis. Part 2: Current Management. J Crohns Colitis 2017;11:769-784.

5. Wang Y, Parker CE, Feagan BG, MacDonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev 2016:CD000544.
6. Mezzina N, Campbell Davies SE, Ardizzone S. Nonbiological therapeutic management of ulcerative colitis. Expert Opin Pharmacother 2018;19:1747-1757.
7. Vedolizumab [prescribing information]. Deerfield, IL: Takeda Pharmaceuticals America Inc; 2018.
8. Infliximab [prescribing information]. Horsham, PA: Janssen Biotech, Inc; 2017.
9. Adalimumab [prescribing information]. North Chicago, IL: AbbVie Inc; 2018.
10. Allen PB, Lindsay H, Tham TC. How do patients with inflammatory bowel disease want their biological therapy administered? BMC Gastroenterol 2010;10:1.
11. Stoner KL, Harder H, Fallowfield LJ, Jenkins VA. Intravenous versus subcutaneous drug administration. Which do patients prefer? A systematic review. Patient 2014.
12. Scarpato S, Antivalle M, Favalli EG, Nacci F, Frigelli S, Bartoli F, Bazzichi L, Minisola G, Matucci Cerinic M, RIVIERA co-authors. Patient preferences in the choice of anti-TNF therapies in rheumatoid arthritis. Results from a questionnaire survey (RIVIERA study). Rheumatology (Oxford) 2010;49:289-94.
13. Williams EL, Edwards CJ. Patient preferences in choosing anti-TNF therapies-R1. Rheumatology (Oxford) 2006;45:1575-6.
14. Chilton F, Collett RA. Treatment choices, preferences and decision-making by patients with rheumatoid arthritis. Musculoskeletal Care 2008;6:1-14.
15. Soler D, Chapman T, Yang LL, Wyant T, Egan R, Fedyk ER. The binding specificity and selective antagonism of vedolizumab, an anti-alpha4beta7 integrin therapeutic antibody in development for inflammatory bowel diseases. J Pharmacol Exp Ther 2009;330:864-75.
16. Vedolizumab [summary of product characteristics]. Taastrup, Denmark: Takeda Pharma A/S; 2017.
17. Feagan BG, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, Sandborn WJ, Van Assche G, Axler J, Kim HJ, Danese S, Fox I, Milch C, Sankoh S, Wyant T, Xu J, Parikh A, Group GS. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2013;369:699-710.

18. Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE, Lukas M, Fedorak RN, Lee S, Bressler B, Fox I, Rosario M, Sankoh S, Xu J, Stephens K, Milch C, Parikh A, Gemini Study Group. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med 2013;369:711-21.
19. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. N Engl J Med 1987;317:1625-1629.
20. Rosario M, Dirks NL, Gastonguay MR, Fasanmade AA, Wyant T, Parikh A, Sandborn WJ, Feagan BG, Reinisch W, Fox I. Population pharmacokinetics-pharmacodynamics of vedolizumab in patients with ulcerative colitis and Crohn's disease. Aliment Pharmacol Ther 2015;42:188-202.
21. Rosario M, Polhamus D, Chen C, Sun W, Dirks N. P490 A vedolizumab population pharmacokinetic model including intravenous and subcutaneous formulations for patients with ulcerative colitis. J Crohns Colitis 2019;13:S357-S357.
22. Certolizumab [prescribing information]. Smyrna, GA: UCB Inc; 2018.
23. Golimumab [prescribing information]. Horsham, PA: Janssen Biotech Inc; 2018.
24. Colombel JF, Sands BE, Rutgeerts P, Sandborn W, Danese S, D'Haens G, Panaccione R, Loftus EV, Jr., Sankoh S, Fox I, Parikh A, Milch C, Abhyankar B, Feagan BG. The safety of vedolizumab for ulcerative colitis and Crohn's disease. Gut 2017;66:839-851.
25. Rosario M, Dirks NL, Milch C, Parikh A, Bargfrede M, Wyant T, Fedyk E, Fox I. A review of the clinical pharmacokinetics, pharmacodynamics, and immunogenicity of vedolizumab. Clin Pharmacokinet 2017;56:1287-1301.
26. Rosario M, Yang L, Wyant T. Results from a new anti-vedolizumab antibody assay [poster]. Presented at the 2018 Advances in Inflammatory Bowel Disease; December 13-15, 2018; Orlando, Florida. Abstract P010.
27. Vermeire S, Gils A, Accossato P, Lula S, Marren A. Immunogenicity of biologics in inflammatory bowel disease. Therap Adv Gastroenterol 2018;11:1756283X17750355.
28. Berger AE, Duru G, de Vries A, Marini JC, Aoucheta D, Cornillie F, Nancey S, Detrez I, Gils A, Roblin X, Paul S. Comparison of immunoassays for measuring serum levels of golimumab and antibodies against golimumab in ulcerative colitis: a retrospective observational study. Ther Drug Monit 2019.
29. Feagan BG, Patel H, Colombel JF, Rubin DT, James A, Mody R, Lasch K. Effects of vedolizumab on health-related quality of life in patients with ulcerative colitis: results from the randomised GEMINI 1 trial. Aliment Pharmacol Ther 2017;45:264-275.

30. De Cock E, Kritikou P, Sandoval M, Tao S, Wiesner C, Carella AM, Ngoh C, Waterboer T. Time Savings with Rituximab Subcutaneous Injection versus Rituximab Intravenous Infusion: A Time and Motion Study in Eight Countries. PLoS One 2016;11:e0157957.
31. Desplats M, Pascart T, Jelin G, Norberciak L, Philippe P, Houvenagel E, Goeb V, Flipo RM. Are abatacept and tocilizumab intravenous users willing to switch for the subcutaneous route of administration? A questionnaire-based study. Clin Rheumatol 2017;36:1395-1400.
32. Bolge SC, Eldridge HM, Lofland JH, Ravin C, Hart PJ, Ingham MP. Patient experience with intravenous biologic therapies for ankylosing spondylitis, Crohn's disease, psoriatic arthritis, psoriasis, rheumatoid arthritis, and ulcerative colitis. Patient Prefer Adherence 2017;11:661-669.

Author names in bold designate shared co-first authorship.

FIGURE LEGENDS

Figure 1. Patient disposition.

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. anti-TNF, anti-tumor necrosis factor; CI, confidence interval; IV, intravenous; SC, subcutaneous; clinical remission: Total Mayo score of ≤2 and no individual subscore >1.

TABLES

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 (years), mean (SD)	39.4 (11.7)	38.1 (13.1)	41.6 (14.1)
Sex (n [%]), Male	34 (60.7)	65 (61.3)	31 (57.4)
Race (n [%]), White	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 (n [%]), Yes	0	11 (10.4)	10 (18.5)
Duration of UC (years), 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)
Week 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	1,554 (30-13,620)	1,735 (42-15,696)	1,589 (130-28,490)
Week 6	917 (14-43,503)	431 (10-76,800)	505 (20-5,043)
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 (only) immunomodulators (n [%]),[a] Yes	1 (1.8)	6 (5.7)	1 (1.9)
Prior use of (only) oral corticosteroids (n [%]),[a] Yes	22 (39.3)	28 (26.4)	21 (38.9)
Prior use of oral corticosteroids and immunosuppressants (n [%]),[a] Yes	32 (57.1)	71 (67.0)	32 (59.3)
Concomitant use of oral corticosteroids at Week 0 (n[%]),[b] Yes	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 (n [%]),[a] Yes	20 (35.7)	40 (37.7)	24 (44.4)
Extraintestinal manifestation (n [%]), Yes	5 (8.9)	13 (12.3)	7 (13.0)

IV, intravenous; SC, subcutaneous; SD, standard deviation; TNF, tumor necrosis factor-alpha.

[a]Data were collected using electronic case report forms (eCRFs).

[b]Data on corticosteroid use were collected using an interactive web response system (IWRS) at the time of patient randomization.

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

52-Week Endpoint	Placebo[b,c,d] (N=56)	Vedolizumab SC (108 mg) Q2W[b,c,e] (N=106)	Vedolizumab IV (300 mg) Q8W[b,c,f] (N=54)	Vedolizumab SC vs Placebo p Value[g]
Primary Endpoint				
Clinical remission, % (95% CI)[h]	14.3 (6.4-26.2)	46.2 (36.5-56.2)	42.6 (29.2-56.8)	<0.001
Secondary Efficacy Endpoints				
Endoscopic improvement, % (95% CI)[i]	21.4 (11.6-34.4)	56.6 (46.6-66.2)	53.7 (39.6-67.4)	<0.001
Durable clinical response, % (95% CI)[j]	28.6 (17.3-42.2)	64.2 (54.3-73.2)	72.2 (58.4-83.5)	<0.001
Durable clinical remission, % (95% CI)[k]	5.4 (1.1-14.9)	15.1 (8.9-23.4)	16.7 (7.9-29.3)	0.076
Corticosteroid-free remission, % (95% CI)[l]	8.3 (1.0-27.0)	28.9 (16.4-44.3)	28.6 (11.3-52.2)	0.067[m]

CI, confidence interval; ITT, intent-to-treat; IV, intravenous; Q2W, every 2 weeks; Q8W, every 8 weeks; SC, subcutaneous.

All patients received open-label vedolizumab IV induction treatment (300 mg vedolizumab IV at Week 0 and Week 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 (Week 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.

[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 only received induction IV treatment and were not randomized into the maintenance phase were not included in the full analysis set.

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

[c]Maintenance treatment was initiated at Week 6 after the open-label induction phase. The last IV injection (vedolizumab or placebo) was administered at Week 46, and the last SC injection (vedolizumab or placebo) was administered at Week 50.

[d]Placebo IV Q8W and placebo SC Q2W.

[e]Vedolizumab SC Q2W and placebo IV Q8W.

[f]Vedolizumab IV Q8W and placebo SC Q2W.

[g]*p* values for clinical remission, endoscopic improvement, and durable clinical response were obtained using a Cochran-Mantel Haenszel

(CMH) test stratified by randomization strata, and those for durable clinical remission and corticosteroid-free remission were obtained using Fisher's Exact test.

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

[i]Endoscopic improvement is defined as Mayo endoscopic subscore of ≤1.

[j]Durable clinical response is defined as clinical response at Weeks 6 and 52.

[k]Durable clinical remission is defined as clinical remission at Weeks 6 and 52.

[l]Corticosteroid-free remission is defined as patients using oral corticosteroids at Baseline (Week 0) who have discontinued oral corticosteroids and are in clinical remission at Week 52. Placebo: n=24, vedolizumab SC: n=45, vedolizumab IV: n=21.

[m]Nominal p value.

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

	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)
SAEs, 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	0	0	0

AE, adverse event; IV, intravenous; SC, subcutaneous; SAE, serious adverse event.

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

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

n (%)	Placebo (N=56)	Vedolizumab SC 108 mg (N= 06)	Vedolizumab IV 300 mg (N=54)
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)

AE, adverse event; IV, intravenous; SC, subcutaneous.

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

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.

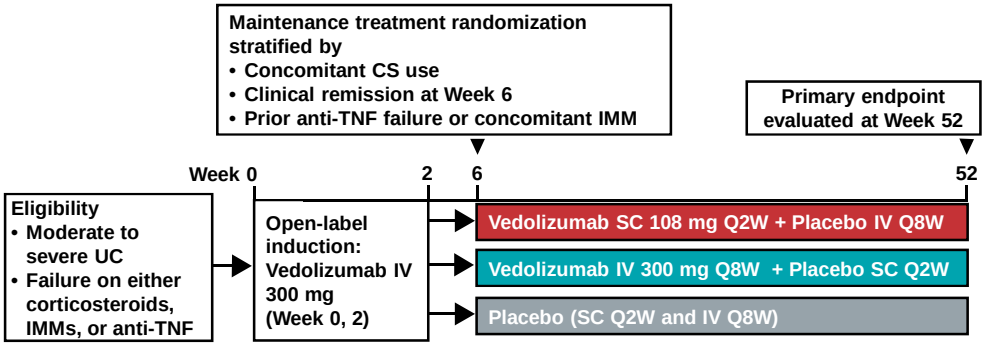
LIMITATIONS: The study was powered to assess the primary endpoint of clinical remission after 52 weeks, but was not sufficient to assess some secondary endpoints.

IMPACT: Patients with moderately to severely active UC can transition from intravenous to subcutaneous vedolizumab for maintenance therapy without losing efficacy or additional safety issues.

Lay Summary: Patients with active ulcerative colitis who responded to intravenous vedolizumab induction therapy maintain the response after transitioning to subcutaneous vedolizumab treatment.

Subcutaneous vedolizumab (vedolizumab SC) is effective as maintenance therapy in patients with moderately to severely active UC who had a clinical response to vedolizumab intravenous (IV) induction therapy. Vedolizumab SC has a favorable safety/tolerability profile that, except for infrequent injection site reactions, is consistent with the well-established safety profile of vedolizumab IV, including for adverse events that are of special interest for biologic treatments.

Study Design

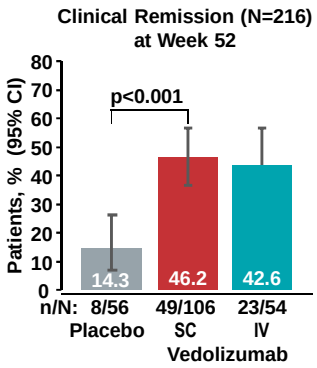


Safety

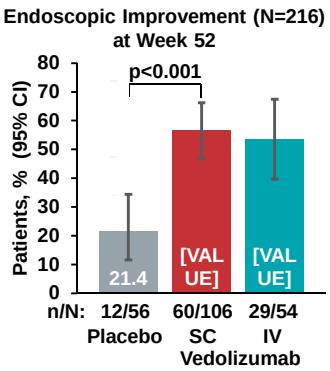
	Placebo (N=56)	Vedolizumab SC (N=106)	Vedolizumab IV (N=54)
Total adverse events, n (%)	43 (76.8)	69 (65.1)	41 (75.9)
Total serious adverse events, n (%)	3 (5.4)	6 (5.7)	1 (1.9)
Abdominal and gastrointestinal infections, n (%)	5 (4.7)	2 (3.7)	1 (1.8)
Injection site reactions, n (%)	0	11 (10.4)	1 (1.9)

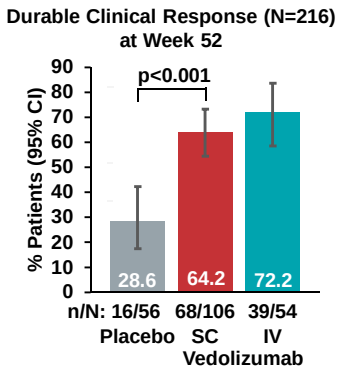
- There were 2 serious infections in the vedolizumab SC group, unrelated to treatment
- There were no cases of *Clostridium difficile* infection
- There were no serious cases of hypersensitivity reactions (including injection site reactions or infusion-related adverse events) or liver injury and no malignancies
- There were no cases of PML and no deaths

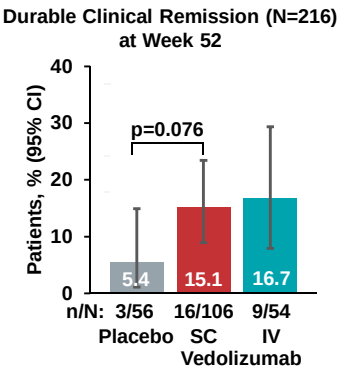
Primary Endpoint



Secondary Endpoints

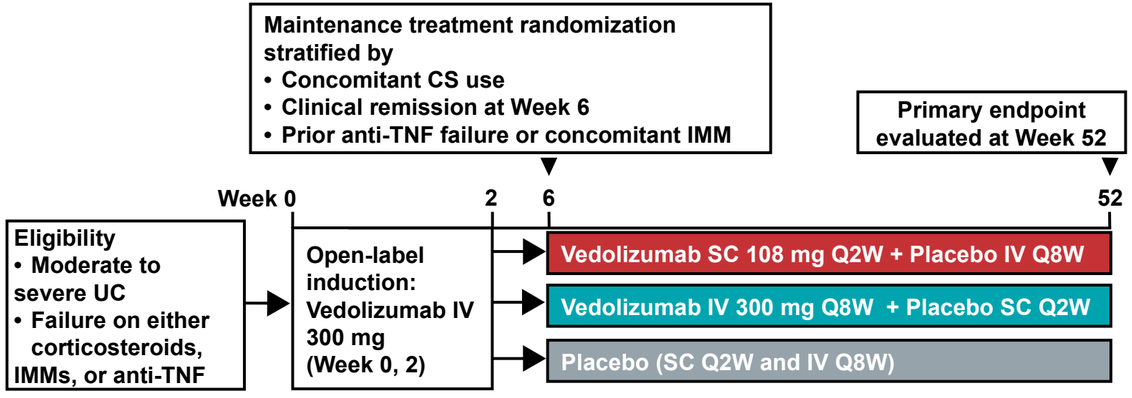






Subcutaneous vedolizumab (vedolizumab SC) is effective as maintenance therapy in patients with moderately to severely active UC who had a clinical response to vedolizumab intravenous (IV) induction therapy. Vedolizumab SC has a favorable safety/tolerability profile that, except for infrequent injection site reactions, is consistent with the well-established safety profile of vedolizumab IV, including for adverse events that are of special interest for biologic treatments.

Study Design

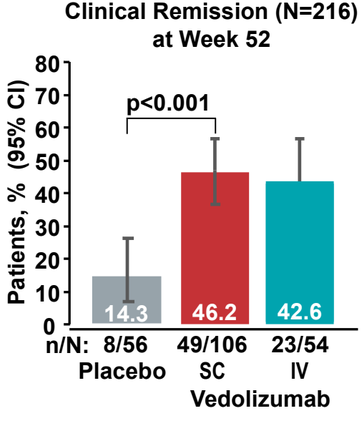


Safety

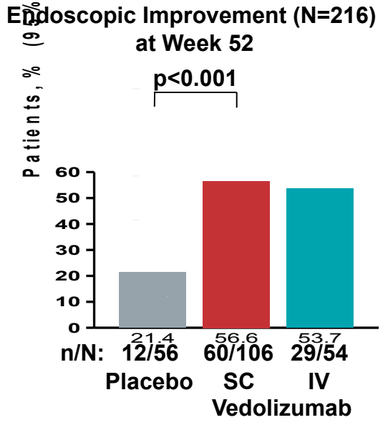
	Placebo (N=56)	Vedolizumab SC (N=106)	Vedolizumab IV (N=54)
Total adverse events, n (%)	43 (76.8)	69 (65.1)	41 (75.9)
Total serious adverse events, n (%)	3 (5.4)	6 (5.7)	1 (1.9)
Abdominal and gastrointestinal infections, n (%)	5 (4.7)	2 (3.7)	1 (1.8)
Injection site reactions, n (%)	0	11 (10.4)	1 (1.9)

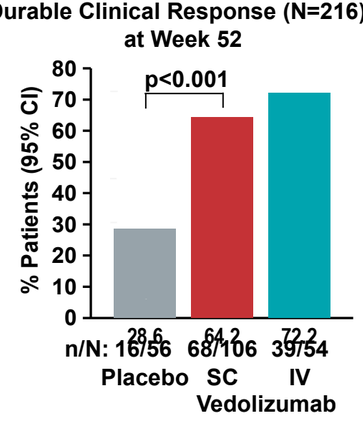
- There were 2 serious infections in the vedolizumab SC group, unrelated to treatment
- There were no cases of *Clostridium difficile* infection
- There were no serious cases of hypersensitivity reactions (including injection site reactions or infusion-related adverse events) or liver injury and no malignancies
- There were no cases of PML and no deaths

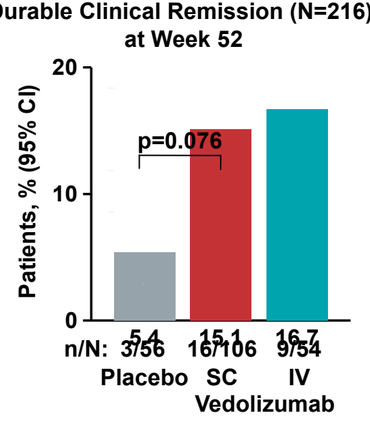
Primary Endpoint



Secondary Endpoints

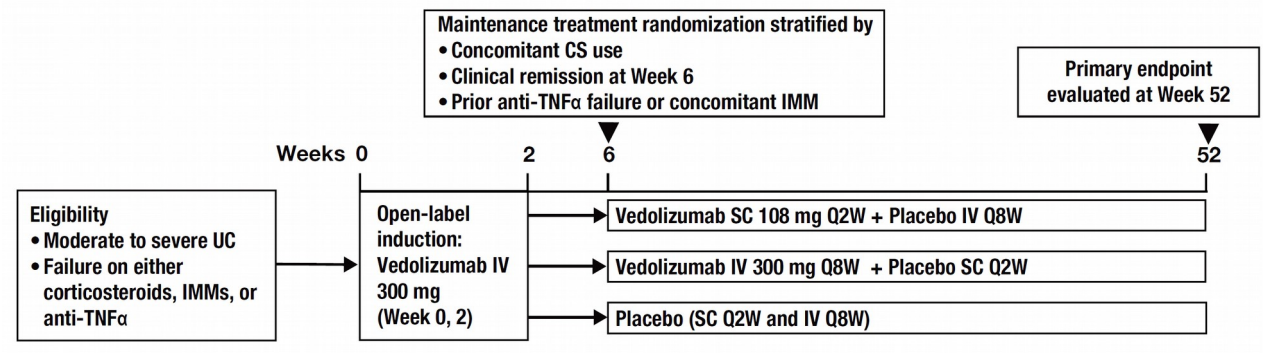




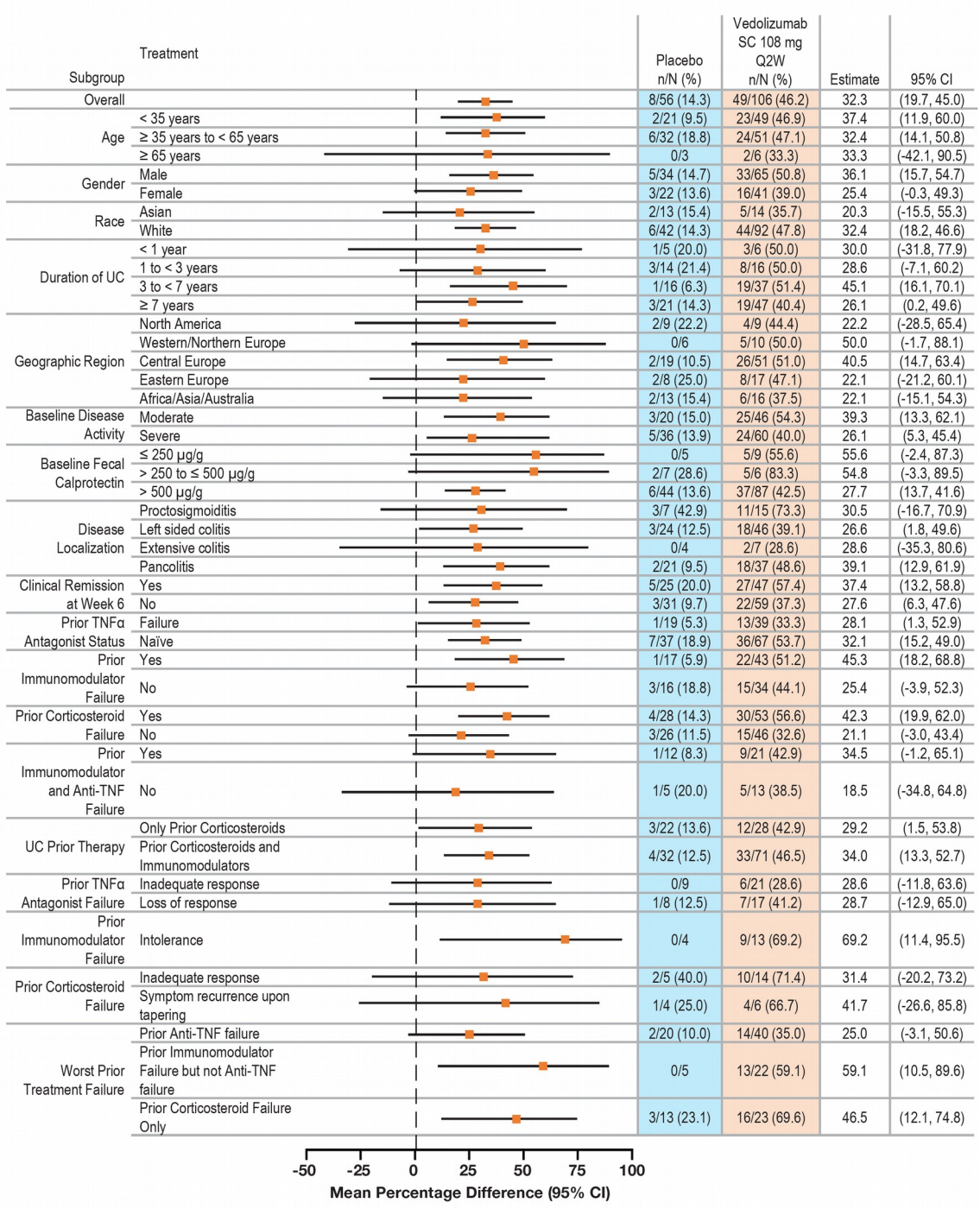


Supplementary Materials

Supplementary Figure S1. Study design. VISIBLE 1 was a phase 3, randomized, placebo-controlled trial. Following 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 ≥3 points and ≥30% from baseline (Week 0) with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤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 use, clinical remission at Week 6, and previous anti-TNF failure or concomitant immunomodulator use.



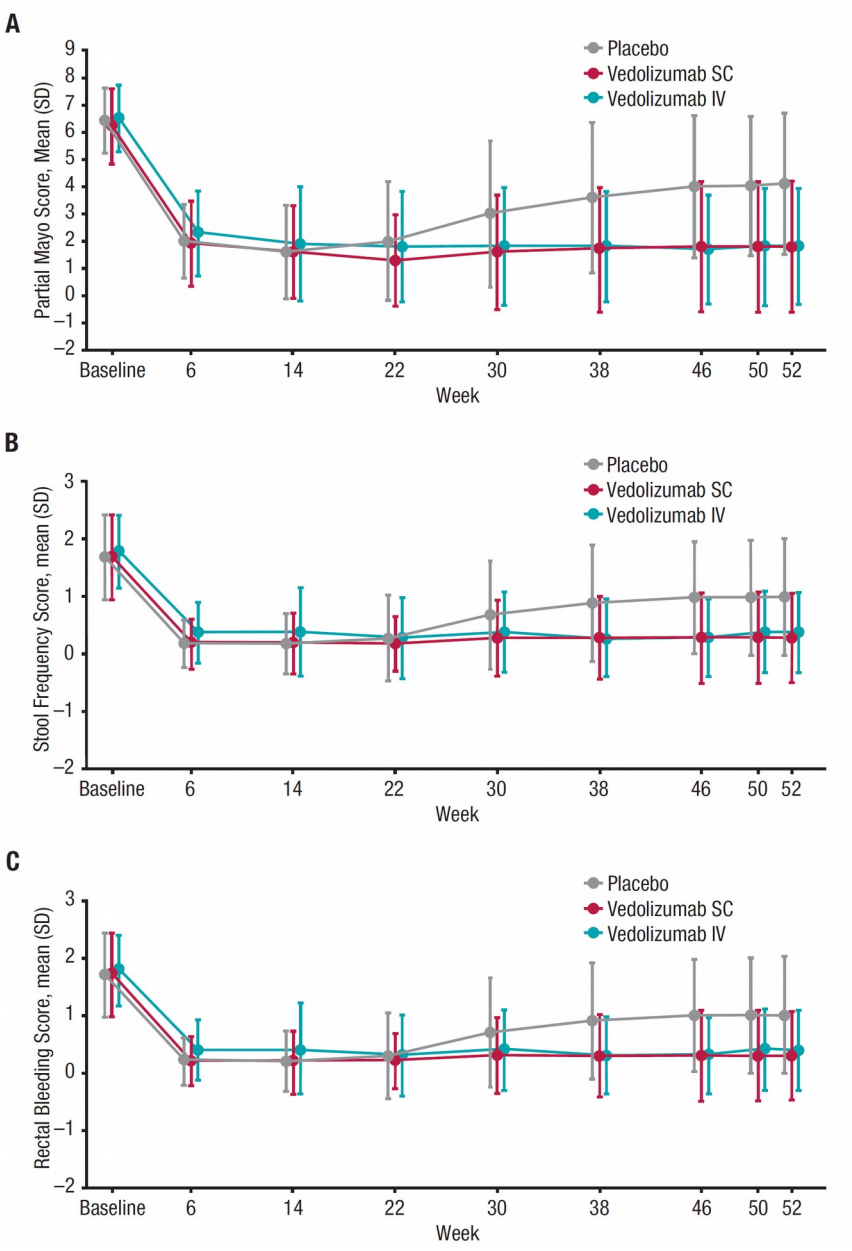
Supplementary Figure S2. Clinical remission at Week 52 by subgroups based on key patient and disease characteristics (full analysis set).[a]



CI, confidence interval; IV, intravenous; SC, subcutaneous; TNF, tumor necrosis factor-alpha.

[a]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.

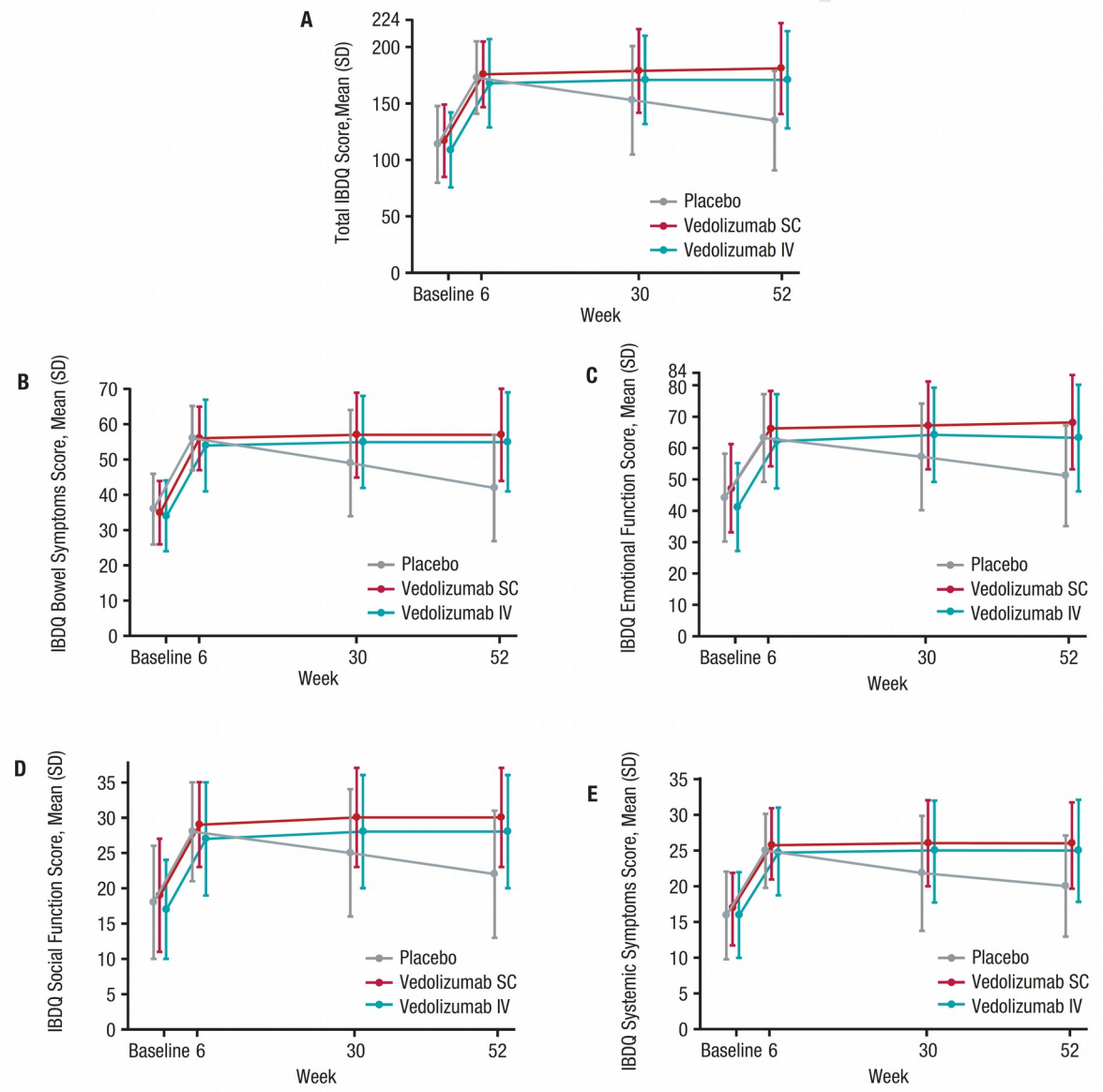
Supplementary Figure S3. Partial Mayo scores and symptom scores by study visit (full analysis set, last observation carried forward).[a] **(A)** The partial Mayo score is composed of the 3 noninvasive symptom score components of the total Mayo score: **(B)** stool frequency, **(C)** rectal bleeding, and physician's global assessment (not shown). The maximum total score is 9 points, whereas each component can score up to 3 points.



IV, intravenous; SD, standard deviation; SC, subcutaneous.

[a]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.

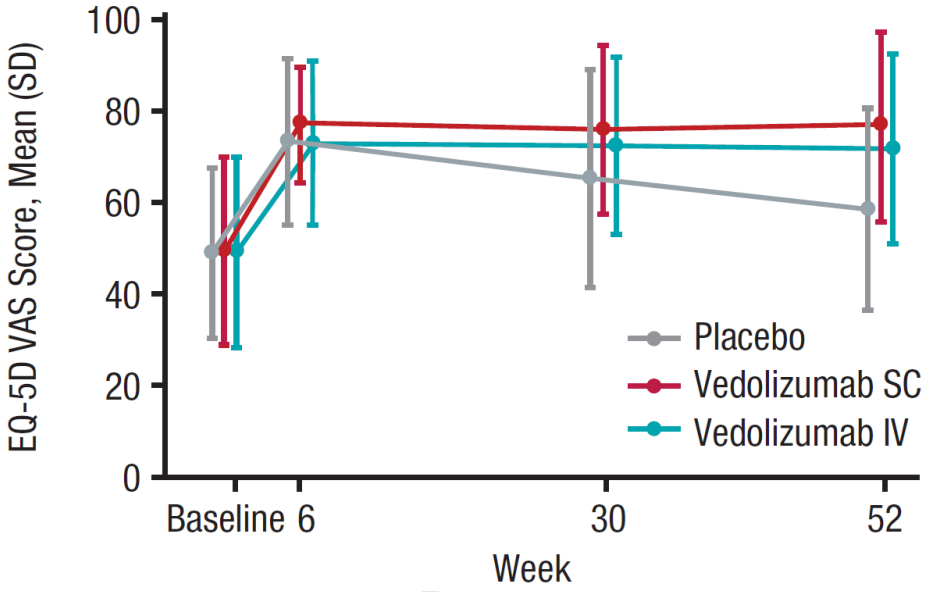
Supplementary Figure S4. The Inflammatory Bowel Disease Questionnaire (IBDQ) includes 32 questions on 4 domains of health-related quality of life (HRQOL): bowel symptoms (10 items), emotional function (12 items), social function (5 items), and systemic function (5 items). A total IBDQ score is calculated 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.[a]



IV, intravenous; SD, standard deviation; SC, subcutaneous.

[a]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.

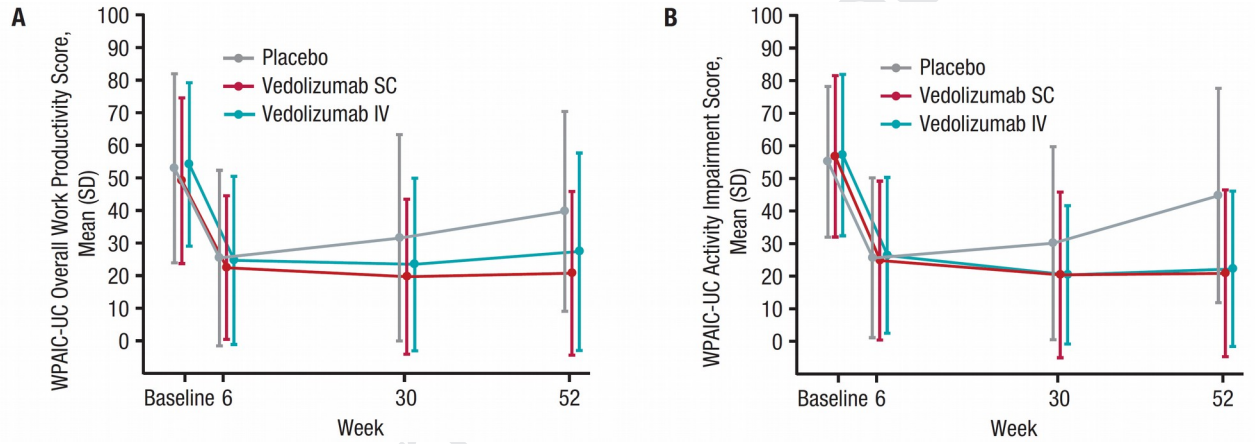
Supplementary Figure S5. The EQ-5D visual analog scale (VAS) score is a self-assessment of overall health using a 20-cm visual, vertical scale, with a score of 0 as the worst and 100 as the best possible health. Data are from the full analysis set, last observation carried forward.[a]



IV, intravenous; SD, standard deviation; SC, subcutaneous.

[a]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.

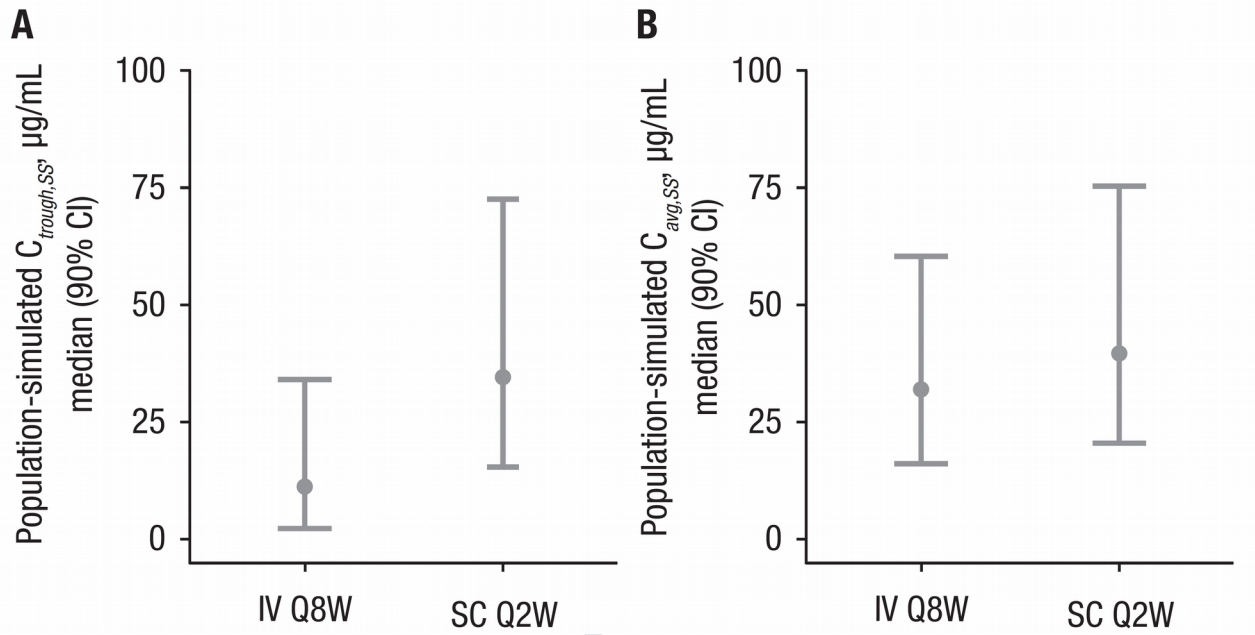
Supplementary Figure S6. The Work Productivity and Activity Impairment–Ulcerative Colitis (WPAI-UC) instrument consists of 4 metrics: absenteeism (the percentage of work time missed because of one's health in the past 7 days), presenteeism (the percentage of impairment experienced because of one's health 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.[a]



IV, intravenous; SD, standard deviation; SC, subcutaneous.

[a]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.

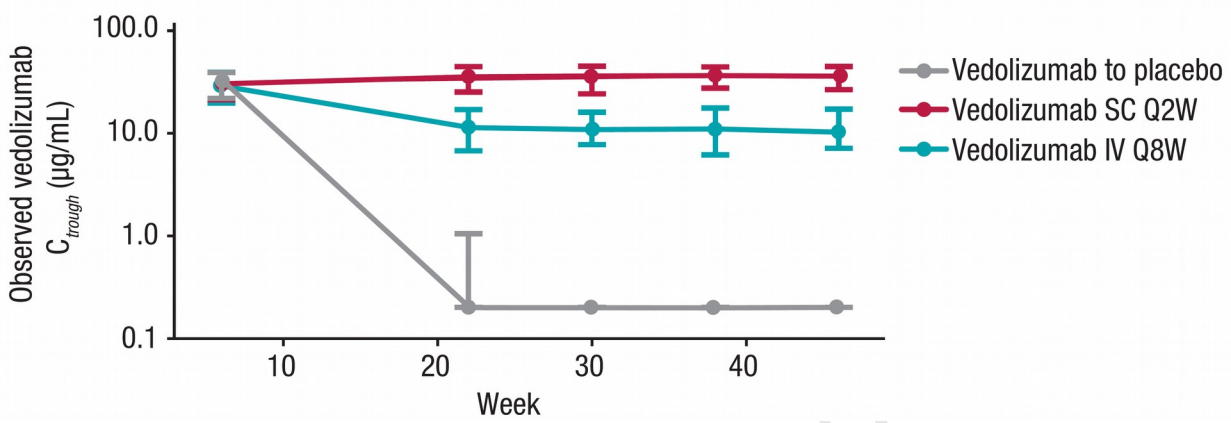
Supplementary Figure S7. Vedolizumab SC and vedolizumab IV model-predicted **(A)** trough concentrations at steady state ($C_{trough,ss}$) and **(B)** average concentrations at steady state ($C_{avg,ss}$). Data are from the pharmacokinetic-evaluable population.[a]



CI, confidence interval; IV, intravenous; Q2W, every 2 weeks; Q8W, every 8 weeks; SC, subcutaneous.

[a]The pharmacokinetic-evaluable population included all randomized patients who received at least 1 dose of study drug and had sufficient blood sampling to allow for evaluation.

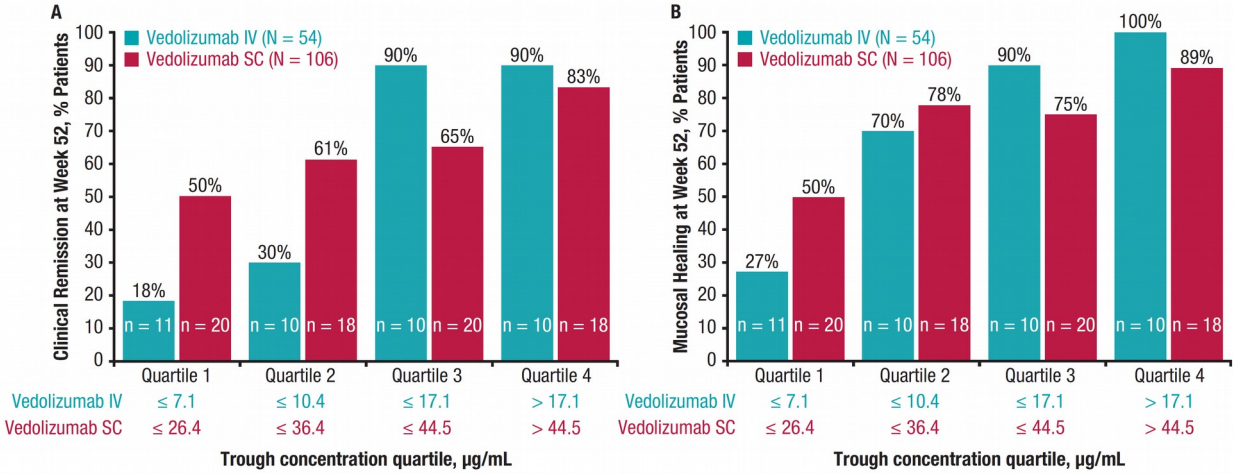
Supplementary Figure S8. Observed median and interquartile range trough values (C_{trough}) by study visit (pharmacokinetic-evaluable population),[a] presented on a semi-log scale (y-axis).



IV, intravenous; Q2W, every 2 weeks; Q8W, every 8 weeks; SC, subcutaneous.

[a]The pharmacokinetic-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 Figure S9. Vedolizumab SC and IV **(A)** Clinical remission and **(B)** endoscopic improvement at Week 52 by trough concentration quartiles. Data are from the pharmacokinetic-evaluable population.[a]



IV, intravenous; SC, subcutaneous.

[a]The pharmacokinetic-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 S1. Clinical Response During Vedolizumab IV Induction at Week 6 and at Week 14

Clinical Response,[a] n (%)	Week 6 Nonresponders Who Received 3rd Vedolizumab IV Induction Dose (N=139)	Patients Randomized to Maintenance Treatment (N=216)[d]	All Enrolled (N=383)
Week 6[b]	0	210 (97.2)[e]	215 (56.1)
Week 14[c]	110 (79.1)	NA	110 (28.7)[f]
Overall for induction treatment	110 (79.1)	210 (97.2)	325 (84.9)

IV, intravenous.

[a]Clinical response is defined as a reduction in total Mayo score of ≥3 points and ≥30% from baseline (Week 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]Determined by complete Mayo score.

[c]Determined by partial Mayo score.

[d]Six patients who did not achieve clinical response at Week 6 were randomized in error.

[e]Five patients with clinical response were not randomized.

[f]Twenty-four patients discontinued before receiving a 3rd vedolizumab IV induction dose, 4 patients received a 3rd vedolizumab IV induction dose although they were Week 6 responders.

Supplementary Table S2. Endoscopic Remission (Mayo Endoscopic Subscore = 0) at Week 52 (Full Analysis Set, Non-Responder Imputation)[a,b,c]

Endoscopic Remission at Week 52	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)[d]		16.9 (5.2, 28.6)	15.1 (0.8, 29.4)
p value, vedolizumab vs placebo[e]		0.014	0.046

CI, confidence interval; IV, intravenous; SC, subcutaneous; TNF, tumor necrosis factor.
[a]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.
[b]All patients with missing data for determination of endpoint status are categorized as "No."
[c]This analysis was conducted post hoc.
[d]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.
[e]The p values were obtained using a Cochran-Mantel-Haenszel (CMH) test stratified by randomization stratum (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 remissions in either treatment group was ≤5.

Supplementary Table S3. 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, Non-Responder Imputation)[a]

	Placebo (N=24)	Vedolizumab SC (N=45)	Vedolizumab IV (N=21)
Corticosteroid use (mg/day)[b]			
Week 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[c]	(-17.6, -7.9)	(-16.5, -10.4)	(-18.5, -9.9)
Difference in adjusted change from baseline vs placebo, mean (SE)[c]		-0.7 (2.9)	-1.5 (3.3)
95% CI[c]		(-6.4, 5.0)	(-8.0, 5.0)
Corticosteroid-free clinical remission and corticosteroid-free for 90 days			
n (%)	2 (8.3)	12 (26.7)	6 (28.6)
95% CI[d]	(1.0, 27.0)	(14.6, 41.9)	(11.3, 52.2)
Difference from placebo		18.3	20.2
95% CI[d]		(-6.7, 41.6)	(-9.8, 47.8)
p value[e]		0.115	0.121
Corticosteroid-free clinical remission and corticosteroid-free for 180 days			
n (%)	2 (8.3)	12 (26.7)	6 (28.6)
95% CI[d]	(1.0, 27.0)	(14.6, 41.9)	(11.3, 52.2)
Difference from placebo		18.3	20.2
95% CI[d]		(-6.7, 41.6)	(-9.8, 47.8)
p value[e]		0.115	0.121

CI, confidence interval; IV, intravenous; SC, subcutaneous; SE, standard error.

[a]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.

[b]Corticosteroid use was defined as usage of prednisone or equivalent.

[c]Adjusted means, SEs, and CIs are based on an analysis of covariance model with treatment as factor and baseline corticosteroid use as a covariate.

[d]The 95% CIs of the percentage are based on the Clopper-Pearson method. 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.

[e]The p values were obtained using a Cochran-Mantel-Haenszel (CMH) test stratified by randomization stratum (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 remissions in either treatment group was ≤5.

Supplementary Table S4. Clinical Remission[a] at ≥80% of Study Visits Including Week 52 (Full Analysis Set)[b,c]

	Placebo (N=56)	**Vedolizumab SC (N=106)**	**Vedolizumab IV (N=54)**
Clinical remission, n (%)[a]	10 (17.9)	59 (55.7)	25 (46.3)
95% CI[d]	(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]		<0.001	0.001

CI, confidence interval; IV, intravenous; SC, subcutaneous; TNF, tumor necrosis factor.

[a]Clinical remission by partial Mayo score is defined as a partial Mayo score of ≤2 points and no individual subscore >1 point

[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]All patients with missing data for determination of endpoint status were categorized as nonresponders.

[d]The 95% CIs of the clinical remission rate were based on the Clopper-Pearson method. 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 (CMH) test stratified by randomization stratum (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 remissions in either treatment group was ≤5.

Supplementary Table S5. Clinical Remission Based on Modified Mayo Score at Week 52 (Full Analysis Set)[a,b]

		Alternate Clinical Remission Definition		
Treatment Group	**Statistic**	**Definition 1[c]**	**Definition 2[d]**	**Definition 3[e]**
Placebo (N=56)	Clinical remission, n (%)	6 (10.7)	8 (14.3)	8 (14.3)
	95% CI[f]	(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[f]	(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]	<0.001	<0.001	<0.001
Vedolizumab IV (N=54)	Clinical remission, n (%)	19 (35.2)	22 (40.7)	22 (40.7)
	95% CI[f]	(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]	0.003	0.002	0.002

CI, confidence interval; IV, intravenous; SC, subcutaneous.

[a]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.

[b]All patients with missing data for the determination of endpoint status were categorized as nonresponders.

[c]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).

[d]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).

[e]Either definition 1 or 2.

[f]The 95% CIs of the clinical remission rate were based on the Clopper-Pearson method. 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 (CMH) test stratified by randomization stratum (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 remissions in either treatment group was ≤5.

Supplementary Table S6. Observed Fecal Calprotectin by Study Visit (Full Analysis Set)[a]

Study Visit	Patients, n (%)		
	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)

CI, confidence interval; IV, intravenous; SC, subcutaneous.

[a]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.

[b]Baseline was defined as the last nonmissing measurement before or on the date of the first dose of study drug (Day 1).

Supplementary Table S7. Histological Remission and Minimal Histological Activity at Week 52 (Full Analysis Set)[a,b,c]

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

CI, confidence interval; IV, intravenous; RHI, Robarts histopathology index; SC, subcutaneous.

[a]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.

[b]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 Non-Evaluable were excluded from the analyses post hoc.

[c]The worst score across locations at a given time point was used in the analyses.

[d]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 endpoint status are categorized as "No."

[e]The 95% CIs of the percentages are based on Clopper-Pearson method.

Supplementary Table S8. Difference in Least Squares Means for Vedolizumab Versus 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, Last Observation Carried Forward)[b]

	Vedolizumab SC			Vedolizumab IV		
Outcome	**LS Mean Difference vs Placebo**	**95% CI**	**p value[c]**	**LS Mean Difference vs Placebo**	**95% CI**	**p value[c]**
IBDQ total score	43.9	(30.6, 57.1)	<0.001	37.1	(21.9, 52.4)	<0.001
IBDQ bowel symptoms domain score	14.9	(10.6, 19.2)	<0.001	12.8	(7.8, 17.7)	<0.001
IBDQ emotional function domain score	15.6	(10.7, 20.6)	<0.001	13.0	(7.3, 18.7)	<0.001
IBDQ social function domain score	7.5	(5.0, 10.0)	<0.001	6.4	(3.5, 9.2)	<0.001
EQ-5D VAS score	17.6	(11.0, 24.3)	<0.001	13.1	(5.5, 20.8)	0.001
WPAI-UC overall work productivity score	-18.8	(-31.1, -6.6)	0.003	-14.2	(-27.9, -0.6)	0.041
WPAI-UC activity impairment score	-24.4	(-33.1, -15.7)	<0.001	-23.2	(-33.2, -13.2)	<0.001

ANCOVA, analysis of covariance; CI, confidence interval; EQ-5D VAS, Euro Quality of Life-5D visual analog scale; IBDQ, Inflammatory Bowel Disease Questionnaire (IBDQ); LS, least squares; WPAI-UC, Work Productivity and Activity Impairment–Ulcerative Colitis.

[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]p values were obtained using an ANCOVA model with treatment as a factor and baseline score as a covariate.

Supplementary Table S9. Gastrointestinal Infections (Safety Analysis Set)[a]

	Patients, n (%)		
	Placebo (N=56)	Vedolizumab SC (N=106)	Vedolizumab IV (N=54)
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

IV, intravenous; SC, subcutaneous.

[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 S10. Injection-Site Reactions (Safety Analysis Set)[a]

	Patients (%)		
	Placebo (N=56)	Vedolizumab SC (N=106)	Vedolizumab IV (N=54)
Patients with any injection-site adverse events	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

IV, intravenous; SC, subcutaneous.

[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 S11. Clinical Remission at Week 52, Injection-Site Reactions During Maintenance Treatment, and Hypersensitivity Reactions by Overall AVA Status (Safety Analysis Set)[a]

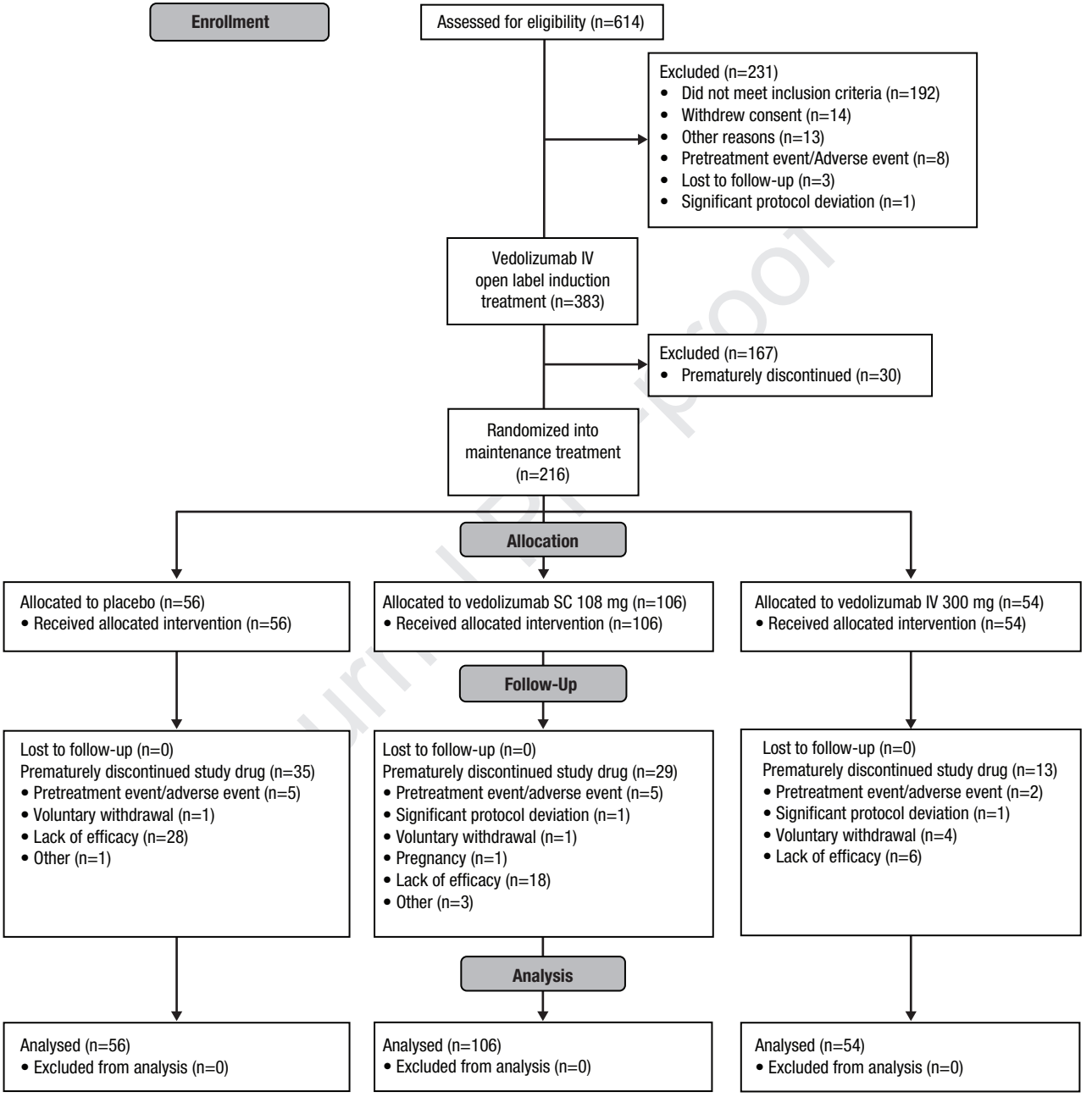
Outcome, Yes/No Overall AVA status	Patients, n (%) Placebo (N=56)	 Vedolizumab SC (N=106)	 Vedolizumab IV (N=54)
Clinical remission at Week 52			
Yes			
N	8	49	23
AVA positive[b]	2 (25.0)	0	0
No			
N	48	57	31
AVA positive	15 (31.3)	6 (10.5)	3 (9.7)
Injection-site reactions during maintenance[c]			
Yes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

AVA, anti-vedolizumab antibody; IV, intravenous; SC, subcutaneous.

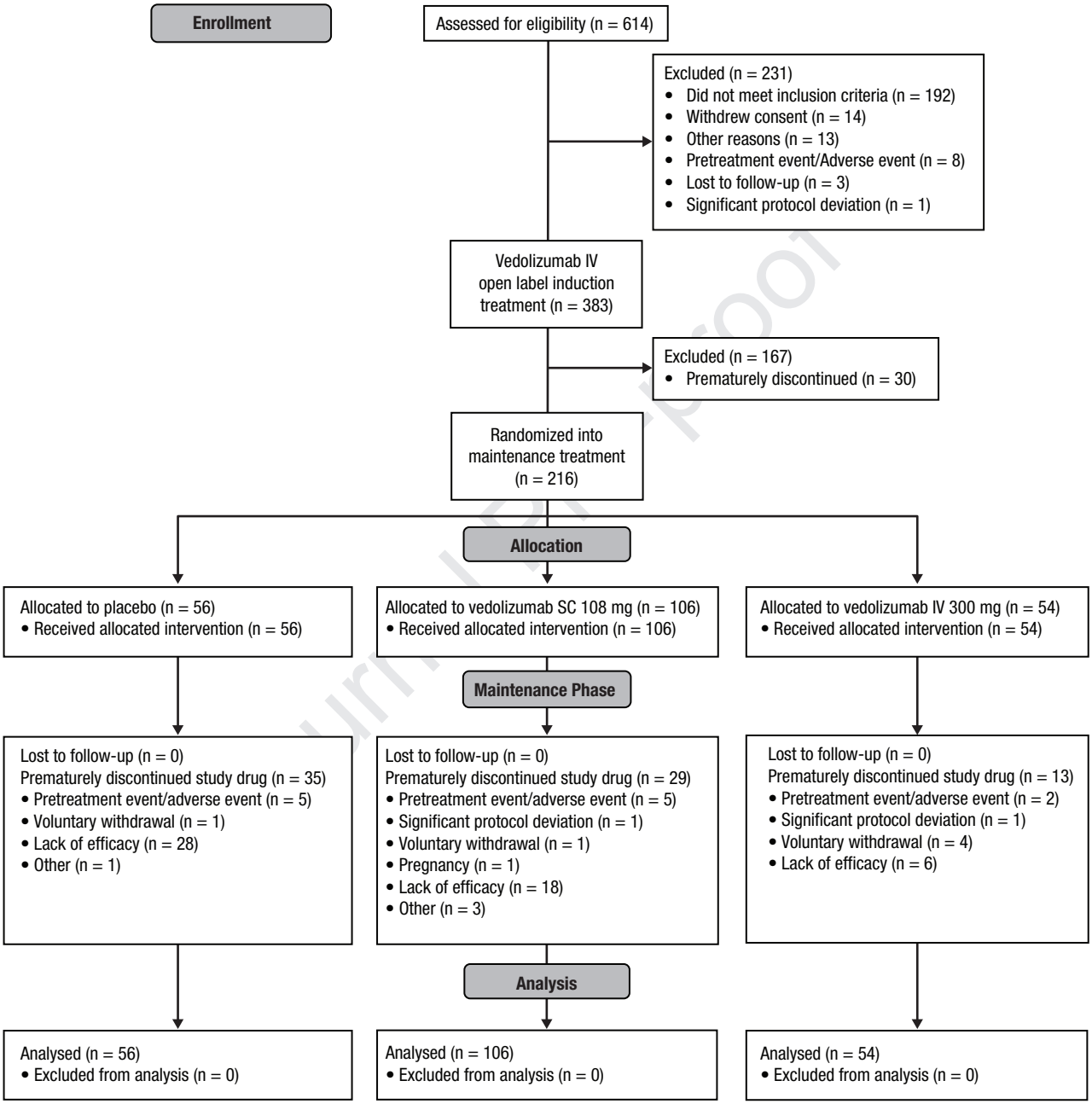
[a]The safety analysis set included all patients who were randomized to the maintenance phase and received at least 1 dose of study drug.

[b]Positive AVA 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 Week 6 and Week 52.



Randomization Procedure: Randomization personnel of the sponsor or designee generated the randomization schedule prior to the start of the study. An interactive web response system (IWRS) system was used for patient randomization. All randomization information was stored in a secured area, accessible only by authorized personnel.



Randomization Procedure: Randomization personnel of the sponsor or designee generated the randomization schedule prior to the start of the study. An interactive web response system (IWRS) system was used for patient randomization. All randomization information was stored in a secured area, accessible only by authorized personnel.