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Endoscopic, Radiologic, and Histologic Healing With Vedolizumab in Patients With Active Crohn's Disease

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BACKGROUND & AIMS: Vedolizumab is a gut-selective monoclonal antibody for the treatment of moderately to severely active Crohn's disease (CD). We performed a prospective study of endoscopic, radiologic, and histologic healing in patients with CD who received vedolizumab therapy. **METHODS:** We performed a phase 3b, open-label, single-group study of 101 patients with at least 3 months of active CD (a CD Activity Index [CDAI] score of 220–450, a simple endoscopic score for CD [SES-CD] of 7 or more, 1 or more mucosal ulcerations [identified by endoscopy], and failure of conventional therapy) from March 2015 through December 2017. Among the patients enrolled, 54.5% had previous failure of 1 or more tumor necrosis factor (TNF) antagonists and 44.6% had severe endoscopic disease activity (SES-CD scores above 15) at baseline. Participants received vedolizumab (300 mg intravenously) at weeks 0, 2, and 6, and then every 8 weeks thereafter, for 26 weeks (primary study) or 52 weeks (substudy, 56 patients). The primary endpoint at week 26 was endoscopic remission (SES-CD score of 4 or less); other endpoints included endoscopic response (50% reduction in SES-CD), radiologic remission (magnetic resonance index of activity score below 7), and histologic response (modified global histologic disease activity score of 4 or less). **RESULTS:** At week 26, 11.9% of patients were in endoscopic remission (95% confidence interval [CI] 6.3–9.8); at week 52, 17.9% of the patients were in endoscopic remission (95% CI 8.9–30.4). Higher proportions of patients naïve to TNF antagonists achieved endoscopic remission than patients with TNF-antagonist-failure at weeks 26 and 52. Higher proportion of patients with moderate CD (SES-CD scores, 7–15) achieved endoscopic remission at weeks 26 and 52 than patients with severe CD (SES-CD scores above 15). The proportion of patients with complete mucosal healing increased over time, with greater rates of healing in the colon than in the ileum. Remission was detected by magnetic resonance enterography in 21.9% of patients at week 26 (95% CI 9.3–40.0) and in 38.1% at week 52 (95% CI 18.1–61.6). At week 26, 24.4% of patients had a histologic response in the colon (95% CI 15.3–35.4) and 28.3% of patients had a histologic response in the ileum (95% CI 17.5–41.4). At week 52, 20.5% of patients had a histologic response in the colon (95% CI 9.8–35.3) and 34.3% of patients had a histologic response in the ileum (95% CI 19.1–52.2). There were no notable safety issues, including worsening of extraintestinal manifestations. **CONCLUSIONS:** In a phase 3b trial, we found that 26 and 52 weeks of treatment with vedolizumab (300 mg, at weeks 0, 2, and 6, and then every 8 weeks thereafter) induces endoscopic, radiologic, and histologic healing in patients with moderately to severely active CD. ClinicalTrials.gov no: NCT02425111.

Keywords: Monoclonal Antibody; Integrin α_4; β_7; mGHAS; Long-Term Outcome.

Crohn's disease (CD) frequently causes structural damage to the gastrointestinal tract resulting in complications of stricture, fistula and abscess formation, loss of function, and impaired health-related quality of life (HRQL).[1–5] Surgery is often required to treat complications of the disease, placing patients at risk for operative morbidity, impaired bowel function, postoperative recurrence, and mortality.[5] Thus, new approaches to treatment are needed.

Currently, it is no longer considered sufficient to target clinical symptoms alone. Support is growing for a new disease management paradigm based on treatment targeting both clinical symptom relief and objective measures of inflammation, such as endoscopy. The goal of this approach is to improve disease prognosis by preventing structural bowel damage.[2,3,6] The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) consensus advocates a composite treatment target of endoscopic healing and symptomatic remission. This includes a recommendation that absence of large ulcers is the most appropriate endoscopic treatment target.[6] However, definitions of endoscopic

Abbreviations used in this paper: **AE, adverse event; CD, Crohn's disease; CDAI, Crohn's disease activity index; CDEIS, Crohn's Disease Endoscopic Index of Severity; CI, confidence interval; CRP, C-reactive protein; EIM, extraintestinal manifestations; EQ-5D, EuroQol-5D; FCP, fecal calprotectin; GHAS, global histologic disease activity score; HRQL, health-related quality of life; IBDQ, inflammatory bowel disease questionnaire; MaRIA, magnetic resonance index of activity; MREn, magnetic resonance enterography; SES-CD, simplified endoscopic activity score for Crohn's disease; TNF, tumor necrosis factor.**

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Crohn's disease (CD) frequently causes structural damage to the gastrointestinal tract, often requiring treatment with risky surgery. Vedolizumab is a gut-selective monoclonal antibody for the treatment of moderately to severely active Crohn's disease (CD).

NEW FINDINGS

The authors observed endoscopic remission in 11.9% and 17.9% of vedolizumab patients at weeks 26 and 52, respectively. Endoscopic remission was greater in patients naïve to anti-TNF agents than patients who have had these drugs fail.

LIMITATIONS

This was an open-label study with no comparison group; a protocol amendment during the study required analysis of 2 study populations (a 26-week primary and a 52-week sub-study population).

IMPACT

These results demonstrate the efficacy of vedolizumab to induce and sustain endoscopic improvements in patients with moderately to severely active CD.

endpoints have not been uniformly incorporated into CD clinical trial protocols, and remain incompletely validated.[7] Endoscopic remission has been defined using different thresholds for the simple endoscopic score for CD (SES-CD) or the CD Endoscopic Index of Severity (CDEIS) score, or as complete absence of ulceration,[8–11] which varies depending on whether or not aphthae are considered. Clinical trial experience shows that endoscopic healing is difficult to achieve in CD. As a result, endoscopic response, a less stringent measure of endoscopic healing (defined as a 50% reduction from baseline in SES-CD score), has become a widely accepted benchmark.

Other methods may provide alternatives to endoscopy for objectively assessing inflammation. Magnetic resonance enterography (MREn) is particularly attractive because healing of the mucosa and deeper layers of the bowel wall can be assessed. The magnetic resonance index of activity (MaRIA) is a quantitative MREn measure of disease activity. Although preliminary validation studies suggest MaRIA is reliable and responsive, experience with MaRIA as an outcome measure in clinical trials is lacking.

Histology, another potential outcome measure, has not been widely used in CD trials because of the lack of a validated scoring system, complex heterogeneity of disease location, and the patchy nature of microscopic inflammation.[12] Nevertheless, quantification of inflammation on endoscopic biopsies seems to be a clinically relevant goal in CD trials, given recent developments in validating tools for histologic assessment in ulcerative colitis trials.[13]

Vedolizumab is an anti-$\alpha4\beta7$-integrin humanized immunoglobulin G1 monoclonal antibody that selectively blocks T-lymphocyte trafficking into the gastrointestinal mucosa.[14] The pivotal GEMINI 2 and 3 trials of vedolizumab in moderately to severely active CD demonstrated the benefit of vedolizumab on clinical outcomes; however, these studies did not include endoscopic, radiologic, or histologic assessments.[15,16] Subsequently, several observational studies have described beneficial effects for vedolizumab therapy on endoscopically defined inflammation, although these reports were mostly retrospective and did not use centrally read endoscopy to score disease activity according to the SES-CD or CDEIS.[17–23]

The objective of the VERSIFY study was to prospectively evaluate the efficacy of vedolizumab therapy on endoscopic remission and response in patients with moderately to severely active CD. We also assessed effects of the drug on radiologically (MREn) and histologically defined inflammation as exploratory endpoints.

Materials and Methods

Patient Population

Eligible patients were adults, 18 to 80 years of age, with a diagnosis of moderately to severely active CD ≥3 months. Active disease was defined by a baseline CD Activity Index (CDAI) score of 220 to 450 and SES-CD score ≥7 with any ulcer (including aphthae) in any bowel segment including the ileum and/or colon documented by centrally read ileocolonoscopy. Patients were required to have inadequate response, loss of response, or intolerance to at least one of the following: corticosteroids, immunosuppressives, and/or tumor necrosis factor (TNF)-antagonists.

Patients with history or clinical evidence of an abdominal abscess, extensive bowel resection, colonic mucosal dysplasia, and those with prior exposure to vedolizumab, natalizumab, efalizumab, or rituximab were ineligible. Concomitant treatment with immunosuppressives, oral 5-aminosalicylic acid, corticosteroids (maximum dose 30 mg/d prednisone or 9 mg/d budesonide), antibiotics, and antidiarrheals was allowed. Corticosteroid tapering was recommended but not mandatory following clinical response or if the investigator felt there was sufficient improvement.

Study Design and Assessments

This was an open-label, single-arm, multicenter phase 3b study conducted between March 2015 and December 2017 (ClinicalTrials.gov: NCT02425111; EudraCT: 2014-003509-13). After a screening period of up to 4 weeks, eligible patients received 26 weeks of treatment (vedolizumab 300-mg intravenous infusion over 30 minutes on day 1 and at weeks 2, 6, 14, and 22 [original protocol, December 2014]). The protocol was subsequently amended ("Amendment 4," April 2016) to extend treatment for a total of 52 weeks with infusions at weeks 30, 38, and 46. Patients in the study at the time of the amendment and those enrolled post-amendment were treated and assessed up to week 52 (Supplementary Figure 1). Increasing the vedolizumab dose frequency was not included in the study design.

Ileocolonoscopy was performed at screening (for eligibility), weeks 14 and 26 (primary study), and week 52 (sub-study). The endoscopic images were evaluated by central readers, who were trained in scoring the SES-CD (score range 0–56; higher score indicates more severe inflammation).[24,25] The central readers were blinded to other clinical data. MREn

was performed at screening, week 26, and week 52 in a subset of patients recruited at preselected study sites. To ensure MREn capture using standardized protocol, sites received expert-to-site technologist training, either face-to-face or via conference call. MaRIA was used to evaluate disease activity (no standard range, score calculated based on MREn features, higher score indicates greater severity).[26] Images were read by a central radiologist experienced in the scoring conventions, and blinded to time point and other endoscopic or clinical data. Biopsies were sampled (2 for each segment regardless of whether active inflammation was present) at screening, week 26, and week 52. Histology was evaluated by a central pathologist, blinded to endoscopic and clinical data, using a modified global histologic disease activity score (GHAS) (score range, 0–12 per segment; higher score indicates more severe microscopic inflammation).[27] Further details on endoscopic, radiologic, and histologic assessments are in the Supplemental Methods.

Clinical assessments using CDAI scores,[28] HRQL assessments using the inflammatory bowel disease questionnaire (IBDQ), and the EuroQOL-5D (EQ-5D) scores,[29,30] and the biomarkers serum C-reactive protein (CRP) and fecal calprotectin (FCP) were analyzed.

Safety assessments were performed at each study visit and at a follow-up visit 18 weeks after the last study treatment dose, and at a final visit a further 8 weeks later (ie, total of 6 months after final dose). Safety also included reports made spontaneously at any time during the study.

Study Endpoints

The primary endpoint was the proportion of patients with endoscopic remission (defined as SES-CD $\leq$4) at week 26. Secondary endoscopic endpoints were the proportions of patients with endoscopic remission at weeks 14 and 52, complete mucosal healing (defined as absence of any ulcers, including aphthae), and endoscopic response (defined as $\geq$50% decrement from baseline in SES-CD score) at weeks 14, 26, and 52. Changes from baseline in SES-CD were assessed.

Secondary clinical endpoints were the proportions of patients with clinical remission (defined as a CDAI $\leq$150), clinical response (defined as a $\geq$100-point CDAI reduction from baseline) at weeks 10, 26, and 52,[28] and durable clinical remission (remission at both weeks 26 and 52). Changes from baseline in CDAI were assessed.

Exploratory endpoints included radiologic remission (defined as MaRIA scores $<$7 in all segments) or $<$11 across all bowel segments in those patients with baseline scores of $\geq$7 or $\geq$11 in $\geq$1 segment, respectively, histologic response (defined as the proportion with modified GHAS $\leq$4 in those patients with baseline score $>$4), and histologic remission (defined as proportion with no neutrophils in the epithelium in those patients with neutrophils at baseline). Changes from baseline in MaRIA and GHAS scores were assessed.

Other exploratory endpoints were changes from baseline in concentrations of the biomarkers serum CRP and FCP, and changes from baseline in the HRQL scores IBDQ and EQ-5D.

Safety endpoints were the proportion of patients with adverse events (AEs) classified by Medical Dictionary for Regulatory Activities terms (version 20.0). Extraintestinal manifestations (EIMs) captured on the CDAI diary card were evaluated.

Statistical Analysis

The full analysis set for both the primary (n = 101) and substudy populations (n = 56) included all patients who received $\geq$1 dose of vedolizumab. Descriptive statistics were used to summarize baseline characteristics. For all proportion-based efficacy endpoints, the point estimates with 2-sided 95% confidence intervals (CIs) were calculated using the Clopper-Pearson method. For all continuous variables, descriptive statistics by study visit and mean or median changes over time were generated. Endpoints from the primary and substudy populations were analyzed separately owing to key differences in baseline characteristics between the populations that would otherwise confound comparison of early vs later time points.

The ulceration status at any visit was determined by the presence/absence of ulceration across all segments evaluated at that visit. Patients with missing data were imputed as non-responders. Endpoints were assessed in subgroups based on key disease characteristics.

The relationship between outcome measures based on all available (nonmissing) data at all study visits was analyzed using Pearson correlation.

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

Results

Patient Characteristics

A total of 191 patients were screened (Figure 1). From March 2015 to June 2017, 101 patients entered the primary study at 42 centers, with 78 completing 26 weeks of treatment; 56 patients were consented under Amendment 4 and thus were eligible for 52 weeks of treatment, with 50 completing follow-up. The most common reasons for premature discontinuation were perceived lack of efficacy (n = 15 and n = 7 in first and second 26 weeks) and AEs (n = 2 and n = 3 in first and second 26 weeks).

Baseline characteristics of the primary and substudy populations are shown in Table 1. Notably, 55 (54.5%) of 101 patients had experienced previous TNF-antagonist therapy failure; 23 (22.8%) of 101 had 1 TNF-antagonist failure; 32 (31.7%) of 101 had 2 or more failures. In the 52-week substudy population, 24 (42.9%) of 56 patients had a prior TNF-antagonist therapy failure (10 [17.9%] of 56 with 1 prior TNF-antagonist; 14 [25.0%] of 56 with $\geq$2).

Endoscopic Disease Activity

For the primary endpoint, 12 (11.9%; 95% CI 6.3–19.8) of 101 patients in the 26-week primary study population achieved endoscopic remission at week 26. In the 52-week substudy population, 9 (16.1%; 95% CI 7.6–28.3) of 56 were in endoscopic remission at week 26, and 10 (17.9%; 8.9–30.4) of 56 at week 52 (Figure 2*A*).

Endoscopic remission rates were consistently greater in patients naïve to TNF antagonists (Figure 2*B*). In the 26-week primary study population, 9 (19.6%; 95% CI 9.4–33.9) of 46 TNF-antagonist-naïve patients achieved endoscopic remission at week 26, compared with 3 (5.5%; 1.1–15.1) of 55 TNF-antagonist-failure patients. These findings were similar in the 52-week substudy population,

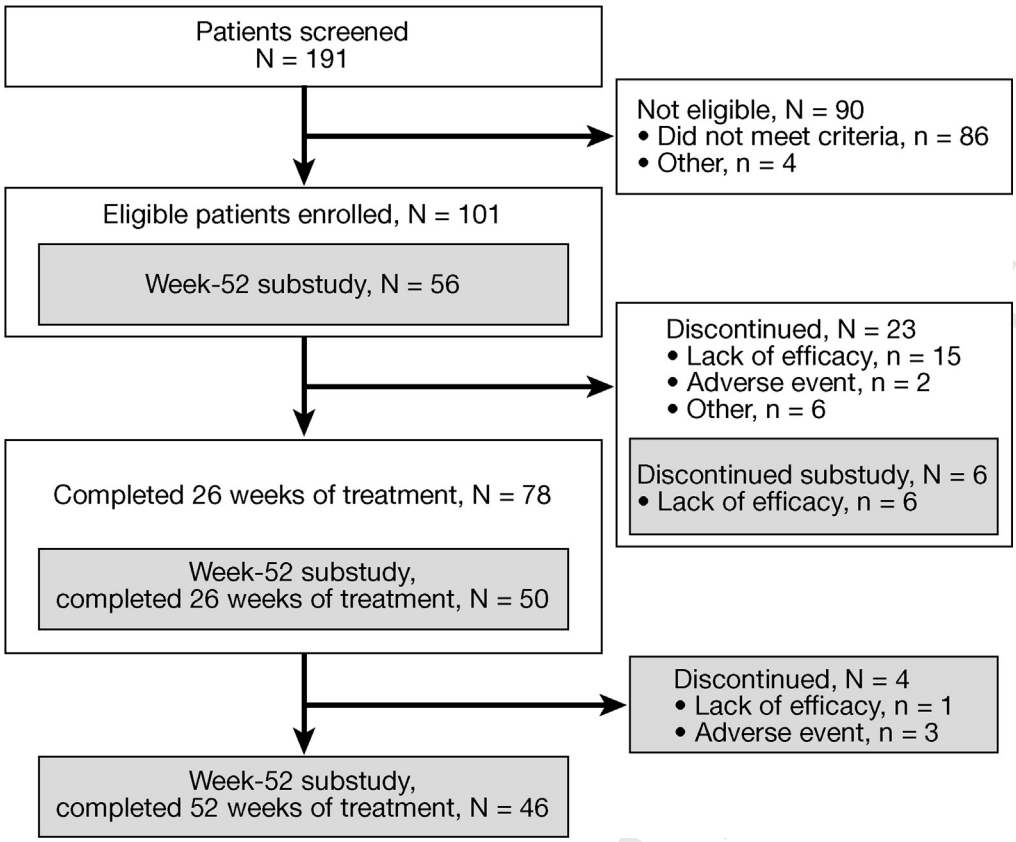

Figure 1. Patient flow for 26-week primary study and 52-week substudy.

Table 1. Key Patient Characteristics of the Study Populations

	26-week primary study n = 101	52-week substudy n = 56
Women, n (%)	49 (48.5)	26 (46.4)
Age, mean (SD), *y*	38.0 (±14.0)	39.6 (±14.8)
Weight, mean (SD), *kg*	73.9 (±18.8)	73.6 (±18.9)
CD duration, mean (SD), *y*	11.5 (±9.6)	11.2 (±10.3)
SES-CD		
Mean (SD)	16.0 (±7.8)	16.7 (±7.4)
Median (min, max)	14.0 (4, 37)	14.5 (7, 34)
SES-CD, n (%)		
SES-CD 7<15, %	53 (52.5)	29 (51.8)
SES-CD ≥15, %	45 (44.6)	27 (48.2)
CDAI		
Mean (SD)	324.2 (±66.3)	306.5 (±65.3)
Median (min, max)	312.0 (193, 440)	294.0 (193, 467)
Smoker, n (%)	33 (32.7)	20 (35.7)
Prior TNF-antagonist failure, n (%)	55 (54.5)	24 (42.9)
Baseline CRP, mg/dL mean (±SD) [range]	17.7 (±28.2) [0.2, 132.9]	15.5 (±26.4) [0.2, 113.8]
Elevated CRP >10 mg/L, n (%)	40 (39.6)	19 (33.9)
Baseline FCP, μg/g mean (±SD) [range]	1484.9 (±1812.0) [44, 11128]	1418.6 (±1723.2) [67, 11128]
Elevated FCP >500 μg/g, n (%)	63 (62.4)	37 (66.1)
Ileal involvement, n (%)	63 (62.3)	36 (64.3)
Fistula present, n (%)	7 (6.9)	3 (5.4)

max, maximum; min, minimum; SD, standard deviation.

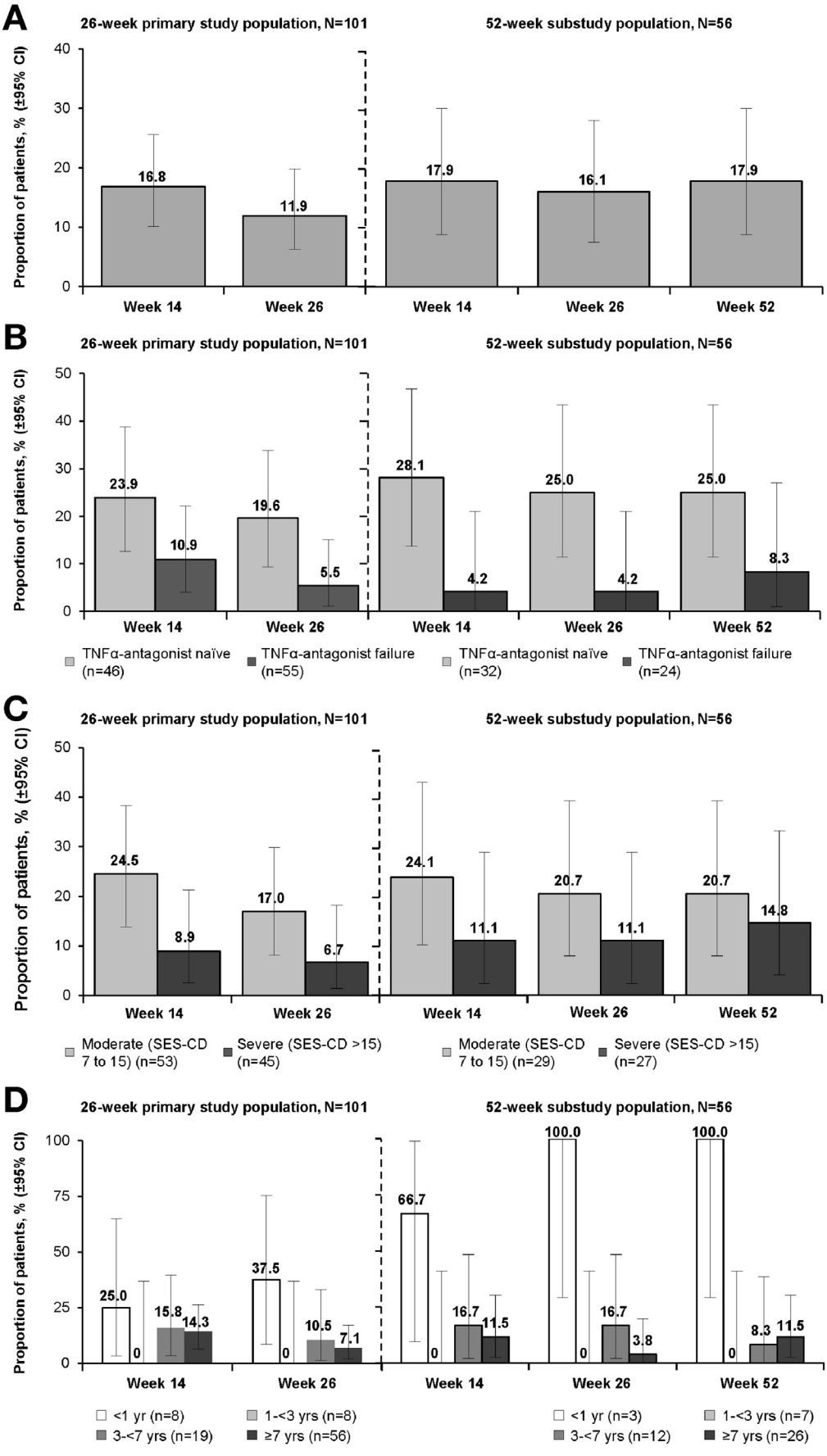

Figure 2. Rate of endoscopic remission (primary endpoint) in the 26-week primary study and 52-week substudy: (*A*) overall populations; (*B*) TNF-antagonist subgroups; (*C*) baseline endoscopic disease activity subgroups; and (D) baseline disease duration subgroups.

Table 2. Rates of Complete Mucosal Healing and Endoscopic Response and Clinical Remission and Response in the 26-week Primary Study and 52-week Substudy (Overall Populations and TNFα Subgroups)

n/N (%) [95% CI]	Primary 26-week study population		52-week substudy population		
Endoscopic outcomes					
Complete mucosal healing	Week 14	Week 26	Week 14	Week 26	Week 52
Overall	12/101 (11.9) [6.3–19.8]	15/101 (14.9) [8.6–23.3]	7/56 (12.5) [5.2–24.1]	11/56 (19.6) [10.2–32.4]	10/56 (17.9) [8.9–30.4]
TNF naïve	7/46 (15.2) [6.3–28.9]	11/46 (23.9) [12.6–38.8]	6/32 (18.8) [7.2–36.4]	9/32 (28.1) [13.7–46.7]	9/32 (28.1) [13.7–46.7]
TNF failure	5/55 (9.1) [3.0–20.0]	4/55 (7.3) [2.0–17.6]	1/24 (4.2) [0.1–21.1]	2/24 (8.3) [1.0–27.0]	1/24 (4.2) [0.1–21.1]
Endoscopic response	Week 14	Week 26	Week 14	Week 26	Week 52
Overall	34/101 (33.7) [24.6–43.8]	25/101 (24.8) [16.7–34.3]	26/56 (46.4) [33.0–60.3]	17/56 (30.4) [18.9–44.1]	30/56 (53.6) [39.7–67.0]
TNF naïve	20/46 (43.5) [28.9–58.9]	13/46 (28.3) [16.0–43.5]	18/32 (56.3) [37.7–73.6]	11/32 (34.4) [18.6–53.2]	21/32 (65.6) [46.8–81.4]
TNF failure	14/55 (25.5) [14.7–39.0]	12/55 (21.8) [11.8–35.0]	8/24 (33.3) [15.6–55.3]	6/24 (25.0) [9.8–46.7]	9/24 (37.5) [18.8–59.4]
Clinical outcomes					
Clinical remission	Week 10	Week 26	Week 10	Week 26	Week 52
Overall	36/101 (35.6) [26.4–45.8]	42/101 (41.6) [31.9–51.8]	26/56 (46.4) [33.0–60.3]	32/56 (57.1) [43.2–70.3]	28/56 (50.0) [36.3–63.7]
TNF naïve	20/46 (43.5) [28.9–58.9]	24/46 (52.2) [36.9–67.1]	15/32 (46.9) [29.1–65.3]	20/32 (62.5) [43.7–78.9]	18/32 (56.3) [37.7–73.6]
TNF failure	16/55 (29.1) [17.6–42.9]	18/55 (32.7) [20.7–46.7]	11/24 (45.8) [25.6–67.2]	12/24 (50) [29.1–70.9]	10/24 (41.7) [22.1–63.4]
Clinical response	Week 10	Week 26	Week10	Week 26	Week 52
Overall	55/101 (54.5) [44.2–64.4]	61/101 (60.4) [50.2–70.0]	34/56 (60.7) [46.8–73.5]	41/56 (73.2) [59.7–84.2]	33/56 (58.9) [45.0–71.9]
TNF naïve	24/46 (52.2) [36.9–67.1]	29/46 (63.0) [47.5–76.8]	18/32 (56.3) [37.7–73.6]	24/32 (75.0) [56.6–88.5]	20/32 (62.5) [43.7–78.9]
TNF failure	31/55 (56.4) [42.3–69.7]	32/55 (58.2) [44.1–71.3]	16/24 (66.7) [44.7–84.4]	17/24 (70.8) [48.9–87.4]	13/24 (54.2) [32.8–74.4]

NOTE. Complete endoscopic healing: absence of any ulcers, including absence of aphthae.
Endoscopic response: $\geq$50% SES-CD score reduction from baseline.
Clinical remission: CDAI $\leq$150.
Clinical response: $\geq$100-point CDAI reduction from baseline.

with 8 (25.0%; 95% CI 11.5–43.4) of 32 TNF-antagonist-naïve patients vs 2 (8.3%; 1.0–27.0) of 24 TNF-antagonist-failure patients achieving endoscopic remission at week 52. In both primary and substudy populations, endoscopic remission rates were consistently greater in patients with moderate rather than severe endoscopic disease activity at baseline (SES-CD 7–15 vs >15) (Figure 2*C*) and in patients with shorter disease duration (Figure 2*D*). Endoscopic remission rates were not consistently greater in other subgroups based on baseline CDAI or biomarker levels (Supplementary Figure 2).

Endoscopic response rates showed improvements over time in both the primary and substudy populations (Table 2). In the primary study, the 26-week response rates for the overall, TNF-antagonist-naïve, and TNF-antagonist-failure populations were 25 (24.8%; 95% CI 16.7–34.3) of 101, 13 (28.3%; 16.0–43.5) of 46, and 12 (21.8%; 11.8–35.0) of 55, respectively. In the substudy, corresponding rates at 52 weeks were 30 (53.6%; 95% CI 39.7–67.0) of 56, 21 (65.6%; 46.8–81.4) of 32, and 9 (37.5%; 18.8–59.4) of 24. The evolution of response rates over time was consistent with that observed for endoscopic remission.

Complete mucosal healing rates also improved in the primary and substudy populations (Table 2). Modest differences were noted in evolution over time for complete mucosal healing rates compared with endoscopic remission or response rates; there were cumulative increases observed with time on treatment. Complete mucosal healing rates were greater in the colonic segments than in the ileum (Supplementary Figure 3). When the mucosal healing definition excluded the presence of aphthous ulcers, rates were substantially higher (25 [28.1%] of 89 at week 26 in the primary study and 13 [26.0%] of 50 at week 52 in the substudy). Endoscopic remission and complete mucosal healing rates were generally in agreement except in 3 patients in the primary study, and 2 in the substudy, who achieved mucosal healing but not endoscopic remission. All 3 patients had no ulcerations but detectable inflammation (patchy erythema) and narrowing.

The mean SES-CD decreased from 16.0 at baseline to 11.1 at week 26 (ΔSES-CD −5.2; 95% CI −3.6 to −6.8) in the primary study population, and from 16.7 at baseline to 8.8 at week 52 (ΔSES-CD −7.9; −5.9 to −9.9) in the substudy population (Figure 3*A*).

MREn-defined Disease Activity

In the primary study population, MREn evaluations were performed in a subset of 37 patients, of which 32 had imaging suitable for analysis and a MaRIA score >7 and >11 at baseline in at least one bowel segment. In the substudy population, 22 patients had MREn evaluations, of whom 21 had suitable imaging and abnormal MaRIA scores in at least one bowel segment.

MaRIA-7 remission occurred in 7 (21.9%; 95% CI 9.3–40.0) of 32 patients at week 26 (primary study) and in 8 (38.1%; 95% CI 18.1–61.6) of 21 at week 52 (substudy). MaRIA-11 remission was achieved by 11 (34.4%; 18.6–53.2) of 32 patients at week 26 (primary study) and by 9 (42.9%; 21.8–66.0) of 21 at week 52 (substudy).

In the primary study, the mean overall MaRIA score was 65.7 at baseline, decreasing to 46.0 at week 26 (Δscore −18.7; 95% CI −7.6 to −29.9). In the substudy population, the mean score was 64.5 at baseline and 42.4 at week 52 (Δscore −21.4; 95% CI −7.2 to −35.7).

Histologic Disease Activity

In the primary study, histologic response (based on colonic-GHAS ≤4 in all 8 colonic biopsies) was achieved in 19 (24.4%; 95% CI 15.3–35.4) of 78 patients at week 26, in patients with baseline colonic-GHAS scores >4, and in the substudy, the response rate was 9 (20.5%; 95% CI 9.8–35.3) of 44 patients at week 52. Histologic response based on ileal-GHAS ≤4 in the 2 ileal biopsies in patients with baseline ileal-GHAS scores >4 occurred in 17 (28.3%; 17.5–41.4) of 60 patients at week 26 (primary study) and in 12 (34.3%; 95% CI 19.1–52.2) of 35 at week 52 (substudy).

The mean colonic-GHAS scores were 7.6 at baseline and 6.4 at week 26 (Δscore −1.3; 95% CI −0.5 to −2.1) in the primary study population, and 7.7 at baseline and 6.7 at week 52 (Δscore −1.0; 95% CI −0.1 to −1.9) in the substudy population. The corresponding mean ileal-GHAS scores were 6.3 and 4.8 (Δscore −1.7; 95% CI −0.7 to −2.7) in the 26-week primary study, and 6.5 and 4.2 (Δscore −2.4; 95% CI −1.3 to −3.5) in the 52-week substudy.

Histologic remission (no neutrophils in the epithelium), in patients with neutrophils in the epithelium at baseline, was observed at week 26 in 14 (15.2%; 95% CI 8.6–24.2) of 92 patients in the primary study population, and at week 52 in 11 (20%; 95% CI 10.4–33.0) of 55 patients in the substudy population.

Clinical Disease Activity and Biomarkers

In the primary study, 42 (41.6%; 95% CI 31.9–51.8) of 101 patients achieved clinical remission at week 26. In the substudy, 28 (50.0%; 95% CI 36.3–63.7) of 56 patients achieved clinical remission at week 52. TNF-antagonist-naïve patients generally had better clinical remission rates than those with prior TNF-antagonist failure (Table 2). In the substudy, the proportion of patients with clinical remission over both week-26 and -52 assessments (durable clinical remission) was 21 (37.5%; 95% CI 24.9–51.5) of 56. Mean CDAI scores decreased after initiation of therapy from 324 at baseline to 173 at week 26 (ΔSES-CD −152; 95% CI −130 to −173) in the primary study; and from 307 at baseline to 130 at week 52 (ΔSES-CD −177; 95% CI −150 to −203) in the substudy (Figure 3*B*). Similarly, CRP and FCP concentrations also showed reductions at the first assessment, which continued over time (Supplementary Figure 4).

Quality of Life

HRQL showed clinically meaningful improvement over the course of the study that paralleled the CDAI results (Supplementary Figure 5). The mean score changes for the

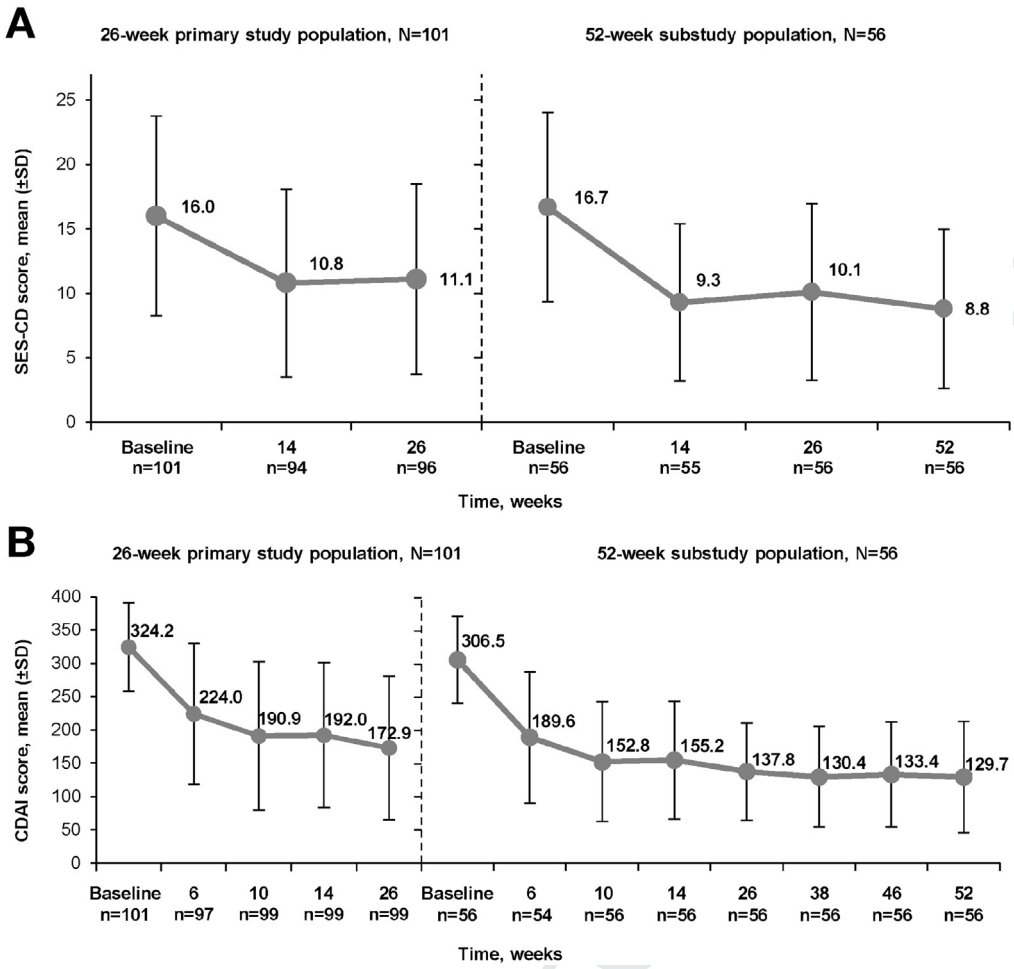

Figure 3. Change over time in endoscopic and clinical disease activity in 26-week primary study and 52-week substudy populations: (*A*) SES-CD; and (*B*) CDAI score. SD, standard deviation.

overall IBDQ (baseline to study end) were 119.8 to 159.7 (Δscore 39.7; 95% CI 33.0–46.4) in the 26-week primary study, and 127.2 to 169.2 (Δscore 42.7; 31.4–54.0) in the 52-week substudy. Likewise, mean EQ-5D visual analog scale scores changed from 48.7 to 65.8 (Δscore 16.9; 95% CI 12.0–21.8) in the primary study and 51.7 to 71.0 (Δscore 19.3; 13.2–25.4) in the substudy.

Relationship Between Outcome Measures

Although only weak agreement was observed between endoscopy (SES-CD), histology (GHAS), and clinical (CDAI) measures in this study, a good agreement was observed between SES-CD and MaRIA score (Supplementary Table 1).

Safety/Tolerability

Vedolizumab showed a generally favorable safety/tolerability profile (Table 3). Treatment-related AEs occurred during the initial 26 weeks in 12 (11.9%) of 101 patients and during the additional 26 weeks in 3 (5.4%) of 56 patients. Few of these events were considered serious or led to study discontinuation. The incidence of AEs of special interest was low, including no cases of liver injury, malignancy, infusion reactions, or hypersensitivities, and few cases of infections, rectal abscess, or EIM worsening. Importantly, no cases of *Clostridium difficile* were observed. A high proportion of patients (65 [64.3%] of 101 patients) had preexisting EIMs at baseline, most frequently inflammatory arthralgia/arthritis (42 patients) (Supplementary Table 2). Arthritis/arthralgia resolved in 19 patients and only 1 patient developed a new case at week 26, and 16 patients resolved and 1 patient had a new case at week 52. No new cases of any other less-frequent EIMs occurred during treatment.

Discussion

VERSIFY is the first large-scale trial to prospectively evaluate the benefits of vedolizumab on endoscopic outcomes in patients with CD. The results demonstrate the efficacy of vedolizumab for endoscopic healing in a CD population with high endoscopic (mean SES-CD score 16.0) and clinical disease activity (mean CDAI score 324.2) and a high rate (54.5%) of prior TNF-antagonist failure. After 26 weeks of treatment in the primary study, endoscopic remission was achieved in 11.9% of patients, complete mucosal healing in 14.9%, and endoscopic response in 24.8%. At week 52 in the substudy population, corresponding rates were 17.9% for endoscopic remission, 17.9% for complete mucosal healing,

Table 3. Incidence of AEs in the First 26 Weeks (Primary Study Population) and Additional 26 Weeks (52-week Substudy Population)

Patients with ≥1 event, n (%)	First 26 weeks (primary study population, n = 101)	Additional 26 weeks (substudy population, n = 56)
Any AE	66 (65.3)	34 (60.7)
Related to treatment	12 (11.9)	3 (5.4)
Mild	28 (27.7)	17 (30.4)
Moderate	29 (28.7)	13 (23.2)
Severe	9 (8.9)	4 (7.1)
Leading to treatment discontinuation	2 (2.0)[a,b]	3 (5.4)[c,d,e]
Any severe AE	9 (8.9)	4 (7.1)
Related to treatment	2 (2.0)	1 (1.8)
Any serious AE	12 (11.9)	6 (10.7)
Related to treatment	1 (1.0)[f]	1 (1.8)[e]
Leading to treatment discontinuation	1 (1.0)[b]	1 (1.8)[e]

NOTE. Incidence data are presented during the first 26 weeks for all patients in the primary study population and during the additional 26 weeks of treatment for the 52-week substudy population. Severe events are events causing considerable interference with the patient's usual activities, as per the investigator's opinion. Serious events are events considered potentially life-threatening or resulting in death, requiring hospitalization or medically significant intervention, or causing persisting incapacitation or disability.
SAE, serious AE.
[a]AE of CD exacerbation not considered treatment-related but led to discontinuation.
[b]SAE of CD exacerbation not considered treatment-related but led to discontinuation.
[c]AE of anal fistula not considered treatment-related and led to discontinuation.
[d]AE of perirectal abscess not considered treatment related and led to discontinuation.
[e]SAE of spontaneous abortion considered treatment-related and led to discontinuation.
[f]SAE of pneumonia, considered treatment-related, which resolved following a short course of antibiotics and did not lead to discontinuation.

and 53.6% for endoscopic response, suggesting improvement over time.

A consistent relationship between prior TNF-antagonist failure and efficacy was observed. TNF-antagonist–naïve patients generally had superior efficacy results compared with those with prior TNF-antagonist failure. This is consistent with observations from studies of other biologic treatments for CD in which previous TNF-antagonist failure has been shown to be a poor prognostic factor.[31–33] Endoscopic improvements were also generally greater in patients with colonic CD than with ileal CD. Similar observations have been reported with other biologic treatments, suggesting ileal and colonic CD may have distinct disease characteristics that influence treatment responsiveness.[34,35]

These data have important implications for clinical practice. First, initial therapy should be carefully chosen, as the likelihood of achieving endoscopic remission or healing after failure of the first biologic agent is reduced. In this context, our results provide further evidence that vedolizumab would be a suitable first-line biologic option, especially in colonic CD. Second, given the relatively low rates of endoscopic remission observed in CD, new approaches must be taken to improve the rate of treatment success. Such strategies include dose intensification of existing therapies, early treatment of high-risk patients with a combination of new and existing therapies, and personalized approaches in which treatment is based on underlying pathobiological features specific to individual patients. The SONIC study demonstrated a relatively high rate of endoscopic healing (43.9% at 6 months) with a combination of azathioprine and infliximab in patients who were TNF-antagonist naïve and had short disease duration (mean of 2 years).[36] The CALM study recently showed that timely escalation of adalimumab therapy in patients with early CD (median disease duration of 1 year) on the basis of clinical symptoms combined with biomarkers resulted in better clinical and endoscopic outcomes than symptom-driven decisions alone.[37] The advantage of using vedolizumab-based combination therapy is being evaluated in a prospective study (EXPLORER, NCT02764762), which will provide further insights into mucosal healing with vedolizumab in combination therapy.

Several previous studies have described endoscopic outcomes with vedolizumab. The VICTORY consortium, a US real-world registry, retrospectively determined endoscopic healing rates of 20% and 63% following 26 and 52 weeks of vedolizumab treatment, respectively.[19] The LOVE-CD trial interim analysis reported an endoscopic remission rate of 30% after 26 weeks of vedolizumab treatment.[23] A recent Canadian observational study reported endoscopic healing rates of 33% and 26% after 6 and 12 months of vedolizumab treatment, respectively.[22] Although the rates described in the current study are nominally lower than these estimates, comparisons across studies should be interpreted with caution due to substantial differences in the design, population, and outcome measures. Importantly, vedolizumab dosing remained constant throughout VERSIFY, whereas dose intensification was permitted in LOVE-CD and the Canadian study. In VICTORY, endoscopic outcomes were assessed cumulatively, whereas in VERSIFY, it was at predefined time points.

Endoscopic outcomes seem generally consistent across studies of biologics, once differences in study design and outcome definitions are considered. In ACCENT I, complete mucosal healing rates with infliximab were 31% at week 10[31] in patients who were TNF-antagonist naïve with relatively low baseline endoscopic disease activity (median CDEIS 7.3).[32] VERSIFY showed complete mucosal healing rates of 23.1% (6/26) at week 14 and 30.8% (8/26) at week 26 in a similar subgroup of TNFα-antagonist–naïve patients with moderate baseline endoscopic disease activity (SES-CD 7–15). In EXTEND, rates of mucosal healing (where residual aphthae were considered as "healed") with adalimumab were 27% at week 12 and 24% at week 52.[32] Using the same definition post hoc for mucosal healing (ulcer size <2 on SES-CD) in VERSIFY, 28% of patients achieved mucosal

healing at week 26. Finally, IM-UNITI/UNITI studies have reported mucosal healing rates of 9.0% at week 8 after ustekinumab intravenous induction therapy and 13.0% at week 44 after ustekinumab subcutaneous 90 mg every 8 or 12 weeks maintenance therapy in responding patients.[34]

The current findings also underscore the lack of clarity around definitions of endoscopic healing in CD[7] and the suitability of SES-CD–defined endpoints.[8–11] Specifically, the results show the large increase in remission rates when patients with aphthae are considered healed. In our study, several patients who achieved mucosal healing (absence of ulcers), still had underlying endoscopic disease activity (patchy erythema) and narrowing, which meant they did not achieve endoscopic remission as per primary endpoint. Prospective evaluation of the relative prognostic importance of these outcomes is greatly needed.

VERSIFY also included radiologic assessments. We used the MaRIA score to measure the MREn-defined disease activity. Although MREn is more commonly reported for disease activity in the terminal ileum, MaRIA score was originally developed including both the terminal ileum and the colon showing similar diagnostic performance.[26,38] Further, the MaRIA score has been found to be responsive for assessing (with and without using luminal contrast) both the terminal ileum and colon.[39–43] The VERSIFY results showed clinically meaningful rates of MREn-defined remission (segmental MaRIA <7) following vedolizumab treatment.

Histologic response was observed based on a modified GHAS score, and found to occur in approximately 20% of patients. The rates were substantially lower than those seen in the LOVE-CD, which may be related to differences in study methods.[23] In VERSIFY, 10 biopsies were evaluated: 2 from each of 5 bowel segments. In LOVE-CD, single paired-samples at sites of active inflammation were evaluated, which may in part explain the differences observed. Scoring in both trials was based on the worst score obtained, and evaluation of more biopsies could be expected to detect more inflammation in a disease with an irregular distribution. Histologic assessment of treatment response has some issues in CD.[12] Inflammation in CD is characteristically discontinuous, leading to potential sampling errors on histologic evaluation. Unlike endoscopic assessments, which can directly evaluate the extent of disease at the macroscopic level, histologic evaluations only allow for the determination of microscopic disease extent at the site of biopsy.[44]

Clinical disease activity improved following treatment with vedolizumab. CDAI scores decreased substantially during induction therapy, and clinically meaningful remission rates were observed in a difficult-to-treat patient population. Corresponding improvements in HRQL scores and serum CRP and FCP concentrations were also observed. These benefits across the different endpoints were more pronounced in TNFα-antagonist–naïve patients.

Treatment effects were seen across the outcome measures, but it is notable that good agreement was observed only between endoscopic and radiologic measures (SES-CD and MaRIA). This may be due to different limitations across each measure. It suggests that these measures explore different aspects of CD, and they should be considered complementary when evaluating treatment efficacy.

The safety/tolerability of vedolizumab in VERSIFY was consistent with the well-known long-term profile.[20,45] No new safety signals for vedolizumab were observed. It is notable that few infections, rectal abscesses, or opportunistic infections, and no cases of *C difficile* colitis were observed. In VERSIFY, a substantial proportion of patients with baseline EIMs, such as arthritis/arthralgia, had their symptoms resolve and few patients developed new EIMs consistent with the findings in the GEMINI studies.[46]

Our study has some limitations. First, VERSIFY was an open-label study with no comparator arm. Second, 2 populations had to be evaluated separately due to a protocol amendment while the study was ongoing, and so long-term evaluation over the full 52-week period was only in the substudy population. Finally, dose intensification was not included in this study. The strengths of the study included the prospective design with predefined endoscopic, radiologic, and histologic endpoints, which were all centrally read endoscopy providing a more consistent evaluation of efficacy.

In conclusion, the VERSIFY results demonstrate the efficacy of vedolizumab to induce and sustain endoscopic improvements, along with good safety/tolerability, in patients with treatment-resistant moderately to severely active CD. Improvements were observed in several clinically relevant treatment targets, supporting vedolizumab as a first-line biologic therapeutic option.

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.2019.06.038.

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Supplementary Materials

SES-CD[1,2]

Endoscopic outcomes were based on SES-CD scored by a central reader of the ileocolonoscopies. SES-CD was scored for each of 5 bowel segments. This instrument consists of 4 items (presence/size of ulcers, proportion of ulcerated mucosal surface, proportion of mucosal surface affected by any other lesions, and presence/type of narrowing/strictures). Scores for each item range from 0 to 3. The total score ranges from 0 to 56, escalating as endoscopic disease severity increases; a score of 15 is considered the threshold for "severe disease."

MaRIA[3]

Radiologic outcomes were based on the MaRIA scored by a central reader of MREn, which were captured in a subset of patients at preselected participating centers. MaRIA was scored for each of 5 bowel segments. This instrument evaluates MREn features of bowel wall thickness, relative contrast enhancement, edema, and ulceration in each segment using the following formula:

$$\begin{aligned}\text{MaRIA}_{\text{seg}} = {} & 1.5 \times \text{wall thickness (mm)} \\ & + 0.02 \times \text{relative contrast enhancement}^{a} \\ & + 5 \times \text{edema} + 10 \times \text{ulceration}\end{aligned}$$

Higher scores indicate more severe inflammation. Although there is no standard range, segmental scores typically do not exceed 40. A segment with a score <11 indicates some active disease with healing of moderate-to-severe ulcers, whereas a score <7 indicates no active disease.

Modified GHAS[4]

Histologic remission was based on mucosal biopsies sampled from each of the 5 segments of the bowel during endoscopy: one sample taken at a normal site and another at a site of severe inflammation, for each of 5 bowel segments. Samples were scored using the GHAS, which was calculated using the worst score for each bowel segment. The ileal GHAS (iGHAS) was defined as the segmental GHAS for the ileum. The colonic GHAS (cGHAS) was defined as the highest segmental GHAS among the rectum, descending/sigmoid colon, transverse colon, and ascending colon. GHAS is calculated using 2 features of chronicity (structural change and chronic inflammatory infiltrate) on a score ranging between 0 and 4, and 5 features of activity (neutrophils in the lamina propria, neutrophils in the epithelium, epithelial damage, erosion or ulceration, epithelioid granuloma) on a score ranging from 0 to 8. The total score, as a sum of the features of chronicity and activities, ranges from 0 to 12, with higher score indicating more severe inflammation.

Supplementary References

1. Moskovitz DN, Daperno M, Van Aassche GA, et al. S1097 Defining and validating cut-offs for the Simple Endoscopic Score for Crohn's disease. In: *Gastroenterology*. Philadelphia, PA: WB Saunders Co.-Elsevier Inc, 2007.
2. Sipponen T, Nuutinen H, Turunen U, et al. Endoscopic evaluation of Crohn's disease activity: comparison of the CDEIS and the SES-CD. Inflamm Bowel Dis 2010; 16:2131–2136.
3. Ordas I, Rimola J, Rodriguez S, et al. Accuracy of magnetic resonance enterography in assessing response to therapy and mucosal healing in patients with Crohn's disease. Gastroenterology 2014;146:374–382.e1.
4. Novak G, Parker CE, Pai RK, et al. Histologic scoring indices for evaluation of disease activity in Crohn's disease. Cochrane Database Syst Rev 2017;7:CD012351.

Supplementary Table 1. Pearson Correlation Coefficients Between Outcome Measures

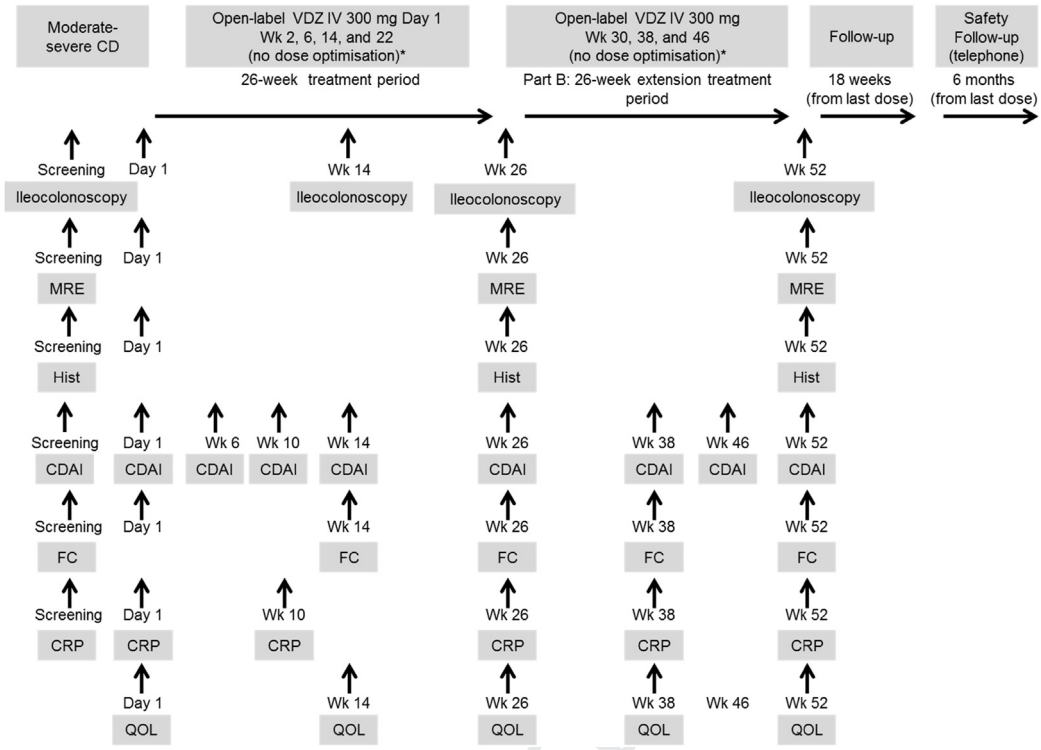
	SES-CD	CDAI	GHAS	MaRIA
SES-CD	1.00000	0.38706	0.46570	0.73931
CDAI	0.38706	1.00000	0.20326	0.42381
GHAS	0.46570	0.20326	1.00000	0.40846
MaRIA	0.73931	0.42381	0.40846	1.00000

NOTE. All available (nonmissing) values for the overall scores from all visits (baseline, week 26, and week 52).

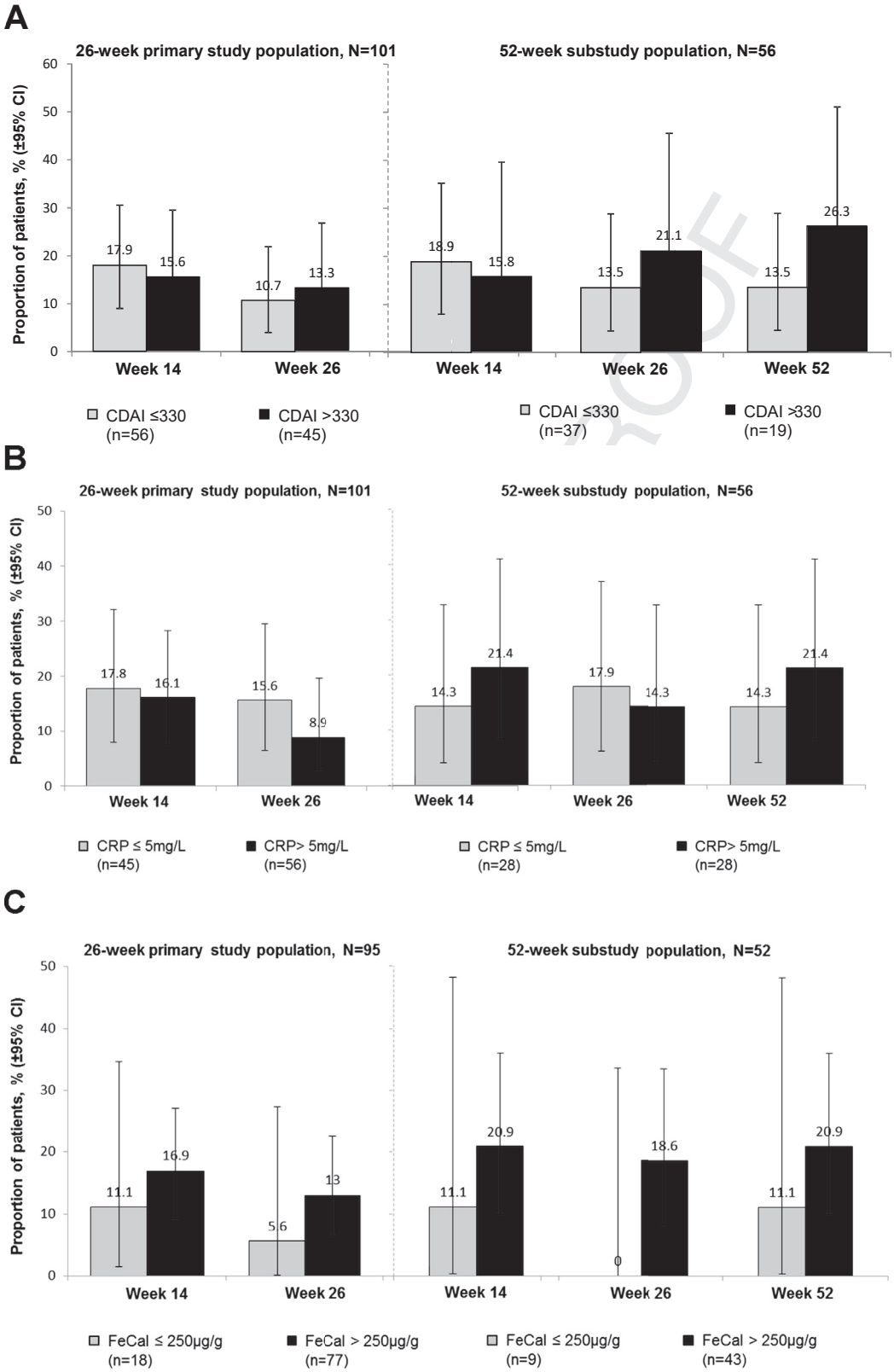
Supplementary Table 2. Incidence of Extraintestinal Manifestations of Inflammatory Bowel Disease: The 26-week Primary Study and the 52-Week Substudy

Week	n	Abscess	Anal fissure	Fistula	Aphthous stomatitis	Erythema nodosum	Pyoderma gangrenosum	Arthritis/ Arthralgia	Fever	Iritis/ Uveitis
0	101	0	5 (5)	8 (8)	4 (4)	2 (2)	0	42 (42)	2 (2)	2 (2)
6	98	1 (1)	2 (2)	7 (7)	1 (1)	1 (1)	0	28 (29)	1 (1)	0
10	95	1 (1)	2 (2)	7 (7)	0	1 (1)	0	25 (26)	1 (1)	0
14	96	1 (1)	2 (2)	8 (8)	0	1 (1)	0	24 (25)	1 (1)	0
26	82	0	1 (1)	6 (7)	0	0	0	16 (20)	1 (1)	0
38	52	0	1 (2)	5 (10)	0	0	0	15 (29)	1 (1)	0
46	46	0	0	4 (9)	0	0	0	18 (39)	0	0
52	45	1 (2)	0	6 (13)	0	0	0	10 (22)	0	0

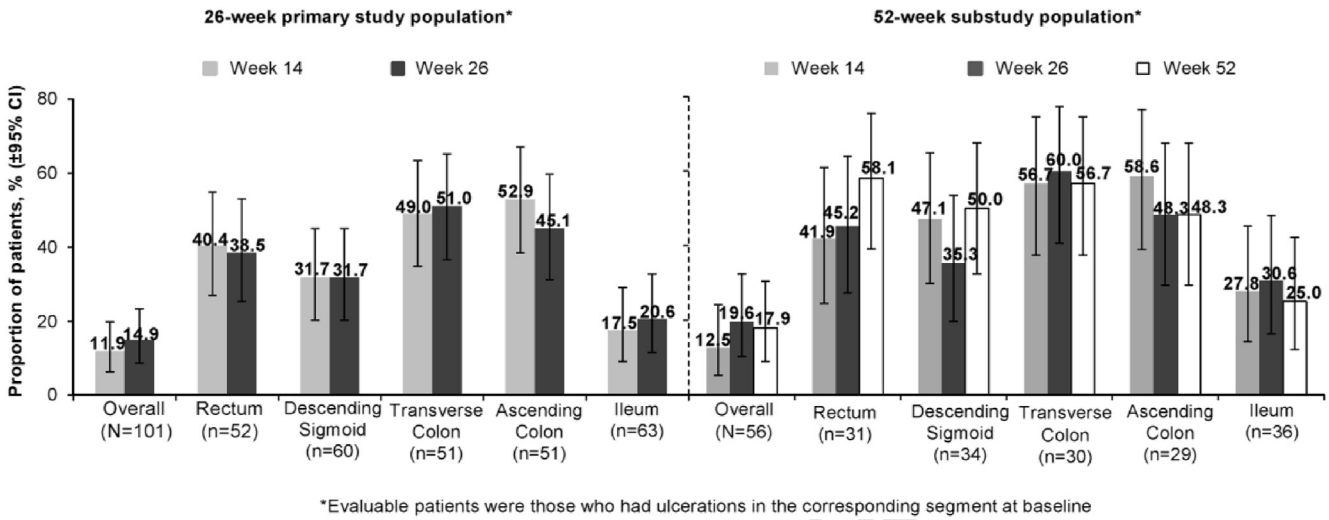
NOTE. Data are incidence in patients with available CDAI data, and do not take into account patients who discontinued. Q11



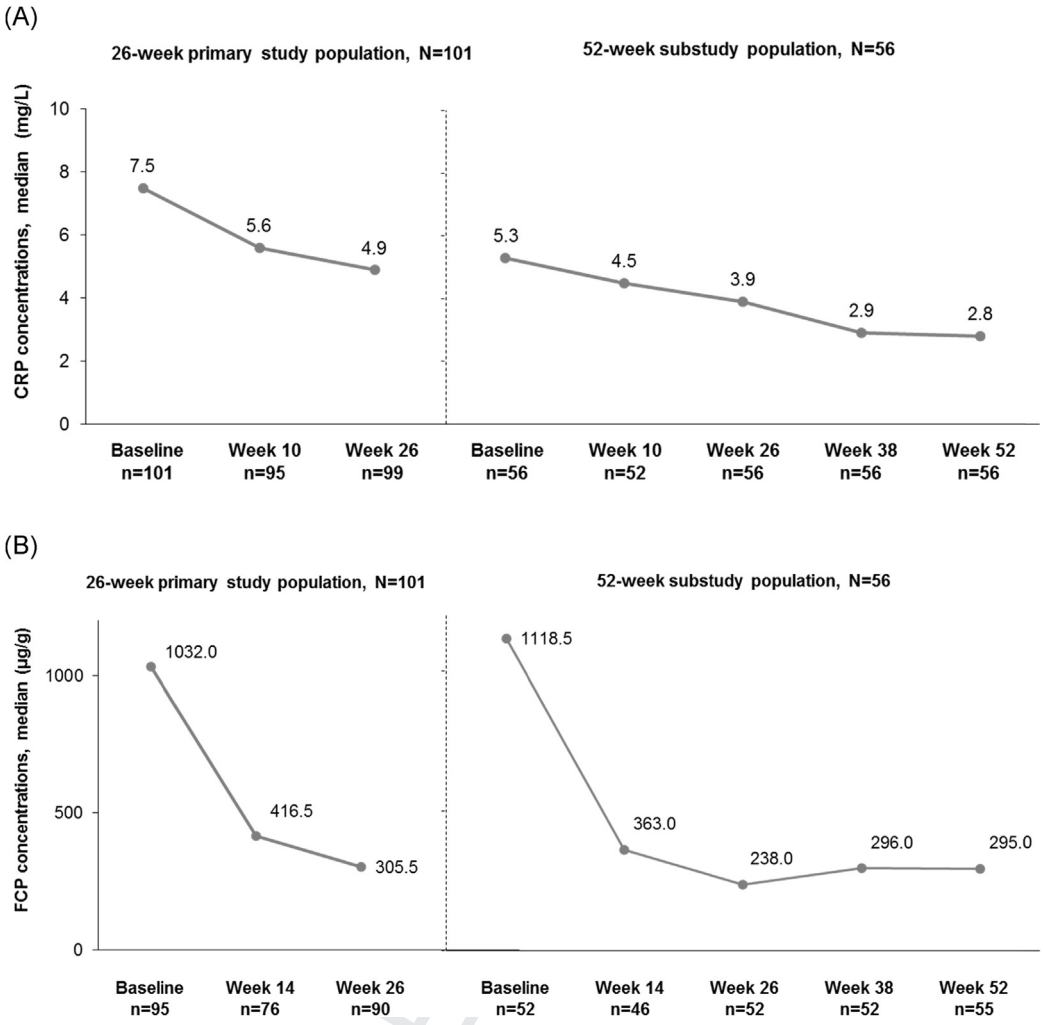
Supplementary Figure 1. Schema of the VERSIFY trial design. FC, fecal calprotectin; IV, intravenous; QOL, quality of life; VDZ, vedolizumab; Wk, week.



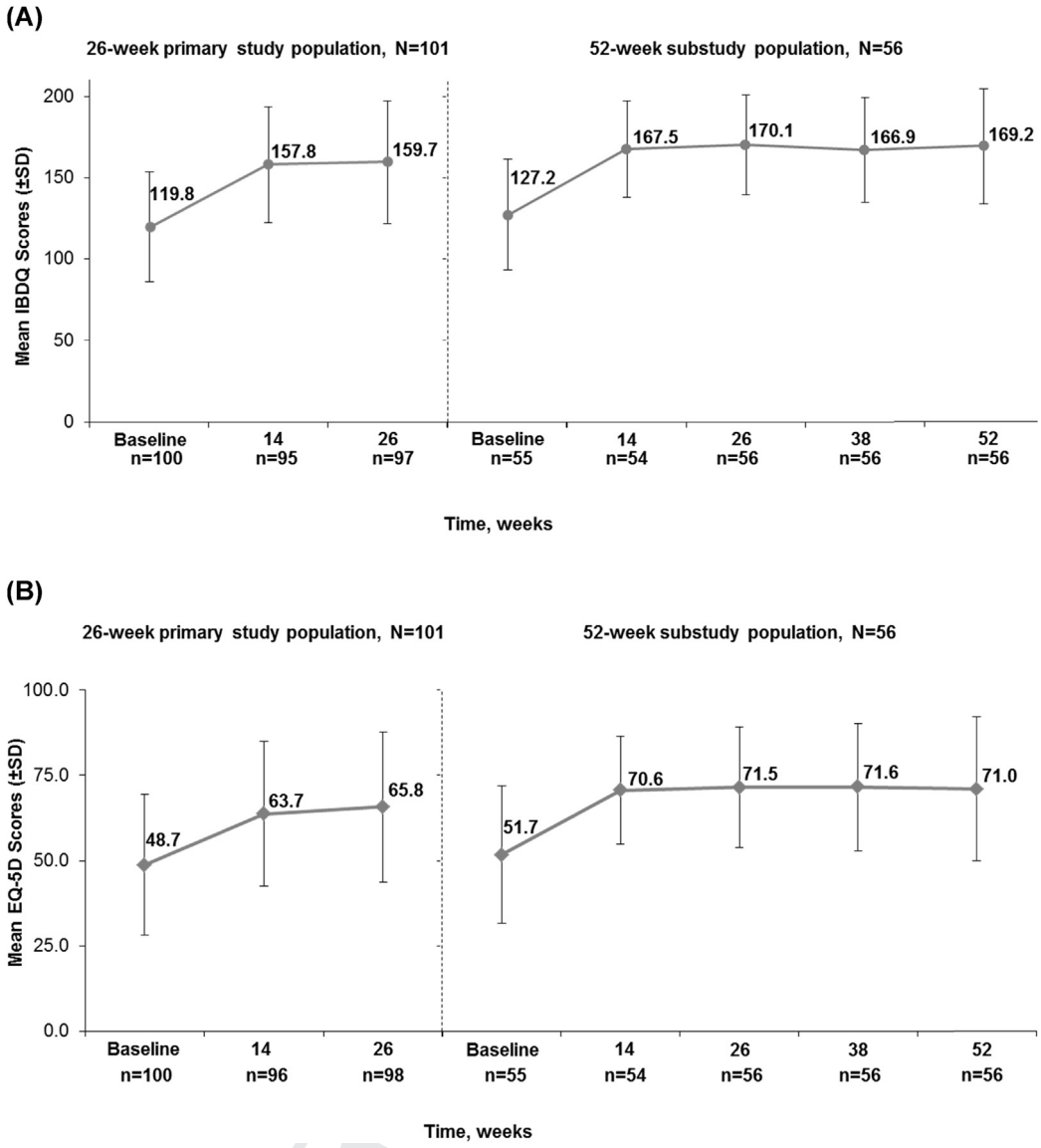
Supplementary Figure 2. Rate of endoscopic remission (primary endpoint) in the 26-week primary study and 52-week substudy: (*A*) baseline CDAI subgroups; (*B*) baseline CRP subgroups; (*C*) baseline FCP subgroups. FeCal, fecal calprotectin. Q10



Supplementary Figure 3. Complete mucosal healing per bowel segment in the 26-week primary study and 52-week substudy.



Supplementary Figure 4. Changes over time in biomarker endpoints: (*A*) CRP serum concentrations and (*B*) FCP concentrations.



Supplementary Figure 5. Quality-of-life endpoints: (*A*) IBDQ and (*B*) EQ-5D scores in the 26-week primary study and the 52-week substudy. SD, standard deviation.