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# Efficacy and Safety of 2 Vedolizumab Intravenous Regimens for Perianal Fistulizing Crohn's Disease: ENTERPRISE Study

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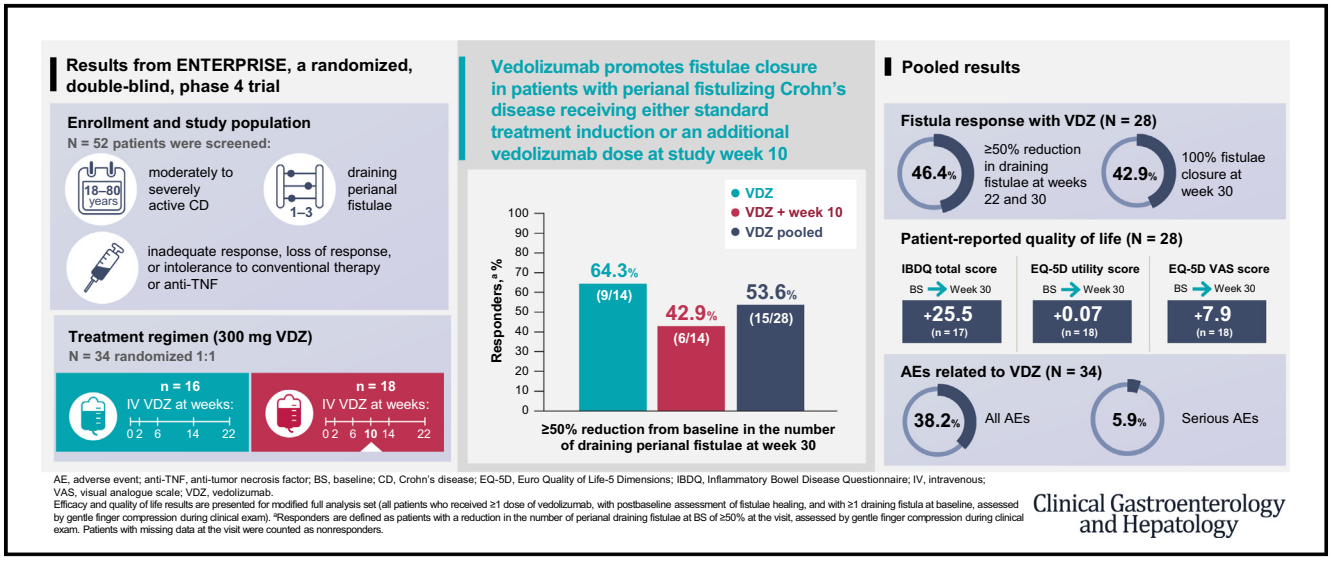


**BACKGROUND & AIMS:** Fistulizing Crohn's disease (CD) is challenging to treat. We report results from ENTERPRISE, a randomized, double-blind, phase 4 trial evaluating 2 vedolizumab intravenous dosing regimens in patients with fistulizing CD.

**METHODS:** Patients with moderately to severely active CD and 1–3 active perianal fistulae (identified on magnetic resonance imaging [MRI]) received vedolizumab 300 mg intravenously at weeks 0, 2, 6, 14, and 22 (VDZ) or the same regimen plus an additional vedolizumab dose at week 10 (VDZ + wk10). Reduction from baseline in draining perianal fistulae and disease activity, MRI assessments, health-related quality of life (HRQoL), and safety were evaluated. Enrollment was stopped prematurely because of recruitment challenges; analyses are descriptive.

**RESULTS:** Of 32 patients with ≥1 active fistulae at baseline per MRI and postbaseline fistulae healing assessment, 28 (14 per dosing regimen) had ≥1 draining fistulae at baseline (assessed by gentle finger compression during clinical exam). Rapid and sustained fistula closure was observed;

*Abbreviations used in this paper:* ADA, antidrug antibody; AE, adverse event; anti-TNF, anti-tumor necrosis factor; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CI, confidence interval; $C_{trough}$, trough serum concentration; EQ-5D, Euro Quality of Life-5 Dimensions; FAS, full analysis set; HRQoL, health-related quality of life; IBDQ, inflammatory bowel disease questionnaire; IV, intravenous; mFAS, modified full analysis set; MRI, magnetic resonance imaging; NA, not assessed; PDAI, Perianal Disease Activity Index; PK, pharmacokinetics; SAE, serious adverse event; SD, standard deviation; VDZ, vedolizumab 300 mg IV at weeks 0, 2, 6, 14, and 22; VDZ pooled, data pooled from both treatment regimens (VDZ and VDZ + wk10); VDZ + wk10, vedolizumab 300 mg IV at weeks 0, 2, 6, 10, 14, and 22.



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**53.6% (VDZ, 64.3%; VDZ + wk10, 42.9%) and 42.9% (VDZ, 50.0%; VDZ + wk10, 35.7%) of patients achieved ≥50% decrease in draining fistulae and 100% fistulae closure, respectively, at week 30. Mean (standard deviation) CD and Perianal Disease Activity Index scores decreased by 51.1 (78.3) and 4.1 (3.3), respectively, at week 30. HRQoL improved throughout the study. No new safety signals were observed.**

**CONCLUSIONS:** **Sustained improvements in fistulizing CD were seen with both vedolizumab regimens. An additional dose at week 10 does not appear to alter treatment outcomes. Safety profile was consistent with other vedolizumab studies. ClinicalTrials.gov no: NCT02630966; EudraCT: 2015-000852-12.**

*Keywords:* Vedolizumab; Fistula; Fistulae Closure; Crohn's Disease.

The development of fistulae is an important complication of Crohn's disease (CD) affecting ≤40% of patients.[1–3] Perianal fistulae are the most common and can be the first manifestation of CD.[1,2] Fistulizing CD is often treatment refractory, and recurrences are frequent.[1,3,4] The disease imposes a significant burden on patients, with a profound impact on health-related quality of life (HRQoL).[2–5]

Treating fistulizing CD is complex and requires a multidisciplinary approach combining medication and surgery for best results.[3–6] Infliximab, an anti-tumor necrosis factor (anti-TNF) medication has demonstrated short-term efficacy in several trials.[3,7,8] Certolizumab pegol and adalimumab were also associated with perianal fistulae closure in 2 subgroup analyses.[9,10] Antibiotics demonstrated efficacy in fistulizing CD and are recommended as adjunct therapy.[1] Nonetheless, current treatments are often inadequate.[2] The combination of anti-TNF therapy with antibiotics showed additional clinical benefit over anti-TNF therapy alone.[11,12] The combination of infliximab/ciprofloxacin tended to be more effective than infliximab alone, but this effect was not significant.[12] The combination of adalimumab/ciprofloxacin showed significant increase in remission rate over ciprofloxacin alone, but this effect was not maintained after discontinuation of ciprofloxacin.[11]

Vedolizumab, a gut-selective anti-lymphocyte trafficking monoclonal antibody that targets the $\alpha_4\beta_7$ integrin, is approved for treating ulcerative colitis and CD.[13,14] Vedolizumab is currently administered intravenously (IV) in patients with moderate to severe CD as standard regimen at weeks 0, 2, and 6 and then every 8 weeks from week 14.[13] In the GEMINI 2 trial,[15] an additional dose of vedolizumab at week 10 increased clinical response rates of CD patients who had not responded at week 6. The regimen, including an additional week 10 infusion, is approved in Europe for patients with CD.[13] Thus, it was hypothesized that an additional dose of vedolizumab 300 mg IV at week 10 may be beneficial for patients with fistulae. Here, we present the results from ENTERPRISE, a multinational phase 4 trial evaluating 2 vedolizumab IV dosing regimens in patients with fistulizing CD.

## Methods

### Study Population

ENTERPRISE enrolled adults (aged 18–80 years) diagnosed with moderate to severe CD (on the basis of clinical and endoscopic evidence, corroborated by a histopathology report) ≥3 months before enrollment. Eligible patients had 1–3 perianal draining fistulae ongoing for ≥2 weeks before enrollment; the presence of other types of fistulae (enterocutaneous, abdominal) was permitted except for rectovaginal fistulae. Active fistulae were identified using magnetic resonance imaging (MRI). Patients were required to have had an inadequate response, loss of response, or intolerance to conventional (5-aminosalicylates, corticosteroids, or immunosuppressants) or anti-TNF therapy for underlying CD (treatment failure was not required for current actively draining fistulae). In France only, patients must have failed infliximab treatment for underlying or fistulizing CD.

Patients with Crohn's Disease Activity Index (CDAI) score >400, perianal abscess >2 cm or that needed draining, history of colostomy or ileostomy, intestinal or rectal stenosis, or contraindications to MRI were excluded from the study.

### Study Design

ENTERPRISE was a phase 4, randomized, double-blind, multicenter study (Supplementary Figure 1) conducted at 13 sites in 7 countries, evaluating safety and efficacy of vedolizumab on the basis of the proportion of patients with healing of draining perianal fistulae. Patients were randomized 1:1 to receive vedolizumab 300 mg IV at weeks 0, 2, 6, 14, and 22 (VDZ regimen) or the same regimen plus an additional vedolizumab dose at week 10 (VDZ + wk10). If a seton was placed as part of the standard of care, it had to be removed by week 14. All patients were prescribed companion antibiotics, per local label, from day 1 until week 6. Patients were followed for 30 weeks for efficacy and up to 48 weeks for safety. Enrollment was stopped prematurely before the planned sample of 100 patients was reached because of

recruitment challenges (including prior vedolizumab exposure, lack of patient interest because of availability of reimbursed vedolizumab, and lengthy study procedures, infliximab availability), not because of safety concerns (Supplementary Methods for further details).

### Study Assessment

Physical examination, vital signs, concomitant medications use, fistulae draining assessment by gentle finger compression during clinical examination, perianal pain, and CDAI were assessed at screening and weeks 0, 2, 6, 10, 14, 22, and 30. The Perianal Disease Activity Index (PDAI) and patients' electronic diary (started at screening) were analyzed at weeks 0, 2, 6, 10, 14, 22, and 30. HRQoL assessments at weeks 0, 14, and 30 included the inflammatory bowel disease questionnaire (IBDQ) (total scores and subscores) and the Euro Quality of Life-5 Dimensions (EQ-5D) (index score and visual analogue scale). Adverse events (AEs) and serious AEs (SAEs) were collected throughout the study. AEs of special interest were also assessed (see Supplementary Materials for other assessments).

### Study Endpoints

The primary endpoint was ≥50% decrease from baseline in the number of draining perianal fistulae at week 30, where closed fistulae are no longer draining despite gentle finger compression. Secondary endpoints included ≥50% decrease from baseline in the number of draining perianal fistulae at weeks 22 and 30, 100% perianal fistulae closure at week 30, time to first perianal fistula closure and time to 100% perianal fistulae closure among fistulae draining at baseline, and the duration of perianal fistulae response (defined as reduction in draining perianal fistulae draining at baseline of ≥50%). See Supplementary Materials for additional endpoints.

### Statistical Analyses

The population sets are summarized in Supplementary Table 1. The modified full analysis set (mFAS) comprises all patients in the FAS with ≥1 draining fistulae at baseline (assessed by gentle finger compression). The primary, secondary, and additional endpoints are presented using mFAS. Pharmacokinetic (PK) data are presented using the PK set and mFAS; safety data are presented using the safety set. Unless stated otherwise, data are provided by dosing regimen and pooled over both regimens (VDZ pooled). Where appropriate, variables were further summarized by study visit. For endpoints related to reduction in the number of draining fistulae from baseline, patients with missing data at a study visit were classed as non-responders at the respective visit. Because enrollment was stopped prematurely, resulting in low patient counts per dosing regimen, all analyses are descriptive. Subgroup analyses were not performed because of small sample size.

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

**What You Need to Know**

**Background**

Fistulizing Crohn's disease is often refractory to treatment and requires a complex multidisciplinary approach for best treatment results.

**Findings**

Sustained improvements in fistulae response from week 2 to 30 were observed with intravenous vedolizumab (2 dosing regimens); no new safety signals were observed.

**Implications for patient care**

The results suggest that intravenous vedolizumab may be beneficial for the treatment of patients with fistulizing Crohn's disease (small number of patients precludes generalizability of the results).

## Results

### Study Population

From August 10, 2016 to November 14, 2018, 52 patients were screened. Of these, 34 were randomized (VDZ, n = 16; VDZ + wk10, n = 18) and received ≥1 dose of vedolizumab (safety/PK set) (Supplementary Figure 2). Thirty-two patients (VDZ, n = 16; VDZ + wk10, n = 16) had postbaseline evaluation (FAS), of which 28 had ≥1 draining fistulae at baseline (n = 10 complex, n = 14 simple; n = 2 not assessed [NA]), assessed during clinical exam (VDZ, n = 14; VDZ + wk10, n = 14, mFAS). The 28 patients with ≥1 draining fistulae at baseline had a total of 39 draining fistulae (n = 16 complex, n = 21 simple; n = 2 NA by MRI at screening). In all, 24 patients (70.6% of those randomized) completed treatment per protocol, and 10 (29.4% of those randomized) prematurely discontinued treatment.

In the mFAS, patients in both groups had long-term refractory disease, with median CD duration of 8.5 years; 9 (64.3%) and 6 (42.9%) patients had CD for ≥7 years in the VDZ and VDZ + wk10 regimens, respectively (Table 1). Median fistulizing disease duration was 3.0 years. In each regimen, 11 patients (78.6%) had prior anti-TNF therapy at baseline. See Supplementary Results for time to seton removal. Companion antibiotics are shown in Supplementary Table 2 and fistula type in Supplementary Table 3. Baseline characteristics of FAS patients are presented in Supplementary Table 4.

**Table 1.** Baseline Demographics and Disease Characteristics (mFAS)

| | VDZ (n = 14) | VDZ + wk10 (n = 14) | VDZ pooled (N = 28) |
|---|---|---|---|
| Median age (min, max), *y* | 31.5 (23, 44) | 36.0 (21, 59) | 34.0 (21, 59) |
| Male, n (%)[a] | 8 (57.1) | 9 (64.3) | 17 (60.7) |
| Smoking classification, n (%) | | | |
| Never smoker | 6 (42.9) | 6 (42.9) | 12 (42.9) |
| Current smoker | 6 (42.9) | 4 (28.6) | 10 (35.7) |
| Ex-smoker | 2 (14.3) | 4 (28.6) | 6 (21.4) |
| Median (min, max) duration of CD, *y*[b] | 11.2 (0.7, 37.6) | 6.1 (0.5, 25.4) | 8.5 (0.5, 37.6) |
| Mean (SD) baseline[b] CDAI | 281.9 (73.1) | 302.8 (90.9) | 292.3 (81.6) |
| Baseline[c] CDAI categories, n (%)[a] | | | |
| ≤220 | 2 (14.3) | 4 (28.6) | 6 (21.4) |
| >220–330 | 9 (64.3) | 5 (35.7) | 14 (50.0) |
| >330 | 3 (21.4) | 5 (35.7) | 8 (28.6) |
| Previous anti-TNF treatment, n (%)[a] | 11 (78.6) | 11 (78.6) | 22 (78.6) |
| Concomitant treatment at baseline,[c] n (%)[a] | | | |
| Corticosteroids | 3 (21.4) | 2 (14.3) | 5 (17.9) |
| Immunosuppressants | 4 (28.6) | 3 (21.4) | 7 (25.0) |
| No. of draining fistulae at baseline,[c] n (%) | | | |
| 1 | 5 (35.7) | 12 (85.7) | 17 (60.7) |
| 2 | 9 (64.3) | 2 (14.3) | 11 (39.3) |
| Median (min, max) duration of fistulizing disease, *y* | 4.6 (0.5, 20.7) | 1.8 (0.1, 15.8) | 3.0 (0.1, 20.7) |
| Mean (SD) baseline[d] PDAI | 8.1 (2.2) | 7.5 (3.1) | 7.8 (2.7) |
| Seton placement[e] at baseline,[b] n (%)[a] | 13 (92.9) | 13 (92.9) | 26 (92.9) |

Anti-TNF, anti-tumor necrosis factor; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; max, maximum; min, minimum; mFAS, modified full analysis set; PDAI, Perianal Disease Activity Index; SD, standard deviation; VDZ, vedolizumab 300 mg intravenously at weeks 0, 2, 6, 14, and 22; VDZ + wk10, vedolizumab 300 mg intravenously at weeks 0, 2, 6, 10, 14, and 22.

[a]Percentages are based on number of patients with non-missing data in the respective column.

[b]Duration of CD refers to duration from date of disease diagnosis.

[c]Number of fistulae at baseline was assessed using magnetic resonance imaging.

[d]Baseline was defined as last observation before first dose of study medication.

[e]For patients without seton placement information at baseline, baseline status was imputed as "yes."

## *Clinical Efficacy*

**Fistulae closure.** At week 30, 15 of 28 mFAS patients (53.6%) achieved the primary endpoint of ≥50% decrease from baseline in the number of draining fistulae, assessed during clinical examination (VDZ, n = 9 [64.3%]; VDZ + wk10, n=6 [42.9%]) (Figure 1).

The proportions of mFAS patients with fistulae responses increased rapidly and remained high through week 30 (Figure 2*A*). Thirteen patients (46.4%) achieved the secondary endpoint of ≥50% decrease in the number of draining fistulae at weeks 22 and 30 (VDZ, n = 8 [57.1%]; VDZ + wk10, n = 5 [35.7%]) (Figure 2*B*). The secondary endpoint of 100% closure of fistulae draining at baseline was observed at week 30 in 12 patients (42.9%) (VDZ, n = 7 [50.0%]; VDZ + wk10, n = 5 [35.7%]) (Figure 2*B*). In the pooled population, 20 patients (71.4%) experienced a fistula closure during the study, with most occurring during the first few weeks (12 patients had closure at week 2: VDZ, n = 7; VDZ + wk10, n = 5). The median (95% confidence interval [CI]) time to first closure was 30.5 (15.0–71.0) days versus 159.0 (16.0 to nonestimable) days in the VDZ versus VDZ + wk10 regimens. Eighteen patients (64.3%) experienced 100% perianal fistulae closure at some point during the study, most of them during the first few weeks (n = 9 with 100% closure at week 2: VDZ, n = 4; VDZ + wk10, n = 5). The median (95% CI) time to 100% closure was 45.0 (15.0–155.0) days versus 159.0 (16.0 to nonestimable) days in the VDZ versus VDZ + wk10 regimens. In the pooled population, the mean duration of perianal fistulae response was 99.7 days (VDZ, 127.5 days; VDZ + wk10, 71.9 days); median (range) duration was 113.5 (0–203) days (VDZ, 158.5 [0–202] days; VDZ + wk10, 33.5 [0–203] days). Fistula closure did not appear to be dependent on rectal involvement (Supplementary Table 5). Subgroup analyses of efficacy endpoints in anti-TNF naive patients (n = 6) compared with those who previously received anti-TNF therapy (n = 22) were not feasible because of small sample size.

**Disease activity.** Mean (standard deviation [SD]) changes from baseline in markers of luminal (CDAI score) and fistulizing (PDAI and perianal pain scores) disease activity in the mFAS population showed overall

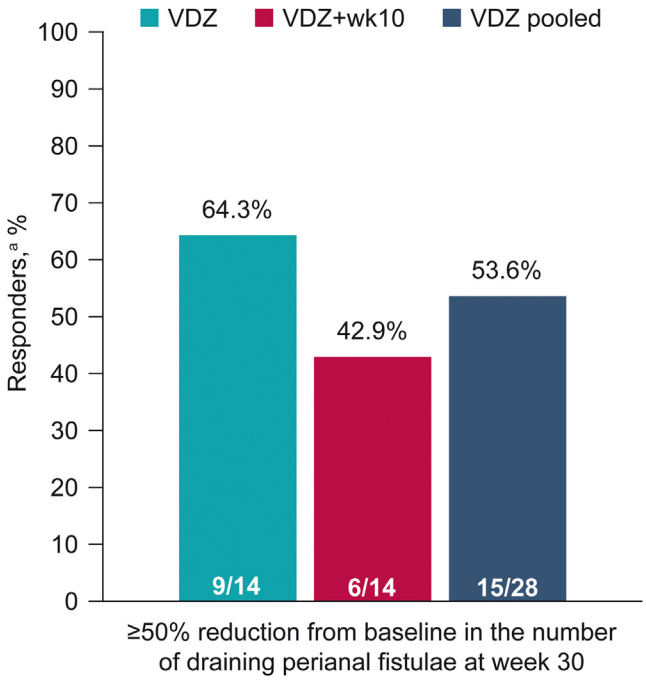


**Figure 1.** Fistulae response with vedolizumab at week 30 (modified full analysis set). [a]Responders are defined as ≥50% decrease from baseline in the number of draining perianal fistulae at the visit, assessed by gentle finger compression during clinical examination. Patients with missing data at the visit were classed as nonresponders. VDZ, vedolizumab 300 mg intravenously at weeks 0, 2, 6, 14, and 22; VDZ + wk10, vedolizumab 300 mg intravenously at weeks 0, 2, 6, 10, 14, and 22.

improvement at week 30; CDAI scores decreased by 52.8 (75.8) points, PDAI by 3.9 (3.3) points, and pain score by 2.2 (2.3) points (Table 2). Of 18 patients with a week 30 assessment, 61.1% (n = 11; 95% CI, 38.6%–83.6%) had a decrease of ≥30% in perianal pain score from baseline.

**Health-related quality of life.** In mFAS patients, mean (SD) baseline value for total IBDQ score was 137.6 (36.9), and mean (SD) change from baseline at week 30 was 25.5 (22.1) (Supplementary Figure 3). All IBDQ subscores followed a similar trend. Similarly, EQ-5D (index and visual analogue scale) scores increased from baseline to week 30 (Supplementary Figure 4).

**Markers of inflammation.** In the mFAS, mean (SD) changes from baseline to week 30 in fecal calprotectin and C-reactive protein were −123.0 (771.2) μg/g and −4.7 (19.4) mg/L, respectively. Changes in concentrations of these biomarkers are summarized in Supplementary Table 6.

**Magnetic resonance imaging findings.** At week 30 in the mFAS, mean (SD) Van Assche scores and gadolinium contrast enhancement scores changed by −1.1 (3.4) and −7.6 (76.3) from screening, respectively (Table 2). The mean T2-signal intensity change in the pooled population was 9.7% (48.6%) compared with screening, with a decrease in VDZ regimen (−0.5% [32.0%]) and an increase in VDZ + wk10 regimen (+23.6% [65.0%]). There was no apparent association seen between the Van Assche score and the change in contrast enhancement scores or the relative mean T2 intensity. Of 39 draining fistulae at baseline, 11 were draining at week 30 (n = 5 complex, n = 4 simple, n = 2 NA), 22 fistulae were closed (n = 7 complex, n=15 simple), and 6 were NA at week 30, possibly because of the patients dropping out of the study.

### *Pharmacokinetics*

In the PK population, mean (SD) vedolizumab trough serum concentration ($C_{trough}$) (VDZ pooled) increased rapidly from baseline, reaching a peak at week 10 (31.7 [11.8] μg/mL) and decreasing to 14.2 (12.2) μg/mL at week 30 (Supplementary Figure 5). A similar trend was observed for the VDZ regimen. For the VDZ + wk10 regimen, the peak concentration of 31.8 (14.8) μg/mL was maintained until week 14, decreasing to 17.6 (14.6) μg/mL at week 30. After week 10, $C_{trough}$ was higher for the VDZ + wk10 versus VDZ regimen at all time points.

Mean vedolizumab $C_{trough}$ in the mFAS population week 30 responders versus nonresponders trended higher among patients in the VDZ + wk10 regimen from week 6 to 22 (Figure 3).

Two patients (5.9%) in the PK population had transient vedolizumab antidrug antibodies (ADAs) (1 per regimen) at day 1 and tested negative at all other time points. No patients had neutralizing ADAs.

### *Safety/Tolerability*

Patients received a mean (SD) total vedolizumab dose of 1421 (420) mg (VDZ, 1425 [232] mg; VDZ + wk10, 1417 [543] mg). Mean (SD) duration of exposure was ~251 (53) days in the pooled population (VDZ, 269 [36] days; VDZ + wk10, 235 [61] days). The apparently lower overall exposure in the VDZ + wk10 group was due to the higher number of patients prematurely discontinuing.

AEs were reported in 32 patients (94.1%); 13 (38.2%) experienced treatment-related AEs (Table 3; Supplementary Table 7). Most AEs were mild to moderate in severity. Four patients (11.8%) discontinued treatment because of AEs. SAEs were reported in 7 patients (20.6%); 2 (5.9%) were treatment-related; 1 event of Crohn's ileitis flare with internal abdominal suppuration (leading to the patient [2.9%] discontinuing), and 1 of perianal abscess. No cases of progressive multifocal leukoencephalopathy or deaths were reported.

## Discussion

In this study, >50% of patients with fistulizing CD treated with vedolizumab (with concurrent seton until week 14 and antibiotics until week 6) had ≥50% decrease in number of draining perianal fistulae, assessed by gentle finger compression during clinical examination. Clinically relevant reductions in draining fistulae were seen as early as week 2 and maintained

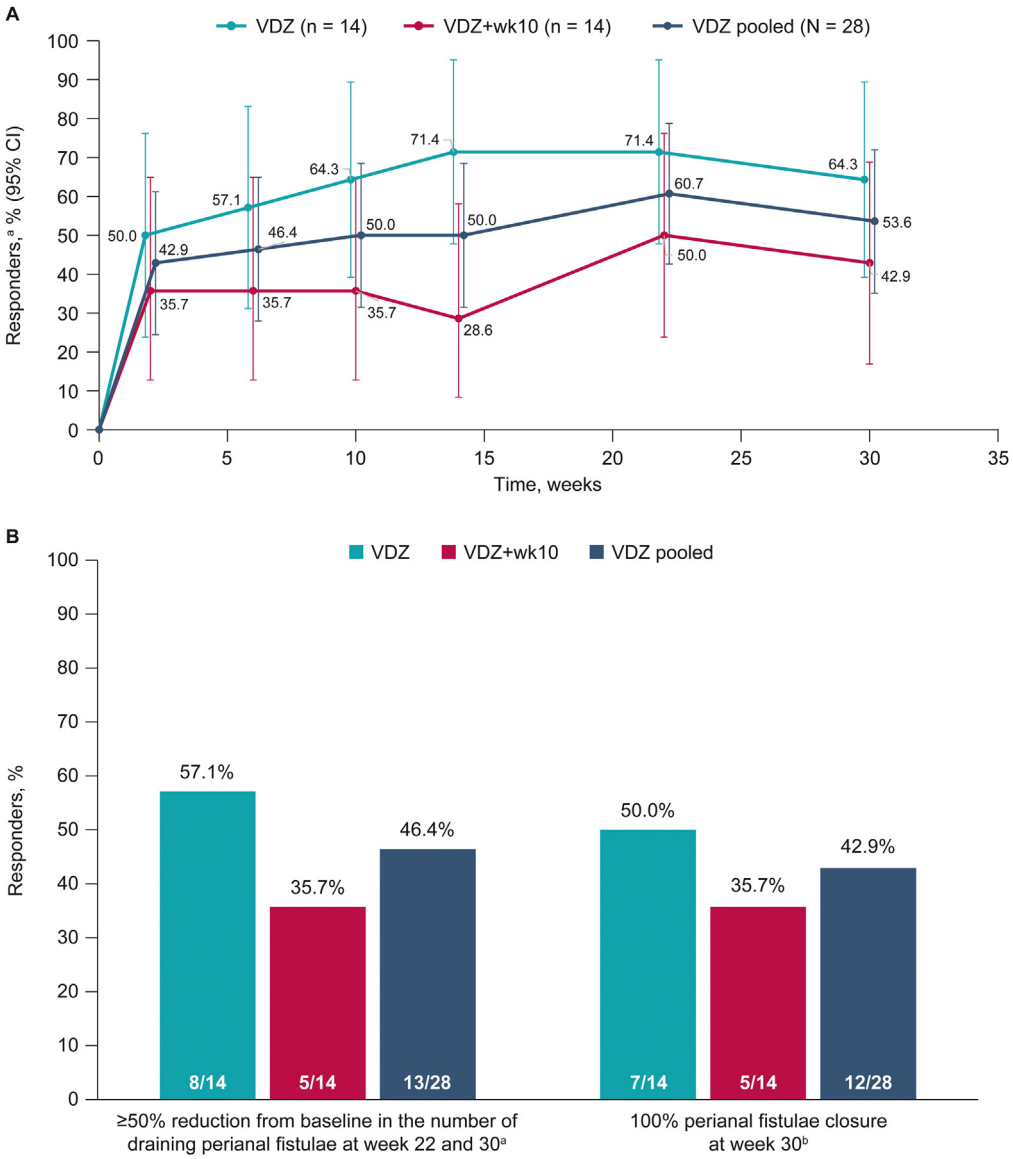


**Figure 2.** (*A*) Fistulae response with vedolizumab by visit and (*B*) at weeks 22 and 30 and 100% fistulae closure at week 30 (mFAS). [a]Responders are defined as ≥50% decrease from baseline in the number of draining perianal fistulae at the visit, assessed by gentle finger compression during clinical examination. [b]Responders are defined as patients without draining fistulae at week 30, assessed by gentle finger compression during clinical examination. Patients with missing data at specific study evaluations were classed as non-responders for that visit. CI, confidence interval; mFAS, modified full analysis set; VDZ, vedolizumab 300 mg intravenously at weeks 0, 2, 6, 14, and 22; VDZ + wk10, vedolizumab 300 mg intravenously at weeks 0, 2, 6, 10, 14, and 22.

through week 30, regardless of dosing regimen. The median time to first closure or to 100% closure appeared different between dosing regimens; however, the datasets were small and 95% CIs wide or incalculable. The proportion of patients responding to treatment is encouraging, indicating vedolizumab efficacy was maintained over 30 weeks of treatment. Comparatively, anti-TNF therapy leads to sustained efficacy in ~30% of patients.[5,8] This study's safety profile was consistent with previous reports and vedolizumab's established safety profile.[16]

One limitation was the lack of a placebo and/or seton plus antibiotic arm, precluding determination of the rate of fistulae closure without vedolizumab treatment. In a meta-analysis of 13 studies, ~1 in 6 placebo-treated patients experienced fistulae closure, a ~2.5-fold lower rate than observed in this study, suggesting vedolizumab treatment would benefit patients with fistulizing CD.[17] Furthermore, the results of this study are consistent with an exploratory analysis of GEMINI 2, which showed patients with fistulizing CD receiving vedolizumab maintenance treatment were more likely to achieve fistulae closure by week 52 than those receiving placebo.[5] Also, in an integrated study of 6 vedolizumab trials, the rate of fistulae in patients with CD was lower in vedolizumab- versus placebo-treated patients.[18] Of note, the generalizability of the results in this study is limited by the small study population resulting from early closure of enrollment.

Among patients with fistulizing CD in GETAID, vedolizumab treatment was associated with fistulae closure in 22.5% of patients (23/102),[19] compared with 43% in this study. The duration of CD and perianal disease was higher in patients in GETAID, with more refractory disease potentially contributing to the observed between-study discrepancy in vedolizumab efficacy.[19] A systematic literature review showed a combined approach of surgery (such as seton placement) and drug therapy was more efficient in inducing fistula healing than medication alone.[20] Thus, the higher rate of perianal fistulae closure observed in this study may have been

**Table 2.** Measures of Disease Activity and MRI Assessments (mFAS)

| | VDZ (n = 14) | VDZ + wk10 (n = 14) | VDZ pooled (N = 28) |
|---|---|---|---|
| CDAI[a] | | | |
| Observed mean (SD) at baseline[b] | 281.9 (73.1) | 302.8 (90.9) | 292.3 (81.6) |
| Patients at week 30, n | 9 | 7 | 16 |
| Observed mean (SD) change from baseline at week 30 | –33.7 (76.7) | –77.4 (72.5) | –52.8 (75.8) |
| PDAI[c] | | | |
| Observed mean (SD) at baseline[b] | 8.1 (2.2) | 7.5 (3.1) | 7.8 (2.7) |
| Patients at week 30, n | 9 | 7 | 16 |
| Observed mean (SD) change from baseline at week 30 | –4.6 (2.9) | –3.1 (3.8) | –3.9 (3.3) |
| Perianal pain score[d] | | | |
| Observed mean (SD) at baseline[b] | 4.8 (2.9) | 3.6 (2.4) | 4.2 (2.7) |
| Patients at week 30, n | 11 | 7 | 18 |
| Observed mean (SD) change from baseline at week 30 | –2.3 (2.7) | –2.1 (1.8) | –2.2 (2.3) |
| Van Assche score[e] | | | |
| Observed mean (SD) at screening | 9.5 (3.7) | 9.7 (3.1) | 9.6 (3.3) |
| Patients at week 30, n | 11 | 8 | 19 |
| Observed mean (SD) change from screening at week 30 | –1.3 (3.8) | –0.9 (2.9) | –1.1 (3.4) |
| Relative gadolinium enhancement | | | |
| Observed mean (SD) at screening[f] | 146.0 (91.9) | 127.8 (106.4) | 136.9 (97.8) |
| Patients at week 30, n | 11 | 8 | 19 |
| Observed mean (SD) change from screening at week 30 | –1.24 (83.6) | –16.4 (69.5) | –7.6 (76.3) |
| Mean relative T2 signal intensity | | | |
| Observed mean (SD) at screening[g] | 3.7 (3.3) | 3.4 (1.8) | 3.5 (2.6) |
| Patients at week 30, n | 11 | 8 | 19 |
| Observed mean (SD) percentage change from screening at week 30 | –0.5 (32.0) | +23.6 (65.0) | +9.7 (48.6) |

CDAI, Crohn's Disease Activity Index; mFAS, modified full analysis set; MRI, magnetic resonance imagining; PDAI, Perianal Disease Activity Index; SD, standard deviation; VDZ, vedolizumab 300 mg intravenously at weeks 0, 2, 6, 14, and 22; VDZ + wk10, vedolizumab 300 mg intravenously at weeks 0, 2, 6, 10, 14, and 22.
[a]CDAI score is calculated by summation of 8 components: number of liquid or very soft stools, abdominal pain, general well-being, extraintestinal manifestations of Crohn's disease, use of Lomotil/Imodium/opiates for diarrhea, abdominal mass, hematocrit level, and body weight. It ranges from 0 to approximately 600, with higher scores indicating greater disease.
[b]Baseline is defined as last observation before first dose of study medication.
[c]PDAI score (0–20) is calculated by summation of 5 components (0–4 for each): presence or absence of discharge, pain or restriction of activities of daily living, restriction of sexual activity, type of perianal disease, and degree of induration. Higher scores indicate more severe disease.
[d]Perianal pain score is assessed with 11-point Likert scale (0–10); 0 = no pain and 10 = worst possible pain.
[e]Van Assche total MRI score (0–22) is calculated by summation of 6 components: number of fistulae tracks (0–3), location (0–3), extension (0–2), hyperintensity on T2-weighted images (0–8), collections (0–4), and rectal wall involvement (0–2). Higher scores indicate more severe disease.
[f]VDZ, n = 13; VDZ + wk10, n = 13; VDZ pooled, N = 26.
[g]VDZ, n = 13; VDZ + wk10, n = 14; VDZ pooled, N = 27.

impacted by the 93% rate of seton placement at baseline, compared with 60% in GETAID.[19]

In addition, vedolizumab binds to a gut-selective subset of T lymphocytes through integrin $\alpha_4\beta_7$, preventing their translocation to the subendothelial space, thus lowering intestinal inflammation.[21] On the basis of this mechanism of action, vedolizumab efficacy in perianal disease may correlate with rectal CD localization at baseline. However, the impact of vedolizumab on fistulae in this study appeared to be independent of rectal involvement, warranting further exploration of mechanisms of action leading to closure of fistulae.

Overall, both regimens of vedolizumab IV 300 mg demonstrated improvement in fistulae response, assessed during clinical examination, and improved perianal disease activity at week 30. The additional IV dose of vedolizumab at week 10 did not appear to further improve outcomes over the standard vedolizumab dose regimen, despite higher $C_{trough}$ in the VDZ + wk10 versus VDZ regimen from week 14 to 30. Although $C_{trough}$ in the VDZ + wk10 regimen appears to be higher in responders than nonresponders from week 6 to 22, this is not observed at week 30. Because more patients terminated early in this regimen, the low number of patients in each group and potential outliers led to high variability; thus, this study does not provide a definitive answer on the impact of vedolizumab concentration on fistulae closure. In a recent study, an additional vedolizumab dose at week 10 or a shortening of the vedolizumab dosing interval benefited patients in the GETAID and VICTORY cohorts identified as being less likely to respond to vedolizumab,[22] suggesting patients exhibiting specific disease characteristics may benefit from the additional dose of vedolizumab.

CDAI reductions were modest in this study; however, CDAI is not an optimal tool for measuring improvements

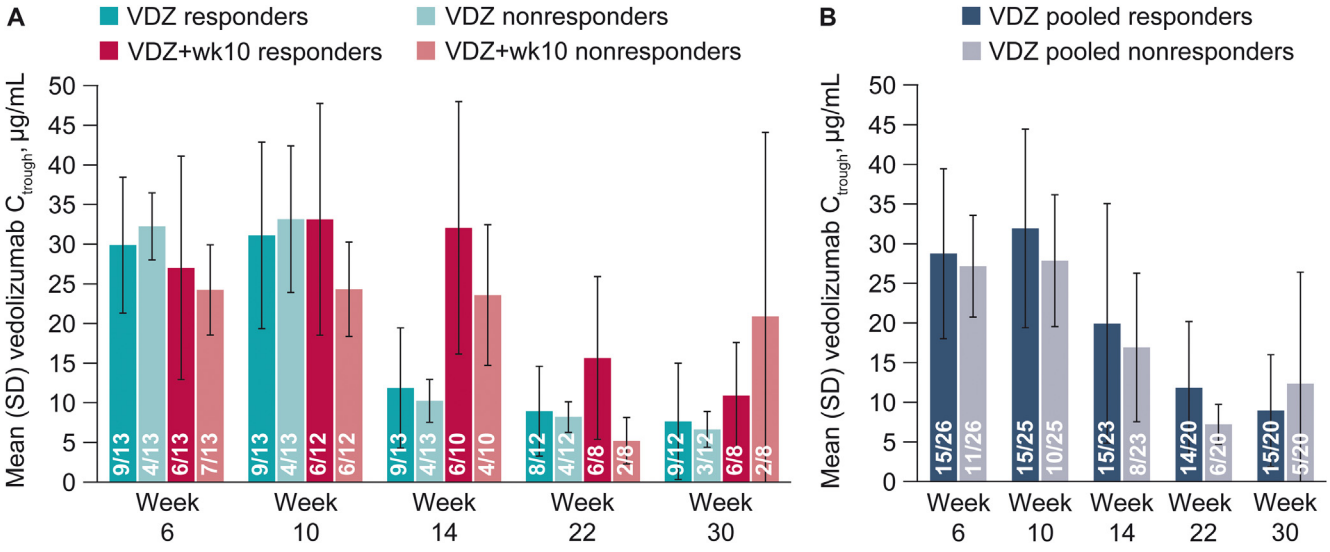


**Figure 3.** Vedolizumab $C_{trough}$ over time by week 30 responder status (mFAS, observed data). (*A*) Responders and nonresponders by treatment group. (*B*) Pooled responders and nonresponders. Responders are defined as ≥50% decrease from baseline in the number of draining perianal fistulae at the visit, assessed by gentle finger compression during clinical examination. $C_{trough}$, trough serum concentration; mFAS, modified full analysis set; SD, standard deviation; VDZ, vedolizumab 300 mg intravenously at weeks 0, 2, 6, 14, and 22; VDZ + wk10, vedolizumab 300 mg intravenously at weeks 0, 2, 6, 10, 14, and 22.

in fistulizing disease. Furthermore, the relatively low baseline CDAI scores (~20% of patients had CDAI ≤220 and 50% had CDAI >220–330) may have contributed to the modest changes.

MRI healing, defined as the disappearance of T2 hyperintensity signal and absence of gadolinium contrast enhancement,[3] was not reached in this study. Although gadolinium contrast enhancement showed improvement at week 30, a longer study may be needed to see greater changes in MRI healing. In fact, MRI studies have shown that internal fistulae healing lags behind clinical remission by a median of 12 months.[1] In this study, although there was no correlation between the Van Assche score and gadolinium contrast enhancement or T2 hyperintensity, combining all 3 measures may provide more insight and predictive response accuracy; this possibility requires additional investigation.

The increases in IBDQ and EQ-5D scores across dosing regimens over time suggest an improvement of HRQoL, consistent with positive HRQoL effects of vedolizumab in CD reported in GEMINI and VERSIFY.[23,24] Furthermore, in this study, decreases in C-reactive protein and fecal calprotectin were consistent with the reduction in draining fistula and HRQoL amelioration, supporting a pattern of global improvement in vedolizumab-treated patients with CD or ulcerative colitis.[23,25–27]

In conclusion, both vedolizumab IV dosing regimens induced sustained improvement in fistulae response from weeks 2 to 30, with parallel ameliorations of MRI parameters and improvements in HRQoL. The additional dose of vedolizumab at week 10 did not substantially alter treatment outcomes. Overall, these results suggest vedolizumab IV may be beneficial in treating patients with fistulizing CD.

**Table 3.** Overview of Adverse Events (Safety Analysis Set)

| Events, n (%) | VDZ (n = 16) | VDZ + wk10 (n = 18) | VDZ pooled (N = 34) |
|---|---|---|---|
| Adverse events | 15 (93.8) | 17 (94.4) | 32 (94.1) |
| Related to treatment | 7 (43.8) | 6 (33.3) | 13 (38.2) |
| Mild | 6 (37.5) | 6 (33.3) | 12 (35.3) |
| Moderate | 6 (37.5) | 10 (55.6) | 16 (47.1) |
| Severe | 3 (18.8) | 1 (5.6) | 4 (11.8) |
| Leading to discontinuation | 1 (6.3) | 3 (16.7) | 4 (11.8) |
| Serious adverse events | 4 (25.0) | 3 (16.7) | 7 (20.6) |
| Related to treatment | 2 (12.5) | 0 | 2 (5.9) |
| Leading to discontinuation | 1 (6.3) | 0 | 1 (2.9) |

VDZ, vedolizumab 300 mg intravenously at weeks 0, 2, 6, 14, and 22; VDZ + wk10, vedolizumab 300 mg intravenously at weeks 0, 2, 6, 10, 14, and 22.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2021.09.028.

## References

1. Gecse KB, Bemelman W, Kamm MA, et al. A global consensus on the classification, diagnosis and multidisciplinary treatment of perianal fistulising Crohn's disease. Gut 2014;63:1381–1392.
2. Gecse KB, Sebastian S, Hertogh G, et al. Results of the Fifth Scientific Workshop of the ECCO [II]: clinical aspects of perianal

fistulising Crohn's disease—the unmet needs. J Crohns Colitis 2016;10:758–765.
3. Thomassin L, Armengol-Debeir L, Charpentier C, et al. Magnetic resonance imaging may predict deep remission in patients with perianal fistulizing Crohn's disease. World J Gastroenterol 2017; 23:4285–4292.
4. Sahnan K, Tozer PJ, Adegbola SO, et al. Developing a core outcome set for fistulising perianal Crohn's disease. Gut 2019; 68:226–238.
5. Feagan BG, Schwartz D, Danese S, et al. Efficacy of vedolizumab in fistulising Crohn's disease: exploratory analyses of data from GEMINI 2. J Crohns Colitis 2018;12:621–626.
6. Caron B, D'Amico F, Danese S, et al. Endpoints for perianal Crohn's disease trials: past, present and future. J Crohns Colitis 2021;15:1387–1398.
7. Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med 1999;340:1398–1405.
8. Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. N Engl J Med 2004;350:876–885.
9. Schreiber S, Lawrance IC, Thomsen OØ, et al. Randomised clinical trial: certolizumab pegol for fistulas in Crohn's disease—subgroup results from a placebo-controlled study. Aliment Pharmacol Ther 2011;33:185–193.
10. Castano-Milla C, Chaparro M, Saro C, et al. Effectiveness of adalimumab in perianal fistulas in crohn's disease patients naive to anti-TNF therapy. J Clin Gastroenterol 2015;49:34–40.
11. Dewint P, Hansen BE, Verhey E, et al. Adalimumab combined with ciprofloxacin is superior to adalimumab monotherapy in perianal fistula closure in Crohn's disease: a randomised, double-blind, placebo controlled trial (ADAFI). Gut 2014;63:292–299.
12. West RL, van der Woude CJ, Hansen BE, et al. Clinical and endosonographic effect of ciprofloxacin on the treatment of perianal fistulae in Crohn's disease with infliximab: a double-blind placebo-controlled study. Aliment Pharmacol Ther 2004; 20:1329–1336.
13. Vedolizumab [summary of product characteristics]. Taastrup, Denmark: Takeda Pharma A/S, 2019.
14. Vedolizumab [prescribing information]. Deerfield, IL: Takeda Pharmaceuticals America Inc, 2014.
15. Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med 2013;369:711–721.
16. Loftus EV Jr, Feagan BG, Panaccione R, et al. Long-term safety of vedolizumab for inflammatory bowel disease. Aliment Pharmacol Ther 2020;52:1353–1365.
17. Ford AC, Luthra P, Hanauer SB, et al. Placebo response rate in clinical trials of fistulizing Crohn's disease: systematic review and meta-analysis. Clin Gastroenterol Hepatol 2014; 12:1981–1990.
18. Colombel JF, Sands BE, Rutgeerts P, et al. The safety of vedolizumab for ulcerative colitis and Crohn's disease. Gut 2017;66:839–851.
19. Chapuis-Biron C, Bourrier A, Nachury M, et al. Vedolizumab for perianal Crohn's disease: a multicentre cohort study in 151 patients. Aliment Pharmacol Ther 2020;51:719–727.
20. Yassin NA, Askari A, Warusavitarne J, et al. Systematic review: the combined surgical and medical treatment of fistulising perianal Crohn's disease. Aliment Pharmacol Ther 2014; 40:741–749.
21. Wyant T, Fedyk E, Abhyankar B. An overview of the mechanism of action of the monoclonal antibody vedolizumab. J Crohns Colitis 2016;10:1437–1444.
22. Dulai PS, Amiot A, Peyrin-Biroulet L, et al. A clinical decision support tool may help to optimise vedolizumab therapy in Crohn's disease. Aliment Pharmacol Ther 2020; 51:553–564.
23. Danese S, Adsul S, Lindner D, et al. Effects of IV vedolizumab on health-related quality of life and work productivity in patients with Crohn's disease: results from the Phase 3b VERSIFY trial (abstract). J Crohns Colitis 2019;13:S293–S294.
24. Vermeire S, Loftus EV Jr, Colombel JF, et al. Long-term efficacy of vedolizumab for Crohn's disease. J Crohns Colitis 2017; 11:412–424.
25. Sandborn WJ, Baert F, Danese S, et al. Efficacy and safety of vedolizumab subcutaneous formulation in a randomized trial of patients with ulcerative colitis. Gastroenterology 2020; 158:562–572 e12.
26. Sands BE, Peyrin-Biroulet L, Loftus EV Jr, et al. Vedolizumab versus adalimumab for moderate-to-severe ulcerative colitis. N Engl J Med 2019;381:1215–1226.
27. Vermeire S, d'Haens G, Baert F, et al. The VISIBLE 2 phase 3 study of efficacy and safety of vedolizumab SC for moderate-to-severe Crohn's disease (abstract). Gastroenterology 2020; 158(Suppl 1):S-194.

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Shashi Adsul (Formal analysis: Equal; Writing – review & editing: Equal)
Silvio Danese (Investigation: Equal; Formal analysis: Equal; Writing – review & editing: Equal)

**Conflicts of interest**
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## Supplementary Methods

### Study Design

Patients were randomized 1:1 on the basis of an interactive web response system (IWRS) to receive vedolizumab 300 mg intravenously at weeks 0, 2, 6, 14, and 22 (VDZ) or the same regimen plus an additional vedolizumab dose at week 10 (VDZ + wk10). Blinding was maintained using the IWRS and by giving a placebo infusion at week 10 in the VDZ arm; intravenous infusion bags for both vedolizumab and placebo were masked after preparation by an unblinded pharmacist.

All patients were prescribed companion antibiotics from day 1 until week 6. Approved antibiotics were metronidazole, ciprofloxacin, amoxicillin clavulanate, and tinidazole per local label.

Approximately 100 patients were planned to be enrolled. The sample size was based on an estimate of precision, not statistical power considerations.

### Additional Study Endpoints

Disease activity was evaluated on the basis of changes in CDAI, PDAI, and perianal pain scores (assessed on 11-point Likert scale for 7 days before week 30 compared with 7 days before baseline; a score of 0 represents no pain and 10 the worst possible pain). Relevant MRI assessments included changes in Van Assche score, relative gadolinium enhancement, and mean relative T2 signal intensity at week 30 compared with screening. Changes in fecal calprotectin and C-reactive protein from baseline to week 30 were also evaluated. Changes from baseline in IBDQ and EQ-5D were evaluated at weeks 14 and 30. $C_{trough}$ of vedolizumab and the presence of vedolizumab ADAs and neutralizing ADAs were reported.

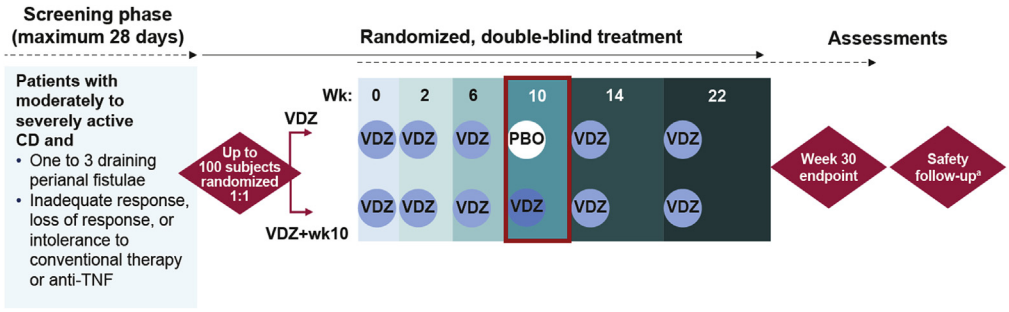
The extent of vedolizumab exposure was monitored throughout the 30 weeks of the study.

### Additional Study Assessments

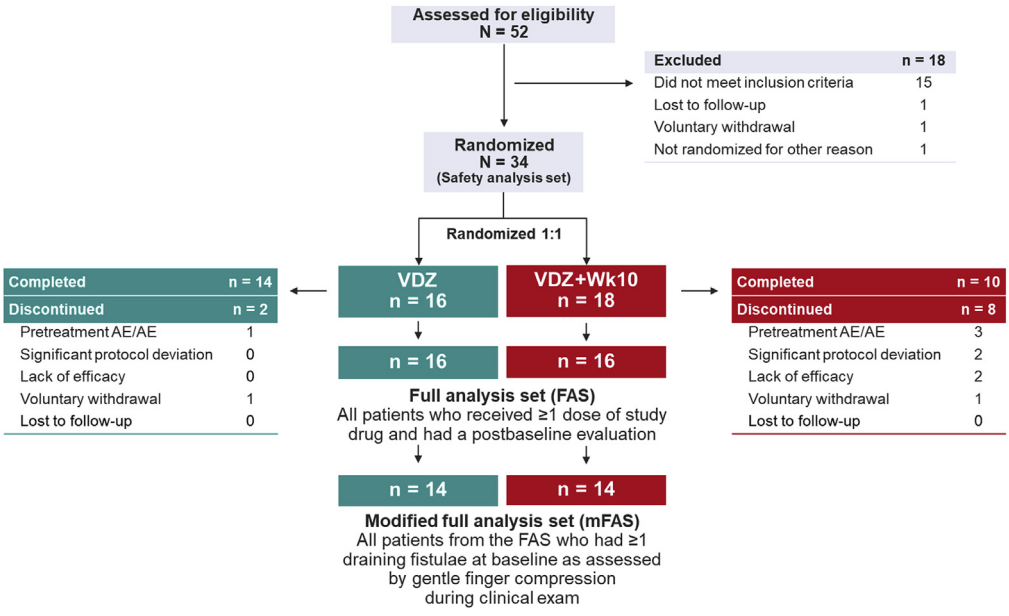
Hematology and serum chemistry parameters were measured at screening and at weeks 0, 10, 22, and 30. Patients were evaluated using MRI at screening and week 30. PK parameters and the presence of vedolizumab ADAs were assessed at weeks 0, 6, 10, 14, 22, 30, and 40 (ADAs only). Biomarkers of inflammation, fecal calprotectin, and C-reactive protein were reported at weeks 0, 10 (C-reactive protein only), 14, and 30.

## Supplementary Results

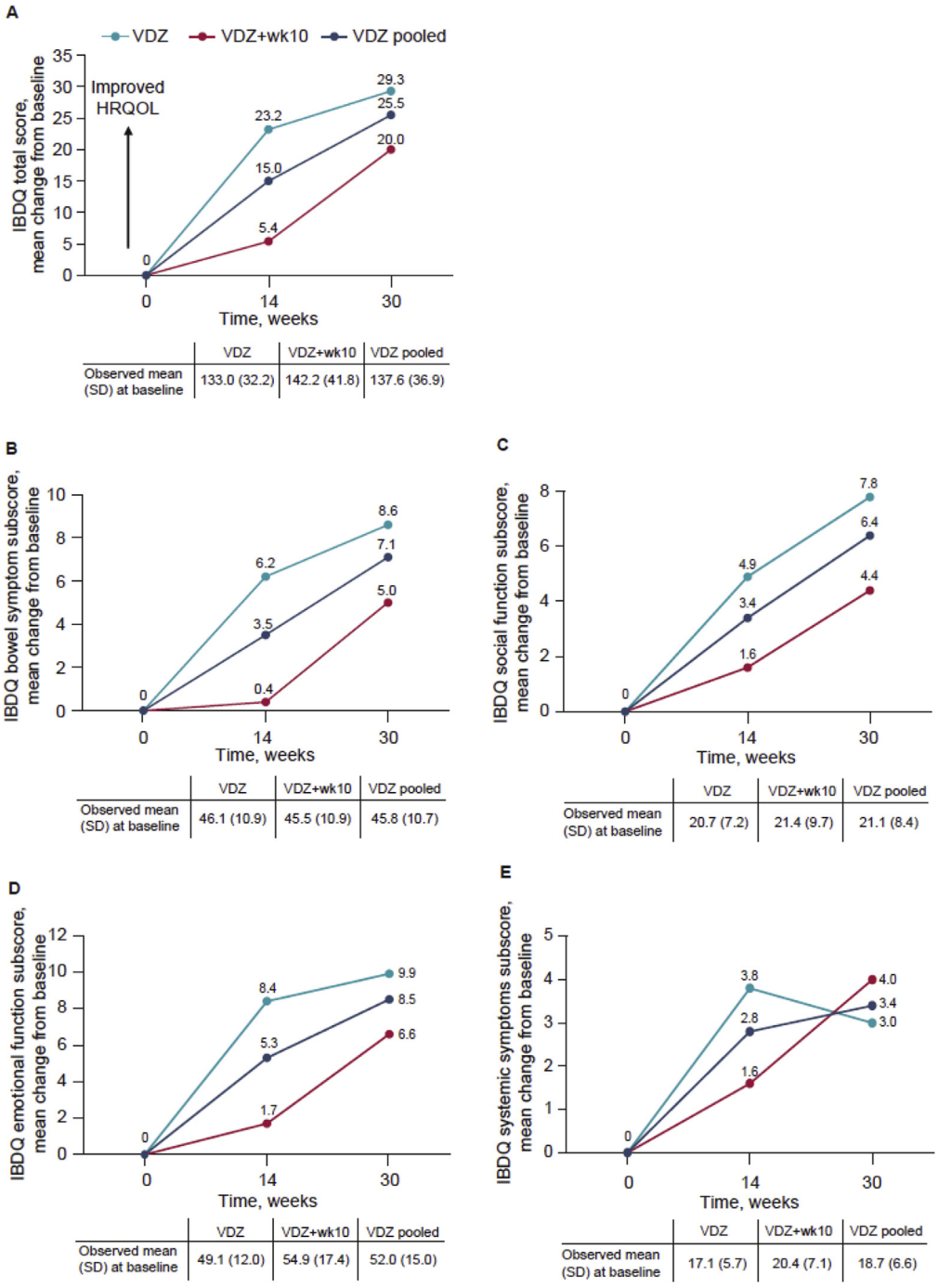
The protocol-specified time frame for seton removal was between week 6 and week 14. Of the 25 patients who had >1 setons at study day 1, 17 were reported as having any seton removed before end of study. In these patients, median time to first removal of any seton was 97 days (minimum 16, maximum 158), and the mean (SD) was 97.1 (31.1) days.



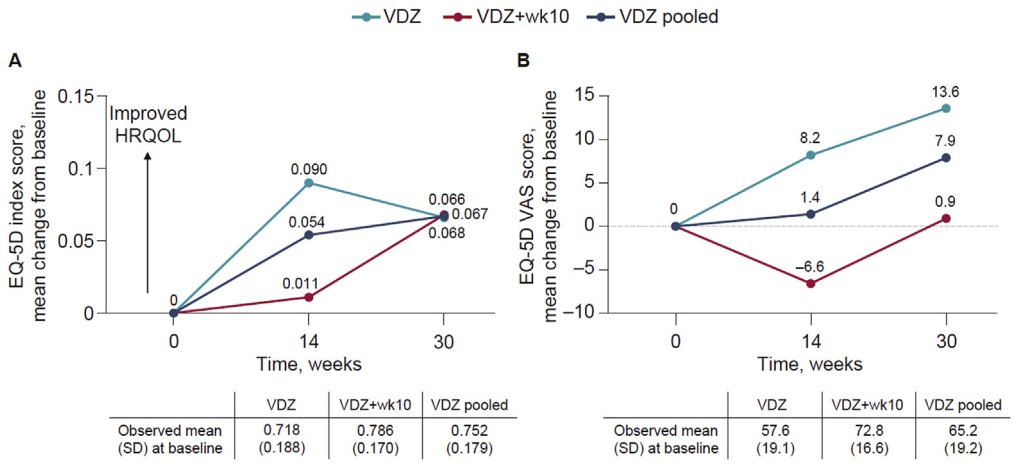

**Supplementary Figure 1.** Study design. [a]Safety follow-up at week 40 and long-term safety follow-up at week 48. Anti-TNF, anti-tumor necrosis factor; CD, Crohn's disease; PBO, placebo; VDZ, vedolizumab; VDZ + wk10, vedolizumab at weeks 0, 2, 6, 10, 14, and 22.




**Supplementary Figure 2.** Patient disposition. AE, adverse event; VDZ, vedolizumab 300 mg intravenously at weeks 0, 2, 6, 14, and 22; VDZ + wk10, vedolizumab 300 mg intravenously at weeks 0, 2, 6, 10, 14, and 22.



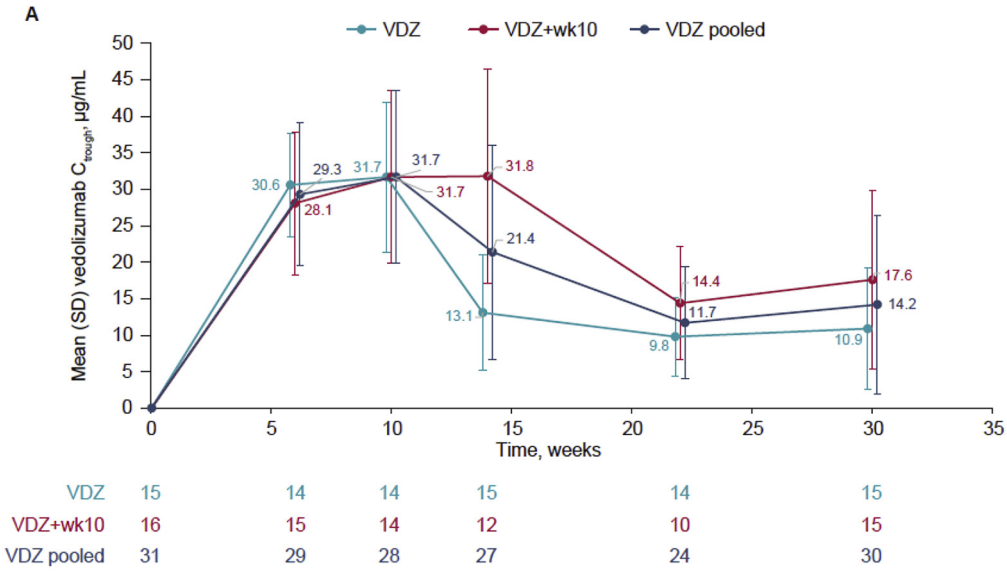

**Supplementary Figure 3.** IBDQ total score and domain subscores at weeks 14 and 30 (modified full analysis set). The IBDQ instrument assesses patient-reported quality of life and has a total (*A*) scoring range of 32–224, with higher scores indicating better patient-reported quality of life. Ranges for possible IBDQ subscores are as follows: bowel symptoms (*B*) range 10–70; social function (*C*) range 5–35; emotional function (*D*) range 12–84; and systemic symptoms (*E*) range 5–35. Baseline was defined as last observation before first dose of the study medication. HRQOL, health-related quality of life; IBDQ, inflammatory bowel disease questionnaire; SD, standard deviation; VDZ, vedolizumab 300 mg intravenously at weeks 0, 2, 6, 14, and 22; VDZ + wk10, vedolizumab 300 mg intravenously at weeks 0, 2, 6, 10, 14, and 22



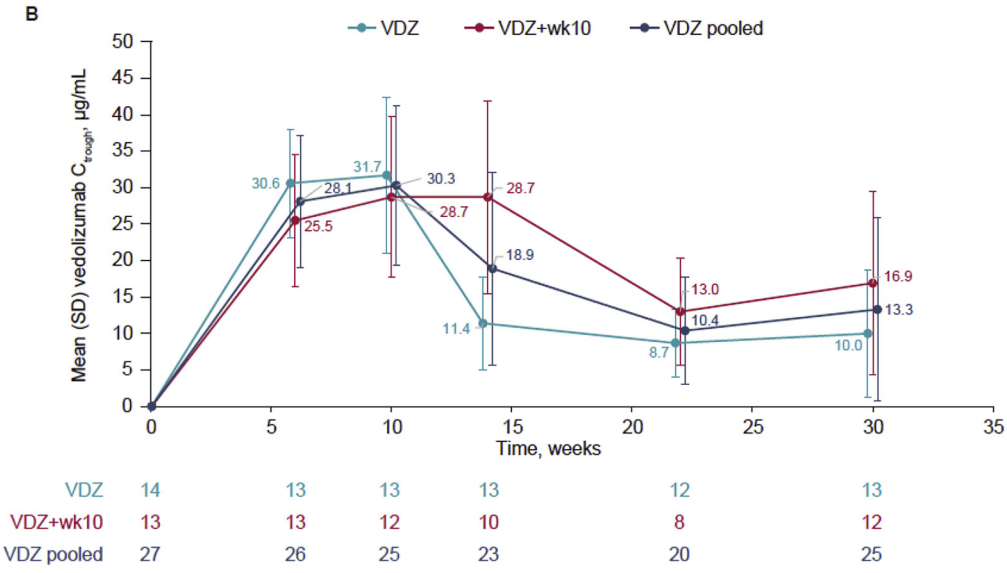

| | VDZ | VDZ+wk10 | VDZ pooled |
|---|---|---|---|
| Observed mean (SD) at baseline | 0.718 (0.188) | 0.786 (0.170) | 0.752 (0.179) |

| | VDZ | VDZ+wk10 | VDZ pooled |
|---|---|---|---|
| Observed mean (SD) at baseline | 57.6 (19.1) | 72.8 (16.6) | 65.2 (19.2) |

**Supplementary Figure 4.** EQ-5D index and visual analogue scale scores at weeks 14 and 30 (modified full analysis set). EQ-5D index score (*A*) measures patient-reported quality of life and includes 5 domain items: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Higher scores indicate better quality of life. EQ-5D visual analogue scale (*B*) is a visual scale from 0 (worst imaginable health state) to 100 (best imaginable health state). Baseline was defined as last observation before first dose of the study medication. EQ-5D, Euro Quality of Life 5D; HRQOL, health-related quality of life; SD, standard deviation; VDZ, vedolizumab 300 mg intravenously at weeks 0, 2, 6, 14, and 22; VDZ + wk10, vedolizumab 300 mg intravenously at weeks 0, 2, 6, 10, 14, and 22.




| | | | | | | |
|---|---|---|---|---|---|---|
| VDZ | 15 | 14 | 14 | 15 | 14 | 15 |
| VDZ+wk10 | 16 | 15 | 14 | 12 | 10 | 15 |
| VDZ pooled | 31 | 29 | 28 | 27 | 24 | 30 |




| | | | | | | |
|---|---|---|---|---|---|---|
| VDZ | 14 | 13 | 13 | 13 | 12 | 13 |
| VDZ+wk10 | 13 | 13 | 12 | 10 | 8 | 12 |
| VDZ pooled | 27 | 26 | 25 | 23 | 20 | 25 |

**Supplementary Figure 5.** Mean (SD) vedolizumab $C_{trough}$ over time: (*A*) pharmacokinetic set; (*B*) modified full analysis set. $C_{trough}$, trough serum concentration; SD, standard deviation; VDZ, vedolizumab 300 mg intravenously at weeks 0, 2, 6, 14, and 22; VDZ + wk10, vedolizumab 300 mg intravenously at weeks 0, 2, 6, 10, 14, and 22.

**Supplementary Table 1.** Analysis Sets

| Analysis set, n | VDZ (n = 16) | VDZ + wk10 (n = 18) | VDZ pooled (N = 34) |
|---|---|---|---|
| Safety analysis set[a] | 16 | 18 | 34 |
| Full analysis set[b] | 16 | 16 | 32 |
| Modified full analysis set[c] | 14 | 14 | 28 |
| Pharmacokinetic set[d] | 16 | 18 | 34 |

VDZ, vedolizumab 300 mg intravenously at weeks 0, 2, 6, 14, and 22; VDZ + wk10, vedolizumab 300 mg intravenously at weeks 0, 2, 6, 10, 14, and 22.
[a]Safety analysis set includes all patients receiving ≥1 doses of vedolizumab.
[b]Full analysis set includes all patients in the safety analysis set with postbaseline assessment of fistulae healing.
[c]The modified full analysis set consists of all patients in the full analysis set with ≥1 draining fistulae at baseline, assessed by gentle finger compression during clinical exam.
[d]The pharmacokinetic set includes all patients in the safety analysis set with sufficient blood sampling to allow for pharmacokinetic evaluation.

**Supplementary Table 2.** Companion Antibiotics (Safety Analysis Set)

| Patients receiving medication, n (%) | VDZ (n = 16) | VDZ + wk10 (n = 16)[a] | VDZ pooled (n = 32)[a] |
|---|---|---|---|
| Metronidazole 250 mg TID | 7 (43.8) | 4 (25.0) | 11 (34.4) |
| Ciprofloxacin 500 mg BID | 8 (50.0) | 12 (75.0) | 20 (62.5) |
| Tinidazole 500 mg QD | 1 (6.3) | 0 | 1 (3.1) |

BID, twice daily; QD, once daily; TID, 3 times daily; VDZ, vedolizumab 300 mg intravenously at weeks 0, 2, 6, 14, and 22; VDZ + wk10, vedolizumab 300 mg intravenously at weeks 0, 2, 6, 10, 14, and 22.
[a]Information not available for 2 patients.

**Supplementary Table 3.** Fistula Type at Baseline, Extracted From Van Assche Score (Modified Full Analysis Set)

| Characteristic | VDZ (n = 14) | VDZ + wk10 (n = 14) | VDZ pooled (N = 28) |
|---|---|---|---|
| Fistula tracks, n (%) | | | |
| Single, unbranched | 9 (64.3) | 9 (64.3) | 18 (64.3) |
| Single, branched | 4 (28.6) | 5 (35.7) | 9 (32.1) |
| Multiple | 1 (7.1) | 0 | 1 (3.6) |
| Location, n (%) | | | |
| Extra or intersphincteric | 8 (57.1) | 7 (50.0) | 15 (53.6) |
| Transsphincteric | 6 (42.9) | 7 (50.0) | 13 (46.4) |

VDZ, vedolizumab 300 mg intravenously at weeks 0, 2, 6, 14, and 22; VDZ + wk10, vedolizumab 300 mg intravenously at weeks 0, 2, 6, 10, 14, and 22.

**Supplementary Table 4.** Baseline Demographics and Disease Characteristics (Full Analysis Set)

| | VDZ (n = 16) | VDZ + wk10 (n = 16) | VDZ pooled (N = 32) |
|---|---|---|---|
| Median age (min, max), *y* | 33.5 (23, 58) | 35.0 (21, 59) | 34.0 (21, 59) |
| Male, n (%)[a] | 10 (62.5) | 9 (56.3) | 19 (59.4) |
| Smoking classification, n (%) | | | |
| Never smoker | 7 (43.8) | 7 (43.8) | 14 (43.8) |
| Current smoker | 7 (43.8) | 4 (25.0) | 11 (34.4) |
| Ex-smoker | 2 (12.5) | 5 (31.3) | 7 (21.9) |
| Median (min, max) duration of CD, *y*[b] | 11.2 (0.7, 37.6) | 8.4 (0.5, 25.4) | 9.4 (0.5, 37.6) |
| Mean (SD) baseline[c] CDAI | 272.7 (72.8) | 300.7 (95.8) | 286.7 (84.9) |
| Baseline[c] CDAI categories, n (%)[a] | | | |
| ≤220 | 3 (18.8) | 5 (31.3) | 8 (25.0) |
| >220–330 | 10 (62.5) | 5 (31.3) | 15 (46.9) |
| >330 | 3 (18.8) | 6 (37.5) | 9 (28.1) |
| Previous anti-TNF treatment, n (%)[a] | 12 (75.0) | 13 (81.3) | 25 (78.1) |
| Concomitant treatment at baseline,[c] n (%)[a] | | | |
| Corticosteroids | 3 (18.8) | 3 (18.8) | 6 (18.8) |
| Immunosuppressants | 5 (31.3) | 3 (18.8) | 8 (25.0) |
| No. of draining fistulae at baseline,[d] n (%) | | | |
| 1 | 5 (31.3) | 12 (75.0) | 17 (53.1) |
| 2 | 9 (56.3) | 2 (12.5) | 11 (34.4) |
| Median (min, max) duration of fistulizing disease, *y* | 4.6 (0.5, 20.7) | 1.8 (0.1, 15.8) | 3.0 (0.1, 20.7) |
| Mean (SD) baseline[c] PDAI | 7.8 (2.2) | 7.8 (3.3) | 7.8 (2.8) |
| Seton placement[e] at baseline,[c] n (%)[a] | 15 (93.8) | 15 (93.8) | 30 (93.8) |

Anti-TNF, anti-tumor necrosis factor; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; max, maximum; min, minimum; PDAI, Perianal Disease Activity Index; VDZ, vedolizumab 300 mg intravenously at weeks 0, 2, 6, 14, and 22; VDZ + wk10, vedolizumab 300 mg intravenously at weeks 0, 2, 6, 10, 14, and 22.
[a]Percentages are based on number of patients with non-missing data in the respective column.
[b]Duration of CD refers to duration from date of disease diagnosis.
[c]Baseline was defined as last observation before first dose of study medication.
[d]Number of fistulae at baseline was assessed using magnetic resonance imaging.
[e]For patients without seton placement information at baseline, baseline status was imputed as "yes."

**Supplementary Table 5.** Response by Rectal Involvement at Baseline (Modified Full Analysis Set)

| | VDZ | | VDZ + wk10[a] | | VDZ pooled[a] | |
|---|---|---|---|---|---|---|
| | Rectal involvement | | Rectal involvement | | Rectal involvement | |
| | No (n = 10) | Yes (n = 4) | No (n = 5) | Yes (n = 8) | No (n = 15) | Yes (n = 12) |
| Response at week 30, n (%) | | | | | | |
| Nonresponder | 4 (40.0) | 1 (25.0) | 2 (40.0) | 6 (75.0) | 6 (40.0) | 7 (58.3) |
| Responder[b] | 6 (60.0) | 3 (75.0) | 3 (60.0) | 2 (25.0) | 9 (60.0) | 5 (41.7) |

VDZ, vedolizumab 300 mg intravenously at weeks 0, 2, 6, 14, and 22; VDZ + wk10, vedolizumab 300 mg intravenously at weeks 0, 2, 6, 10, 14, and 22.
[a]One patient with missing information on baseline disease location not included.
[b]Responders are defined as patients with ≥50% decrease from baseline in number of perianal draining fistulae at the visit, assessed by gentle finger compression during clinical exam. Patients with missing data at the visit were classed as nonresponders.

**Supplementary Table 6.** Measures of Biomarkers of Inflammation (Modified Full Analysis Set)

| | VDZ (n = 14) | VDZ + wk10 (n = 14) | VDZ pooled (N = 28) |
|---|---|---|---|
| FCP, *μg/g* | | | |
| Observed mean (SD) at baseline[a,b] | 556.8 (499.5) | 2430.8 (3409.5) | 1531.3 (2615.3) |
| Patients at week 30, n | 9 | 6 | 15 |
| Observed mean (SD) change from baseline at week 30 | 109.7 (613.8) | –472.0 (904.9) | –123.0 (771.2) |
| CRP, *mg/L* | | | |
| Observed mean (SD) at baseline[a] | 17.6 (23.1) | 13.0 (22.7) | 15.3 (22.6) |
| Patients at week 30, n | 12 | 8 | 20 |
| Observed mean (SD) change from baseline at week 30 | –7.1 (21.7) | –1.1 (16.2) | –4.7 (19.4) |

CRP, C-reactive protein; FCP, fecal calprotectin; SD, standard deviation; VDZ, vedolizumab 300 mg intravenously at weeks 0, 2, 6, 14, and 22; VDZ + wk10, vedolizumab 300 mg intravenously at weeks 0, 2, 6, 10, 14, and 22.
[a]Baseline was defined as last observation before first dose of study medication.
[b]VDZ, n = 12; VDZ + wk10, n = 13; VDZ pooled, N = 25.

**Supplementary Table 7.** Most Frequent Adverse Events[a] and Serious Adverse Events by Preferred Term[b] (Safety Analysis Set)

| | VDZ (n = 16) | VDZ + wk10 (n = 18) | VDZ pooled (N = 34) |
|---|---|---|---|
| Any AE | 15 (93.8) | 17 (94.4) | 32 (94.1) |
| Most frequent AEs[a] | | | |
| Proctalgia | 2 (12.5) | 0 | 2 (5.9) |
| Crohn's disease | 2 (12.5) | 5 (27.8) | 7 (20.6) |
| Abdominal pain | 4 (25.0) | 2 (11.1) | 6 (17.6) |
| Anal fistula | 2 (12.5) | 2 (11.1) | 4 (11.8) |
| Vomiting | 0 | 2 (11.1) | 2 (5.9) |
| Pyrexia | 2 (12.5) | 4 (22.2) | 6 (17.6) |
| Anal abscess | 4 (25.0) | 0 | 4 (11.8) |
| Sinusitis | 0 | 2 (11.1) | 2 (5.9) |
| Upper respiratory tract infection | 0 | 2 (11.1) | 2 (5.9) |
| Arthralgia | 1 (6.3) | 5 (27.8) | 6 (17.6) |
| Myalgia | 2 (12.5) | 0 | 2 (5.9) |
| Headache | 2 (12.5) | 4 (22.2) | 6 (17.6) |
| Any SAE | 4 (25.0) | 3 (16.7) | 7 (20.6) |
| Crohn's disease | 1 (6.3) | 1 (5.6) | 2 (5.9) |
| Ileal stenosis | 1 (6.3) | 0 | 1 (2.9) |
| Hyperpyrexia | 0 | 1 (5.6) | 1 (2.9) |
| Anal abscess | 3 (18.8) | 0 | 3 (8.8) |
| Abdominal infection | 1 (6.3) | 0 | 1 (2.9) |
| Arthralgia | 0 | 1 (5.6) | 1 (2.9) |

AE, adverse event; SAE, serious adverse event; VDZ, vedolizumab 300 mg intravenously at weeks 0, 2, 6, 14, and 22; VDZ + wk10, vedolizumab 300 mg intravenously at weeks 0, 2, 6, 10, 14, and 22.

[a]Frequency of >10% for either treatment regimen.

[b]Adverse events were coded using the Medical Dictionary for Regulatory Activities, version 21.0.