Journal of Crohn's and Colitis, 2017, 412–424
doi:10.1093/ecco-jcc/jjw176
Advance Access publication September 28, 2016
Original Article

Original Article

Long-term Efficacy of Vedolizumab for Crohn's Disease

Severine Vermeire,[a] Edward V. Loftus Jr,[b] Jean-Frédéric Colombel,[c] Brian G. Feagan,[d] William J. Sandborn,[e] Bruce E. Sands,[c] Silvio Danese,[f] Geert R. D'Haens,[g] Arthur Kaser,[h] Remo Panaccione,[i] David T. Rubin,[j] Ira Shafran,[k] Megan McAuliffe,[l] Arpeat Kaviya,[m] Serap Sankoh,[l] Reema Mody,[n] Brihad Abhyankar,[m] Michael Smyth[m]

[a]University Hospitals Leuven, Belgium [b]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota, USA [c]Icahn School of Medicine at Mount Sinai, Mount Sinai Hospital, New York, New York, USA [d]Robarts Clinical Trials, Robarts Research Institute, University of Western Ontario, London, Ontario, Canada [e]University of California San Diego and UC San Diego Health System, La Jolla, California, USA [f]Istituto Clinico Humanitas, Milan, Italy [g]Academic Medical Center, Amsterdam, The Netherlands [h]Department of Medicine, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK [i]Inflammatory Bowel Disease Clinic, University of Calgary, Calgary, Alberta, Canada [j]University of Chicago Inflammatory Bowel Disease Center, Chicago, Illinois, USA [k]Shafran Gastroenterology Center, Winter Park, Florida, USA [l]Takeda Pharmaceuticals International Co., Cambridge, Massachusetts, USA [m]Takeda Development Centre Europe Ltd, London, UK [n]Takeda Pharmaceuticals International, Inc., Deerfield, Illinois, USA

Corresponding author: Severine Vermeire, MD, University Hospitals Leuven, Department of Gastroenterology, B-3000 Leuven, Belgium. Tel.: +32 16 34 42 18; fax: +32 16 34 44 19; email: severine.vermeire@uzleuven.be

Conference presentations: Long-term efficacy of vedolizumab for Crohn's disease, ACG 2014 [Philadelphia, PA, USA]/UEGW 2014 [Vienna, Austria]; Effects of vedolizumab increased dosing frequency on disease activity in ulcerative colitis and Crohn's disease, ACG 2014 [Philadelphia, PA, USA]/UEGW 2014 [Vienna, Austria]; Efficacy and safety of retreatment with vedolizumab in patients with Crohn's disease, ECCO 2015 [Barcelona, Spain]/DDW 2015 [Washington DC, USA]; Response and remission rates with up to 3 years of vedolizumab treatment in patients with Crohn's disease, ECCO 2016 [Amsterdam, Netherlands]/DDW 2016 [San Diego, CA, USA].

ClinicalTrials.gov ID NCT00790933

Abstract

Background and Aims: Vedolizumab is a gut-selective $\alpha_4\beta_7$ integrin antagonist therapy for ulcerative colitis and Crohn's disease. The GEMINI long-term safety [LTS] trial is an ongoing open-label study investigating the safety of vedolizumab. We present interim exploratory analyses of efficacy in patients with Crohn's disease.

Methods: Patients from the C13004, GEMINI 2 and GEMINI 3 studies and vedolizumab-naïve patients could enrol in GEMINI LTS and received vedolizumab every 4 weeks. Data were collected from May 22, 2009 to June 27, 2013. Outcomes of clinical response and remission, defined by the Harvey-Bradshaw Index, and health-related quality of life [HRQL] were assessed for up to 152 weeks of treatment in the efficacy population.

Results: Among patients with response at week 6 in GEMINI 2 who received vedolizumab continuously, 83% [*n*=100/120] and 89% [*n*=62/70] of patients with available data were in remission after 104 and 152 weeks, respectively. Increased dosing frequency from every 8 weeks [GEMINI 2] to every 4 weeks [GEMINI LTS] improved outcomes in patients who had withdrawn early from

GEMINI 2, with 47% [*n*=27/57] experiencing clinical response and 32% [*n*=18/57] in remission at week 52 of GEMINI LTS [up from 39% and 4% before the dose increase]. Similar improvements were observed regardless of prior tumour necrosis factor [TNF] antagonist exposure. Long-term benefits of HRQL were also observed.

Conclusions: The clinical benefits of vedolizumab continued with long-term treatment regardless of prior TNF antagonist exposure. Increased dosing frequency might improve outcomes in patients who lose response to conventional 8-weekly dosing.

Key Words: vedolizumab, Crohn's disease, long-term efficacy

1. Introduction

Crohn's disease [CD] is a chronic idiopathic inflammatory bowel disease [IBD] characterized by inflammation that usually occurs in the ileum and proximal colon. Patients typically present with symptoms of abdominal pain, diarrhoea and fatigue.[1,2] Conventional non-biologic therapies include corticosteroids, thiopurines and methotrexate.[1–4] Biologic therapies such as tumour necrosis factor [TNF] antagonists are usually reserved for patients who fail conventional treatment.[1,2] However, the long-term value of many of these agents may be limited by lack of efficacy and/or the potential for serious side effects.[2,5] For example, approximately 40% of patients either fail to respond to TNF antagonist induction therapy or lose response over time.[2] There remains a need for effective and safe long-term therapy.

Vedolizumab, a monoclonal antibody specifically targeting the $\alpha_4\beta_7$ integrin heterodimer, is a new treatment for moderately to severely active CD.[6] Vedolizumab inhibits migration of $\alpha_4\beta_7$ integrin-positive inflammatory cells into intestinal tissue by blocking their interaction with endothelial cells expressing mucosal addressin cell adhesion molecule-1 [MAdCAM-1].[7–9] MAdCAM-1 is preferentially – but not exclusively – expressed in the gastrointestinal tract,[10] primarily restricting the suppressive effect of vedolizumab on inflammatory cell migration to the gut, in contrast to other biologic agents, such as TNF antagonists, which have systemic effects.

We present interim analysis of data from the continuing GEMINI long-term safety [LTS] study [ClinicalTrials.gov ID NCT00790933] describing the clinical efficacy of long-term vedolizumab treatment in patients with moderately to severely active CD. We were specifically interested in the durability of clinical benefit associated with continued therapy, experience with vedolizumab retreatment following interrupted therapy, and the value of increased dosing frequency from every 8 weeks to every 4 weeks. Efficacy data were analyzed for the overall patient population as well as stratified by prior TNF antagonist exposure. Safety data are summarized.

2. Methods

2.1. Study design and patient enrolment

GEMINI LTS was an ongoing single-arm, open-label phase 3 extension study in patients with CD and ulcerative colitis at 292 centres internationally at the time of these interim analyses. The primary objective was to evaluate the safety profile of long-term vedolizumab treatment. Patient-reported health-related quality of life [HRQL] assessments and efficacy endpoints of response and remission were pre-specified exploratory objectives. This interim report represents efficacy data for patients with moderately to severely active CD enrolled in GEMINI LTS from May 22, 2009 to June 27, 2013.

The study was designed and implemented by the GEMINI Steering Committee [see online Supplementary Material] in collaboration with the sponsor [Millennium Pharmaceuticals, Inc., d/b/a Takeda Development Center Americas, Inc.]. The study protocol was reviewed and approved by the institutional review board[s] and/or independent ethics committee[s] at each participating investigational centre. GEMINI LTS is being conducted compliant with good clinical practice and applicable regulatory requirements and according to the ethical principles founded in the Declaration of Helsinki.[11] All patients gave written informed consent.

Patients from qualifying studies, which included the long-term phase 2 C13004 study [ClinicalTrials.gov ID NCT00619489][12] and the phase 3 GEMINI 2 [ClinicalTrials.gov ID NCT00783692] and GEMINI 3 [ClinicalTrials.gov ID NCT01224171] studies were eligible for enrolment.[13,14] The remainder of the CD population were vedolizumab naïve and enrolled directly into GEMINI LTS [Supplementary Figure 1]. As of June 27, 2013, the maximum duration of exposure for patients in the vedolizumab-naïve cohort was 399 days [57 weeks]. In contrast, patients who entered the study from GEMINI 2 or GEMINI 3 had a maximum duration of exposure of up to 1531 days [219 weeks] or 948 days [135 weeks], respectively. Interim data for up to 100 weeks of vedolizumab treatment in GEMINI LTS are reported here with the potential for approximately 3 years [152 weeks] of total exposure for patients who completed the 52-week GEMINI 2 study.

Patients were withdrawn from the study if they met any of the criteria for long-term treatment failure [i.e. need for rescue medication, major surgical intervention for the treatment of CD, and occurrence of a study drug-related adverse event that led to discontinuation], if they were not benefiting from therapy [in the opinion of the investigator or patient] or if they became pregnant. Furthermore, withdrawal of therapy was strongly recommended for patients who required recurrent courses of corticosteroids or those who could not discontinue these drugs beyond 6 months because of persistent disease activity.

2.1.1. GEMINI 2 patients

GEMINI 2 was a randomized placebo-controlled trial designed to explore the safety and efficacy of vedolizumab induction and maintenance therapy in patients with moderately to severely active CD [Supplementary Figure 1]. Details of the GEMINI 2 study design have been published elsewhere.[13] Briefly, during the induction phase, patients enrolled in Cohort 1 were randomized 3:2 to receive either vedolizumab or placebo and those enrolled in Cohort 2 received open-label vedolizumab; all patients were dosed at weeks 0 and 2. Patients from both cohorts who responded to therapy (i.e. ≥70-point decrease from baseline in the Crohn's Disease Activity Index [CDAI] score) at week 6 were randomized to receive vedolizumab maintenance therapy every 4 weeks or every 8 weeks or placebo (the maintenance intent-to-treat [ITT] population). Patients who did not respond to vedolizumab at week 6 and those originally assigned to placebo during the induction phase received vedolizumab or placebo,

respectively, every 4 weeks [maintenance non-ITT population] or discontinued from the study [Supplementary Figure 1].[13] Patients from GEMINI 2 who completed or withdrew early because of sustained non-response, disease worsening or the need for rescue medication [Supplementary Table 1], and for whom, in the opinion of the investigator, the study drug was well tolerated could enrol in GEMINI LTS.

2.1.2. GEMINI 3 patients

GEMINI 3 was a 10-week induction trial in which patients with moderately to severely active CD were randomized 1:1 to receive three doses of vedolizumab or placebo at weeks 0, 2 and 6.[14] Unlike GEMINI 2, which included a broad patient population, GEMINI 3 assessed induction therapy in patients who, in the majority, had failed a TNF antagonist. Only completers of GEMINI 3 were eligible for GEMINI LTS enrolment.

2.1.3. Vedolizumab-naïve patients

Eligibility criteria for vedolizumab-naïve patients were similar to those specified in GEMINI 2 except for the use of the Harvey-Bradshaw Index [HBI] in GEMINI LTS instead of the CDAI to define disease activity for enrolment.[13] The HBI is a simplified version of the CDAI that consists of five items [general well-being, abdominal pain, number of liquid stools per day, abdominal mass and complications]. Scores range from 0 to ≥18 with higher scores indicating greater disease activity.[15] Scores of ≤4 are observed in patients who are in remission. The HBI score has been extensively correlated with the CDAI score and has been demonstrated to be responsive to meaningful change in disease activity. Eligible vedolizumab-naïve patients had an HBI score of 8–18 [moderately to severely active CD] within 7 days before the first dose of vedolizumab and at least one of the following additional criteria: a C-reactive protein [CRP] concentration >2.87 mg/l; ileocolonoscopy with evidence of ≥3 non-anastomotic or ≥10 aphthous ulcerations within 4 months before screening; or a faecal calprotectin concentration >250 µg/g and evidence of CD ulcerations on imaging within 4 months before screening. Vedolizumab-naïve patients were ineligible if they had any prior exposure to natalizumab, efalizumab or rituximab, or had received adalimumab or any investigational or approved non-biological therapy for IBD in the past 30 days, or had received infliximab, certolizumab pegol or any investigational or approved biological agent within the past 60 days.

2.2. Treatment regimen and follow-up

Participants received intravenous vedolizumab 300 mg every 4 weeks. Patients could continue treatment until December 2016 [or March 2016 in countries where the drug is commercially available] or until withdrawal. For C13004, GEMINI 2 and GEMINI 3 patients, the first dose of open-label vedolizumab in GEMINI LTS was given no later than 9 weeks after the last dose of study drug [placebo or vedolizumab] in the prior study.

Patients could continue to receive stable doses of aminosalicylates and corticosteroids [≤30 mg/day of prednisone or equivalent] during GEMINI LTS; however, at sites in the United States, patients with a clinical response to vedolizumab or who, in the opinion of the investigator, demonstrated sufficient improvement in clinical signs and symptoms were tapered off corticosteroids using a defined regimen [Supplementary Material] required by the United States Food and Drug Administration for these investigational studies. Outside of the United States, corticosteroid tapering was recommended, but not required. Immunosuppressives [i.e. azathioprine, mercaptopurine and methotrexate] were permitted at stable doses at sites outside of the United States only.

2.3. Evaluation of safety

Patients were evaluated at least every 4 weeks during treatment. At each visit, including unscheduled visits, the patients' vital signs, concomitant medications and procedures, adverse events and serious adverse events were recorded. Adverse events were reported according to the Medical Dictionary for Regulatory Activities and were defined as any untoward medical occurrence. Serious adverse events were defined as any adverse event that was life-threatening or resulted in death, required hospitalization or was considered an important medical event, or resulted in significant disability or birth defect, or as any occurrence of progressive multifocal leucoencephalopathy [PML]. Infusion-related reactions were defined as any adverse event that occurred on the calendar day of or one calendar day after any study drug infusion or any event defined by the investigator as infusion-related. Disease activity, evaluated using the HBI score, was recorded at weeks 0, 4, 8 and 12, and every 8 weeks thereafter. A urine pregnancy test was performed and a PML symptom checklist was administered before dosing.

2.4. Evaluation of clinical efficacy and health-related quality of life

GEMINI LTS was not primarily designed or powered to investigate specific efficacy-related hypotheses. Accordingly, the efficacy data are presented using descriptive statistical techniques. All available data for enrolled patients in the efficacy population are included. For all change from baseline assessments, baseline score was defined as week 0 of the study in which the patient first participated [i.e. before any study drug treatment].

Evaluation of clinical efficacy included assessment of serum CRP concentration, clinical response [≥3-point decrease from baseline in HBI score] and clinical remission [HBI score ≤4]. For the evaluation of serum CRP concentration, the mean change from baseline was reported; a lower, more negative change indicates improvement. The proportions of patients with response or remission were calculated in two ways: [1] as observed rates using the number of patients at the study visit as the denominator; or [2] with non-responder imputation using the number of enrolled patients as the denominator, based on the principle that patients with missing data were considered failures because of loss of response.

Patient-reported HRQL outcomes were evaluated using the Inflammatory Bowel Disease Questionnaire [IBDQ], European Quality of Life-5 Dimension [EQ-5D] visual analogue scale [VAS], and 36-item Short-Form Health Survey [SF-36] physical component summary [PCS] and mental component summary [MCS] during screening and at weeks 6, 30 and 52 during GEMINI 2, and week 28, every 24 weeks for the first 4 years, and yearly from year 5 onward during GEMINI LTS. Improvements in HRQL measures were reported as the mean change from the baseline score; a higher, more positive change indicated improvement. Increases from baseline score of ≥16 points for IBDQ,[16] ≥3 points for SF-36 MCS and PCS,[16] and ≥9 points for EQ-5D VAS are considered the minimums for clinically meaningful improvement.[17]

2.4.1. Populations studied in the efficacy analyses

For the purpose of this interim efficacy report, we focused on patients with moderately to severely active CD. Patients from C13004 were excluded from the analyses because that study included some patients with mild CD. The efficacy population comprised vedolizumab-naïve, GEMINI 2 and GEMINI 3 patients who received at least one dose of vedolizumab in GEMINI LTS and had at least one post-baseline efficacy assessment analyzed. Data were summarized

from the first assessment in any study through GEMINI LTS according to treatment in the prior study when applicable. Patients from GEMINI 2 who responded to vedolizumab induction therapy [VDZ] and were randomized to receive vedolizumab every 8 weeks [Q8W] or every 4 weeks [Q4W] or placebo [PBO] before open-label vedolizumab every 4 weeks [Q4W] in GEMINI LTS were termed *VDZ/Q8W→Q4W*, *VDZ/Q4W→Q4W* or *VDZ/PBO→VDZ Q4W*, respectively [Table 1]. Patients who completed GEMINI 2 and those who withdrew early formed pre-specified subgroups of the efficacy population.

Long-term efficacy was evaluated for patients who completed GEMINI 2 on the *VDZ/Q8W→Q4W* and *VDZ/Q4W→Q4W* treatment regimens. These patients continued vedolizumab after clinical response at week 6. Data for these patients were combined since both groups received vedolizumab Q4W during GEMINI LTS and since similar treatment outcomes were observed in GEMINI 2[13] for the Q8W and Q4W maintenance dosing groups. Patients in the *VDZ/PBO→VDZ Q4W* group constituted an inherent retreatment population in GEMINI LTS. That is, these patients experienced an interruption in therapy for up to 1 year when receiving placebo during GEMINI 2 maintenance after initially responding to vedolizumab induction. An increase in vedolizumab dosing frequency was analyzed in the *VDZ/Q8W→Q4W* population who responded to vedolizumab induction, but withdrew early from maintenance dosing every 8 weeks – for example because of a loss of response [Supplementary Table 1] – in GEMINI 2 before receiving vedolizumab every 4 weeks in GEMINI LTS.

Patients who had prior TNF antagonist failure or those who were TNF antagonist-naïve formed subpopulations for efficacy assessments. TNF antagonist failure was pre-specified on the case report form during baseline evaluation as patients who had an inadequate response, loss of response or intolerance to prior TNF antagonist therapy. Patients who were TNF antagonist-naïve were identified on the interactive voice response system during screening as those who had no prior exposure to a TNF antagonist. Given that some of the TNF antagonist-exposed patients were not recorded as having failed the drug, the sum of these two subcategories [failure and naïve] did not equal the total enrolled population.

2.5. Immunogenicity

The potential effect of immunogenicity on retreatment was examined in *VDZ/PBO→VDZ Q4W* patients by measuring serum anti-vedolizumab antibody [AVA] concentrations during the time off vedolizumab in the maintenance phase of GEMINI 2. The last dose of vedolizumab during GEMINI 2 for these patients was week 2. Samples for AVA measurement were collected 30 min before dosing during GEMINI 2 at weeks 0, 6, 14, 26, 38 and 52. AVAs were detected by enzyme-linked immunosorbent assay with a drug tolerance of 1 μg/ml.[18] Patients with at least one positive AVA sample were classified as AVA positive.

3. Results

3.1. Patient disposition and vedolizumab exposure

In total, 1349 patients with CD enrolled in the GEMINI LTS study and constituted the safety population [Figure 1a]. The efficacy population comprised 1297 patients with moderately to severely active CD – 700 from GEMINI 2, 372 from GEMINI 3 and 225 vedolizumab-naïve patients [Figure 1]. Of the GEMINI 2 patients analyzed for efficacy, 391 completed the 52-week study and 309 withdrew early. All GEMINI 3 patients enrolled in GEMINI LTS had completed the 10-week study [Figure 1].

At the time of this interim data cut, the median duration of vedolizumab exposure was 616 days [range: 113–1964 days] in the safety population. Discontinuation had occurred in 42% [*n*=569] of the safety population; 20% had discontinued because of lack of efficacy. Within the efficacy population, treatment for 775 [60%] patients was still ongoing. At week 100, 428 patients [33%] were ongoing treatment, but had yet to reach that time point in GEMINI LTS or had missing data for that visit [Figure 1b].

Patient demographics and baseline disease characteristics are provided in Table 2 for the total enrolled CD population except for C13004 patients. Additional patient demographics and baseline disease characteristics are reported in Supplementary Table 2. At the time of entry into GEMINI LTS, the mean HBI score was 8.1 and over half of patients were receiving concomitant corticosteroids and/or immunosuppressives. Patients who completed GEMINI 2 had a much lower baseline HBI score at entry into GEMINI LTS [4.5 ± 3.7] than those who withdrew early from the study [11.3 ± 5.7]. Subpopulations of patients with TNF antagonist failure [63%] or who were TNF antagonist-naïve [33%] demonstrated similar characteristics to the overall population, except for disease duration and history of prior surgery [Table 2]. Patients with TNF antagonist failure had a mean disease duration of 11.6 years, whereas the TNF antagonist-naïve subpopulation had a shorter mean disease duration of 7.0 years. In addition, 49% of TNF antagonist-failure patients had a history of prior surgery versus 26% of TNF antagonist-naïve patients.

3.2. Safety

The interim GEMINI LTS safety profile as of June 27, 2013 [Table 3] was consistent with that previously reported in patients with CD.[13,19] The most common adverse events, occurring in ≥20% of patients, were exacerbation of CD, nasopharyngitis and arthralgia. Adverse events that resulted in study discontinuation occurred in 12% of GEMINI LTS patients. Serious adverse events were reported in 31% of patients, with serious infections occurring in 8% of patients. Infusion-related reactions occurred in 4% of patients. Six patients developed a malignancy [one each of malignant lung neoplasm, colon cancer, basal cell carcinoma, B-cell lymphoma, squamous cell carcinoma and malignant hepatic neoplasm]. No cases of PML were reported.

Table 1. GEMINI LTS subpopulations of patients from GEMINI 2.

Subpopulation	Treatment		
	GEMINI 2 induction [6 weeks][a]	GEMINI 2 maintenance [46 weeks]	GEMINI LTS [100 weeks]
VDZ/PBO→VDZ Q4W	VDZ	PBO	VDZ Q4W
VDZ/Q8W→Q4W	VDZ	VDZ Q8W	VDZ Q4W
VDZ/Q4W→Q4W	VDZ	VDZ Q4W	VDZ Q4W

LTS, long-term safety; PBO, placebo; Q4W, every 4 weeks; Q8W, every 8 weeks; VDZ, vedolizumab.
[a]Includes patients from Cohort 1 and Cohort 2.

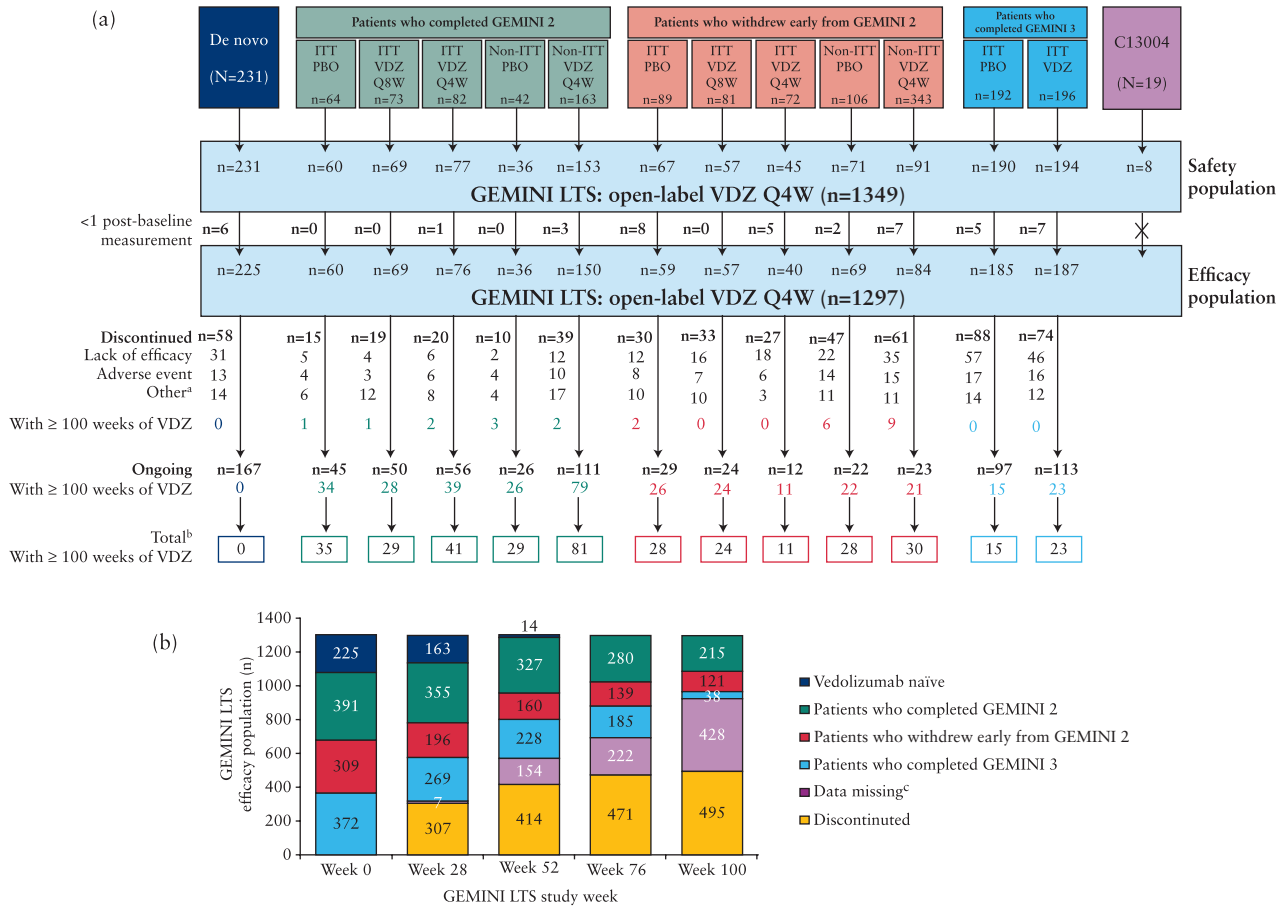

Figure 1. Distribution of the CD patient population in the GEMINI LTS study. [a] Patient disposition. In total, 1349 patients with CD entered GEMINI LTS. Patients who completed GEMINI 2 and those who withdrew early are shown according to treatment received during the maintenance phase. Patients who completed the 10-week GEMINI 3 study are shown according to induction treatment received. The efficacy population [*n*=1297] is a subset of the safety population in which the patient must have had moderately to severely active CD on enrolment [i.e. excludes patients from C13004] as well as baseline and at least one post-baseline disease activity measurements. [b]The efficacy population over time. [a]Includes patients who discontinued for the following reasons: protocol violation, withdrawal of consent, lost to follow-up, and other. [b]Sum of discontinued and ongoing patients with ≥100 weeks of open-label vedolizumab treatment. [c]Includes patients who are still ongoing, but have yet to reach 100 weeks of vedolizumab treatment during GEMINI LTS. CD, Crohn's disease; ITT, intent-to-treat; LTS, long-term safety; PBO, placebo; Q4W, every 4 weeks; Q8W, every 8 weeks; VDZ, vedolizumab.

3.3. Long-term efficacy

Disease activity using the HBI score was analyzed for the evaluation of clinical efficacy [Figure 2]. For the vedolizumab-naïve population, the percentage of patients with an HBI score of >7 was lowered from 99% [*n*=222/225] at study entry to 24% [*n*=40/164] after 28 weeks of treatment; 57% [*n*=94/164] of patients were in remission [Figure 2a]. Few vedolizumab-naïve patients [*n*=14] had reached 52 weeks of exposure at the time of the interim analysis [Figure 1b and Figure 2a]. Vedolizumab-naïve patients also experienced improvements in HRQL after 28 weeks of treatment as measured by changes in IBDQ, EQ-5D VAS, SF-36 PCS and SF-36 MCS scores from baseline [Supplementary Table 3]. Among vedolizumab-naïve patients who had previously failed a TNF antagonist or who were TNF antagonist-naïve, 49% [*n*=55/113] and 78% [*n*=35/45], respectively, were in remission after 28 weeks of vedolizumab treatment [Supplementary Table 4].

Among patients who were previously exposed to vedolizumab in the GEMINI 2 and GEMINI 3 trials, a reduction in disease activity was sustained with long-term open-label vedolizumab therapy [Figure 2b and 2c]. After an additional 100 weeks [week 152] of treatment, 74% [*n*=156/212] of all patients who completed GEMINI 2 were in remission [Figure 2b], including 66% [*n*=75/113] of those with prior TNF antagonist failure and 82% [*n*=69/84] of TNF-antagonist naïve patients [Supplementary Table 4]. Improvements were similar among GEMINI 3 patients overall and among those with prior TNF antagonist failure or who were TNF antagonist-naïve, with 69% [*n*=127/184], 67% [*n*=91/136] and 74% [*n*=34/46] in remission after a total exposure of 86 weeks, respectively [Figure 2c and Supplementary Table 4]. Few GEMINI 3 patients [*n*=38] had reached 110 weeks of exposure [Figure 1b and Figure 2c].

For further evaluation of long-term clinical efficacy, clinical response, remission, CRP concentration and HRQL were evaluated specifically for the subgroup of patients who received 152 weeks of continuous vedolizumab treatment. These patients responded to vedolizumab at week 6 of GEMINI 2 and completed maintenance dosing of vedolizumab every 8 or every 4 weeks before receiving open-label vedolizumab every 4 weeks during GEMINI LTS [*VDZ/Q8W→Q4W* and *VDZ/Q4W→Q4W* populations combined]. The mean change from baseline HBI score and 95% confidence intervals for GEMINI 2 patients who continued vedolizumab treatment in GEMINI LTS are shown in Supplementary Tables 5–7. In contrast to the population represented in Figure 2b, the following analyses

Table 2. Patient demographics and baseline disease characteristics.

Characteristic	By study				By TNF antagonist exposure[a]		All studies[a]
	GEMINI 2		GEMINI 3	Vedolizumab-naïve	TNF antagonist-failure	TNF antagonist-naïve	Total
	Patients who completed [*n*=395]	Patients who withdrew early [*n*=331]	Patients who completed [*n*=384]	[*n*=231]	[*n*=848]	[*n*=447]	[*n*=1341]
Age [years], mean ± SD[b]	37.6 ± 12.5	36.9 ± 11.9	38.3 ± 12.9	38.0 ± 13.8	38.1 ± 12.8	36.9 ± 12.4	37.7 ± 12.7
Sex [male], *n* [%]	192 [49]	150 [45]	168 [44]	94 [41]	345 [41]	238 [53]	604 [45]
BMI [kg/m^2], mean ± SD	25.0 ± 5.9	24.2 ± 6.1	24.6 ± 5.8	–[c]	25.0 ± 6.1	23.9 ± 5.4	24.6 ± 5.9
Current smoker, *n* [%][d]	113 [29]	91 [27]	111 [29]	48 [21]	218 [26]	131 [29]	363 [27]
Duration of disease [years], mean ± SD[e]	9.2 ± 8.0	10.4 ± 8.0	10.4 ± 8.4	10.7 ± 9.0	11.6 ± 8.4	7.0 ± 7.1	10.1 ± 8.3
HBI score, mean ± SD	4.5 ± 3.7	11.3 ± 5.7	7.4 ± 4.1	11.2 ± 2.8	8.9 ± 4.9	6.7 ± 5.3	8.1 ± 5.1
Disease location, *n* [%][d]							
Ileum only	65 [16]	60 [18]	60 [16]	33 [14]	122 [14]	87 [19]	218 [16]
Colon only	112 [28]	85 [26]	94 [24]	53 [23]	216 [25]	113 [25]	344 [26]
Ileocolonic	218 [55]	186 [56]	230 [60]	145 [63]	510 [60]	247 [55]	779 [58]
CRP [mg/l], mean ± SD	9.3 ± 12.2	17.2 ± 21.4	14.7 ± 17.7	18.5 ± 26.9	15.7 ± 22.0	11.9 ± 15.2	14.2 ± 19.7
Faecal calprotectin [µg/g], mean ± SD[d]	1053 ± 1476	1423 ± 2115	1202 ± 1961	1097 ± 1507	1302 ± 2005	1024 ± 1416	1195 ± 1804
History of prior surgery, *n* [%][d]	147 [37]	147 [44]	164 [43]	102 [44]	419 [49]	117 [26]	560 [42]
History of fistulizing disease, *n* [%][d]	141 [36]	135 [41]	133 [35]	87 [38]	351 [41]	124 [28]	496 [37]
History of EIMs, *n* [%][d]	322 [82]	286 [86]	315 [82]	201 [87]	738 [87]	348 [78]	1124 [84]
Concomitant medications, *n* [%]							
CS	44 [11]	161 [49]	202 [53]	136 [59]	382 [45]	150 [34]	543 [40]
IS	108 [27]	82 [25]	113 [29]	46 [20]	166 [20]	171 [38]	349 [26]
CS and IS	11 [3]	42 [13]	59 [15]	29 [13]	80 [9]	57 [13]	141 [11]
Neither CS nor IS	254 [64]	130 [39]	128 [33]	78 [34]	380 [45]	183 [41]	590 [44]
Prior TNF antagonist therapy, *n* [%][d]	194 [49]	227 [69]	293 [76]	180 [78]	848 [100]	0	894 [67]
Prior TNF antagonist failure, *n* [%][d]	169 [43]	218 [66]	290 [76]	171 [74]	848 [100]	0	848 [63]
Prior IS and TNF antagonist failure, *n* [%][d]	147 [37]	184 [56]	242 [63]	119 [52]	692 [82]	0	692 [52]

BMI, body mass index; CRP, C-reactive protein; CS, corticosteroid; EIM, extraintestinal manifestation; HBI, Harvey-Bradshaw Index; IS, immunosuppressive; SD, standard deviation; TNF, tumour necrosis factor.

[a]Excludes patients from C13004.

[b]Age was defined as [1+first dose date in GEMINI LTS–birth date]/365.25.

[c]BMI was not calculated for vedolizumab-naïve patients because height information was not collected.

[d]Collected on the case report form at baseline of GEMINI 2 or GEMINI 3 for rollover patients and at baseline of GEMINI LTS study for vedolizumab-naïve patients.

[e]Duration of disease is defined as [1+first dose date in GEMINI LTS–diagnosis date]/365.25.

Table 3. Summary of adverse events in the safety population of GEMINI LTS.

	Safety population [*n*=1349]
Category	Patients, *n* [%]
Any adverse event	1246 [92]
Drug-related adverse event[a]	571 [42]
Adverse event resulting in study discontinuation[b]	156 [12]
Serious adverse event	420 [31]
Serious infection adverse event	113 [8]
Drug-related serious adverse event[a]	70 [5]
Serious adverse event resulting in study discontinuation[b]	96 [7]
Death	4 [<1]
Malignancy	6 [<1]
Progressive multifocal leucoencephalopathy	0
Infusion-related reactions[c]	59 [4]
Common adverse events reported by ≥7% of patients	
Crohn's disease	356 [26]
Nasopharyngitis	288 [21]
Arthralgia	267 [20]
Headache	259 [19]
Abdominal pain	245 [18]
Nausea	187 [14]
Pyrexia	172 [13]
Upper respiratory tract infection	156 [12]
Vomiting	145 [11]
Diarrhoea	137 [10]
Fatigue	122 [9]
Sinusitis	110 [8]
Back pain	108 [8]
Gastroenteritis	105 [8]
Cough	98 [7]
Bronchitis	94 [7]
Influenza-like illness	91 [7]
Urinary tract infection	91 [7]
Dizziness	88 [7]

LTS, long-term safety.
[a]Relation to drug determined by investigator.
[b]Includes events requiring action taken regarding study drug.
[c]Defined by investigator.

exclude both non-ITT treatment groups and the ITT population of patients who were randomized to placebo maintenance during GEMINI 2. Clinical response was reported in 94% [*n*=113/120] and 97% [*n*=68/70] of patients with data available after 104 and 152 weeks of continuous vedolizumab treatment, respectively [Figure 3a]. Corresponding proportions of patients were in remission with 83% [*n*=100/120] at week 104 and 89% [*n*=62/70] at week 152 [Figure 3b]. It should be noted that the patients who had discontinued from the study were excluded in the analyses. Alternatively, when including all patients without data as treatment failures, rates of response after 104 and 152 weeks of vedolizumab treatment were 78% [*n*=113/145] and 47% [*n*=68/145], respectively, and rates of remission were 69% [*n*=100/145] and 43% [*n*=62/145], respectively [Figure 3c and 3d]. Regardless of GEMINI 2 maintenance dosing group, similar results were observed among those who received vedolizumab every 8 weeks or every 4 weeks before initiating treatment in GEMINI LTS [Supplementary Figure 2]. Among patients with prior TNF antagonist failure and those who were TNF antagonist-naïve, clinical response rates were similar to those observed with the total population [Figure 3a and 3c]. Rates of clinical remission were numerically higher in patients who were TNF antagonist-naïve [Figure 3b and 3d]

A reduction in CRP levels, measured by the mean change from baseline, among patients with available data was observed in the total and TNF antagonist subpopulations [Figure 4]. That is, the magnitude of improvement increased with longer exposure. Furthermore, HRQL scores achieved after maintenance therapy in GEMINI 2 were sustained in GEMINI LTS. After 80 weeks of exposure – when HRQL was first assessed in GEMINI LTS – the mean changes from baseline HRQL scores were >51 for IBDQ, >23 for EQ-5D VAS, >9 for SF-36 PCS and >10 for SF-36 MCS [Figure 5]. Smaller improvements in IBDQ and SF-36 PCS scores were consistently observed for TNF antagonist-naïve patients than for patients with prior TNF antagonist failure [Figure 5a and 5c], probably because TNF antagonist-naïve patients had higher scores at baseline.

3.4. Efficacy following retreatment

Patients who responded to vedolizumab during GEMINI 2 induction and were randomized to placebo maintenance at week 6 formed an inherent retreatment population upon re-initiation of vedolizumab during GEMINI LTS [*VDZ/PBO→VDZ Q4W*]. These patients experienced up to 1 year of interrupted vedolizumab therapy [median duration, 285 days] during GEMINI 2 before retreatment in GEMINI LTS. For patients who withdrew early from GEMINI 2 [*n*=59], response and remission rates improved upon retreatment with vedolizumab to 56% [*n*=33/59] and 48% [*n*=28/59], respectively, at week 28 of GEMINI LTS (up from 42% [*n*=25/59] and 9% [*n*=5/59] at week 0 of GEMINI LTS) [Figure 6]. Similar improvements were observed among patients with TNF antagonist failure or who were TNF antagonist-naïve [Figure 6]. However, rates of response and remission were generally higher for patients who were TNF antagonist-naïve within the first year of retreatment [Figure 6]. Among *VDZ/PBO→VDZ Q4W* patients who completed the 46-week GEMINI 2 maintenance phase on placebo [*n*=60], re-initiation of treatment resulted in 68% [*n*=41/60] of patients with response and 63% [*n*=38/60] in remission at week 52 of GEMINI LTS (vs 77% [*n*=46/60] and 53% [*n*=32/60] at week 0 of GEMINI LTS) [Supplementary Figure 3].

Since *VDZ/PBO→VDZ Q4W* patients were initially exposed to vedolizumab before experiencing up to 1 year of interrupted therapy, AVAs were analyzed in this population – in those who completed GEMINI 2 and those who withdrew early – during the GEMINI 2 maintenance phase to examine the association between length of interruption of therapy and development of immunogenicity. When the duration of interrupted therapy was divided into quartiles, the percentage of patients who developed AVAs was consistent regardless of time off drug [Supplementary Table 8].

3.5. Effects of increased dosing frequency

The vedolizumab dosing frequency in patients who received vedolizumab every 8 weeks during GEMINI 2 maintenance was increased to vedolizumab every 4 weeks during GEMINI LTS [*VDZ/Q8W→Q4W*]. Within this subpopulation, patients who withdrew early from GEMINI 2 were analyzed to evaluate the efficacy of an increase in dosing frequency. Specifically, 57 patients [45%] receiving vedolizumab every 8 weeks during GEMINI 2 withdrew from the study early because of sustained non-response, disease worsening or need for rescue medication before enrolling in GEMINI LTS [Figure 1 and Supplementary Table 1]. When patients enrolled in GEMINI LTS, 39% [*n*=22/57] were in clinical response and 4% [*n*=2/57] were in remission. By week 28, these

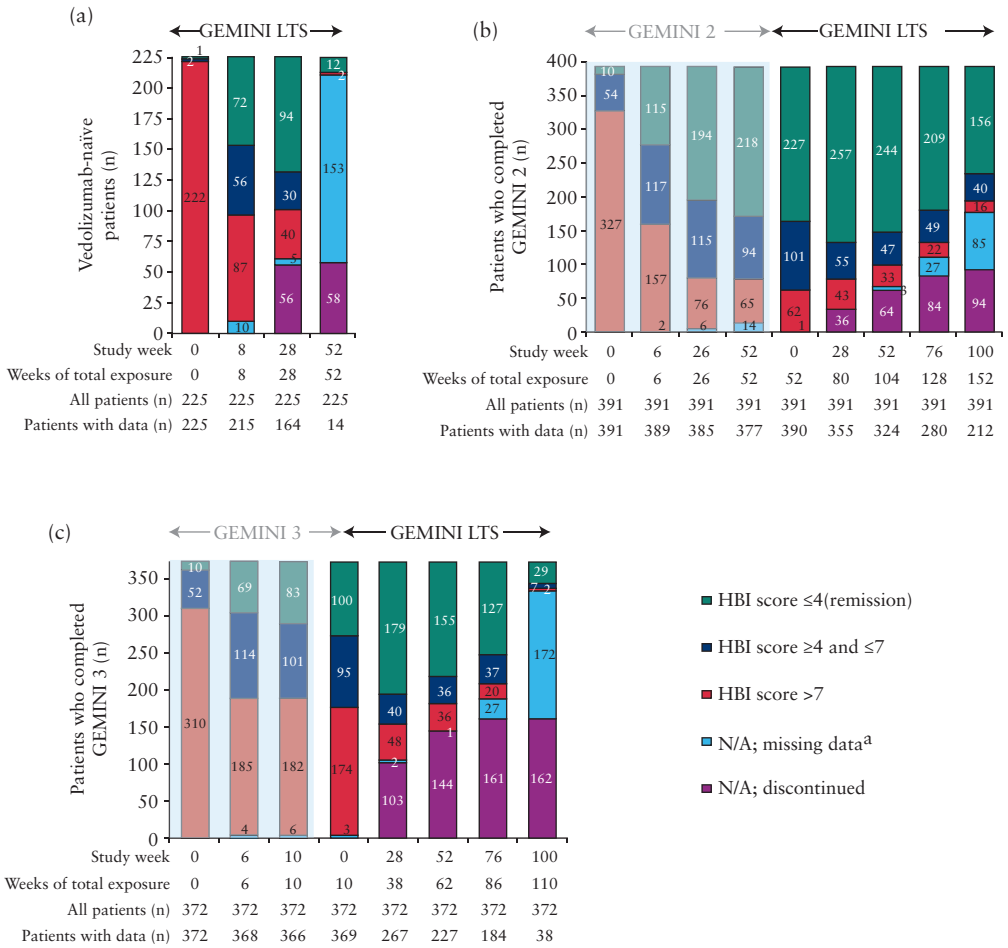

Figure 2. Distribution of disease activity. Numbers of patients with an HBI score ≤4, an HBI score >4 and ≤7, or an HBI score >7 during GEMINI 2 or GEMINI 3 and GEMINI LTS are depicted. Disease activity is shown in the population of [a] vedolizumab-naïve patients, [b] patients who completed GEMINI 2 and [c] patients who completed GEMINI 3. [a]Includes patients who are still ongoing, but have yet to reach 100 weeks of vedolizumab treatment during GEMINI LTS. HBI, Harvey-Bradshaw Index; LTS, long-term safety; N/A, not available.

proportions had increased to 54% [*n*=31/57] and 23% [*n*=13/57], respectively [Figure 7]. Corresponding values at week 100 were 35% [*n*=20/57] with clinical response and 19% [*n*=11/57] in clinical remission. A similar trend in efficacy was observed with increased dosing frequency regardless of prior TNF antagonist exposure [Figure 7].

4. Discussion

GEMINI LTS was designed to evaluate the long-term safety of vedolizumab in patients with IBD. However, it also allowed for exploratory analysis of long-term clinical efficacy because efficacy information was systematically captured at each study visit. Although not powered or designed to assess efficacy endpoints, this study represents the largest cohort of CD patients treated with vedolizumab and provides valuable information regarding continuous exposure for up to 152 weeks [approximately 3 years], increased dosing frequency and interruption of treatment.

Until recently, long-term maintenance treatment options for patients with CD were limited to TNF antagonists and/or immunosuppressive agents. These approaches were hampered by concerns over waning efficacy, immunogenicity and unwanted and, sometimes serious, side effects, such as the development of opportunistic infections, non-melanoma skin cancers and lymphoma.[1,2] Therefore, the need to evaluate therapies that are efficacious and well-tolerated remains. The results presented here demonstrate the durability of vedolizumab treatment in patients initially responding to vedolizumab, including vedolizumab-naïve, TNF antagonist-naïve and TNF antagonist-experienced patients. These benefits included sustainability of clinical response, clinical remission, long-term HRQL improvements and suppression of the inflammatory biomarker CRP.

After response at week 6, clinical remission was observed in 74% of 145 patients after 52 weeks of vedolizumab maintenance, with continued treatment resulting in 83% of 120 and 89% of 70 patients after 104 and 152 weeks, respectively. However, patients who had discontinued the study, for example because of lack of efficacy, were not included in this analysis. To address this limitation, response and remission rates were conservatively calculated with patients with missing data considered treatment failures: among the enrolled population, 71% of patients were in remission at week 52, 69% at week 104 and 43% at week 152. However, a limitation of this latter approach is that a large proportion of patients had not completed 152 weeks of treatment at the time of this interim analysis and may have been misrepresented as treatment failures. Endoscopy was also not prospectively evaluated during the study, precluding evaluation of mucosal healing. Mucosal healing in CD patients treated with vedolizumab is currently being investigated in a large prospective multicentre study [ClinicalTrials.gov ID NCT02425111], and results

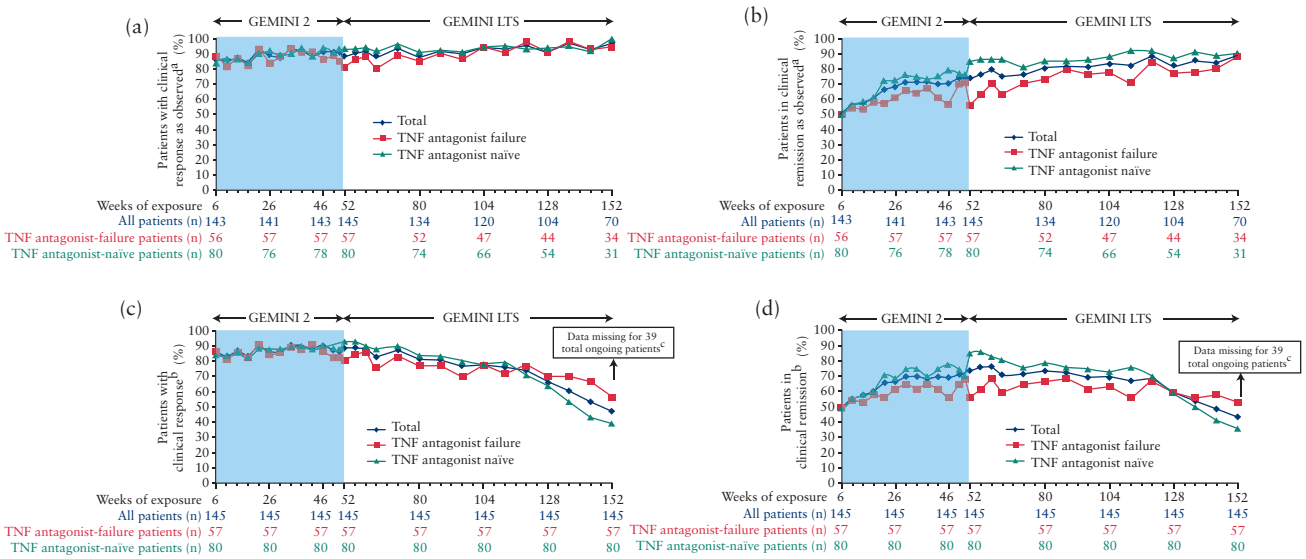

Figure 3. Clinical response and remission among patients who completed double-blind vedolizumab maintenance in GEMINI 2. Percentages of patients with [a] clinical response and in [b] clinical remission as observed[a] overall and by TNF antagonist exposure were assessed by changes in HBI score[d] and are plotted over time without imputation for missing data. Percentages of patients with [c] clinical response and in [d] clinical remission are plotted over time with missing data counted as failure[b]. The number of patients evaluated at each time point is listed below each graph: for panels [a] and [b], these are the number of patients at the study visit, and for panels [c] and [d], these are the number of patients enrolled in the study. [a]Percentages were calculated as observed [i.e. no imputation for missing data]. [b]Percentages were calculated with missing data considered treatment failures. [c]Ongoing patients in the total population with missing data who, in large part, have yet to reach 100 weeks of vedolizumab treatment during GEMINI LTS. [d]Mean change from baseline HBI score and 95% CI are reported in Supplementary Tables 5–7. CI, confidence interval; HBI, Harvey-Bradshaw Index; LTS, long-term safety; TNF, tumour necrosis factor.

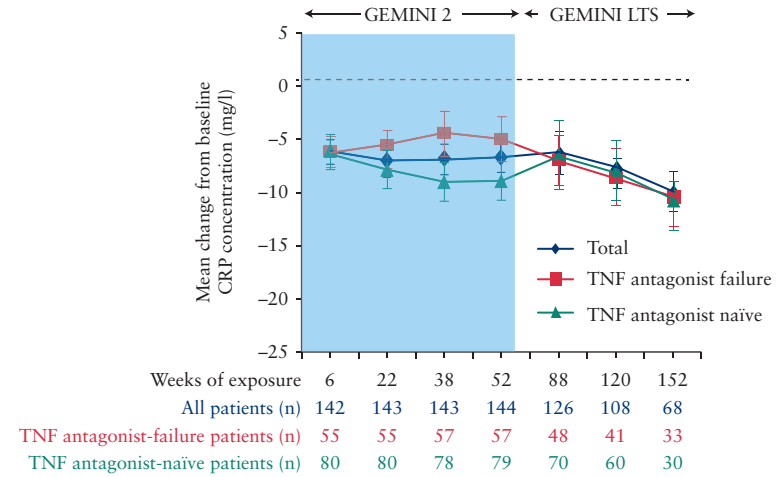

Figure 4. Mean change from baseline CRP concentration among patients who completed double-blind vedolizumab treatment in GEMINI 2. Mean change from baseline CRP concentrations [mg/l] are plotted with standard error for patients who completed GEMINI 2. A lower CRP concentration or a greater reduction from baseline indicates improvement. The number of patients with data available at each time point is listed below each graph. CRP, C-reactive protein; LTS, long-term safety; TNF, tumour necrosis factor.

are expected in 2017. However, observed improvements in serum CRP concentration, a quantifiable measure of inflammation, and HRQL provide further evidence to support the long-term efficacy of vedolizumab.

In any chronic disease, patients may need to interrupt therapy for medical or non-medical reasons. The concern with interruption of therapy is the potential for the development of anti-drug antibodies and subsequent loss of response.[20] The efficacy of vedolizumab upon retreatment was evaluated in patients who responded to vedolizumab induction in GEMINI 2 and received double-blind placebo maintenance before re-initiation of vedolizumab in GEMINI LTS. Some of these patients lost response after switching to placebo and are included in the population who withdrew early from GEMINI 2, while others appeared to do well while receiving placebo and completed the 52-week GEMINI 2 study. During the period of time between vedolizumab doses, while patients were receiving placebo, AVAs were detectable in a similar proportion of patients regardless of the duration of time since the last vedolizumab dose. It is possible that the relatively long terminal elimination half-life of vedolizumab [25 days][18] provides some protection from sensitization.[21] We report that patients with up to 1 year of interrupted therapy [median duration 285 days] experienced clinical benefits following retreatment in GEMINI LTS. In

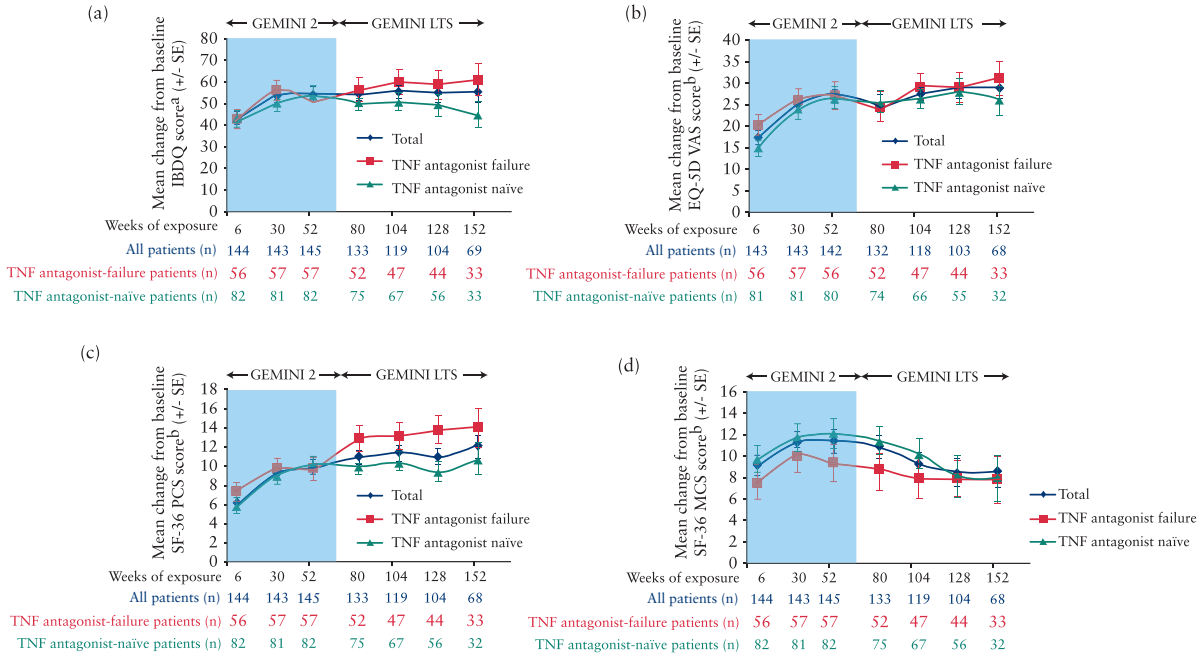

Figure 5. Health-related quality of life among patients who completed double-blind vedolizumab treatment in GEMINI 2. Mean change from baseline scores were plotted for [a] IBDQ, [b] EQ-5D VAS, [c] SF-36 PCS and [d] SF-36 MCS according to weeks of exposure to vedolizumab during GEMINI 2 and GEMINI LTS for the combined population of vedolizumab-treated ITT patients [*VDZ/Q8W→Q4W* and *VDZ/Q4W→Q4W*] overall and by TNF antagonist treatment history. For all populations, the number of patients with data available at each study visit is listed below each graph. [a]Total IBDQ score can range from 32 to 224; a higher score indicates better HRQL. [b]EQ-5D VAS, SF-36 PCS and SF-36 MCS scores can range from 0 to 100; a higher score indicates better HRQL. EQ-5D, European Quality of Life-5 Dimension; HRQL, health-related quality of life; IBDQ, Inflammatory Bowel Disease Questionnaire; ITT, intent-to-treat; LTS, long-term safety; MCS, mental component score; PCS, physical component score; Q4W, every 4 weeks; Q8W, every 8 weeks; SE, standard error; SF-36, 36-item Short-Form Health Survey; TNF, tumour necrosis factor; VAS, visual analogue scale; VDZ, vedolizumab.

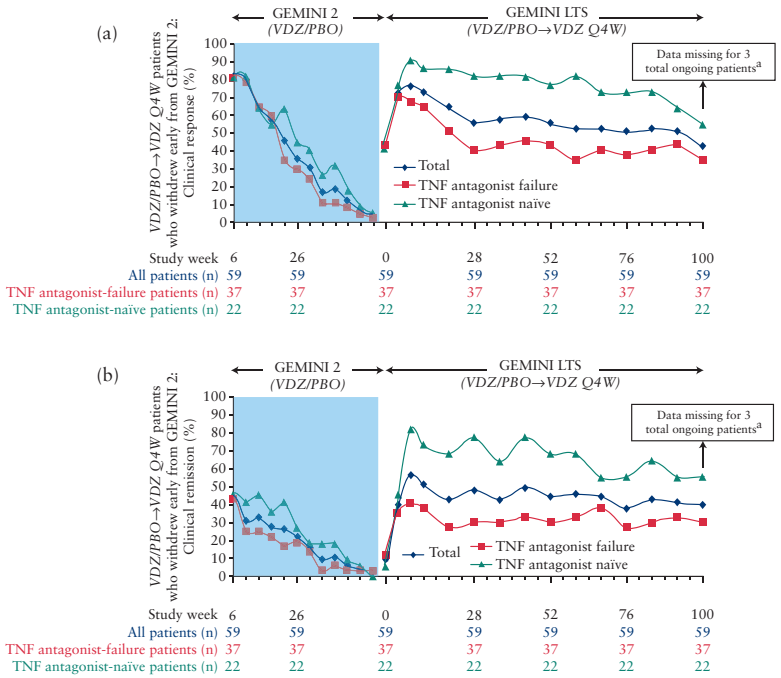

Figure 6. Clinical response and remission following retreatment. Patients in the *VDZ/PBO→VDZ Q4W* population who had response to vedolizumab at week 6 of GEMINI 2 and were randomized to placebo maintenance before retreatment with vedolizumab in GEMINI LTS were evaluated. In the population who withdrew early from GEMINI 2,[b] percentages of [a] clinical response and [b] clinical remission were assessed by changes in HBI score[c] with missing data counted as failure and are plotted over time. The number of patients evaluated at each time point [i.e. the number of patients enrolled in the study] is listed below each graph. [a]Ongoing patients in the total population with missing data who, in large part, have yet to reach 100 weeks of vedolizumab treatment during GEMINI LTS. [b]Corresponding data for the population who completed GEMINI 2 are shown in Supplementary Figure 3. [c]Mean change from baseline HBI score and 95% CI are reported in Supplementary Tables 5–7. CI, confidence interval; HBI, Harvey-Bradshaw Index; LTS, long-term safety; PBO, placebo; Q4W, every 4 weeks; TNF, tumour necrosis factor; VDZ, vedolizumab.

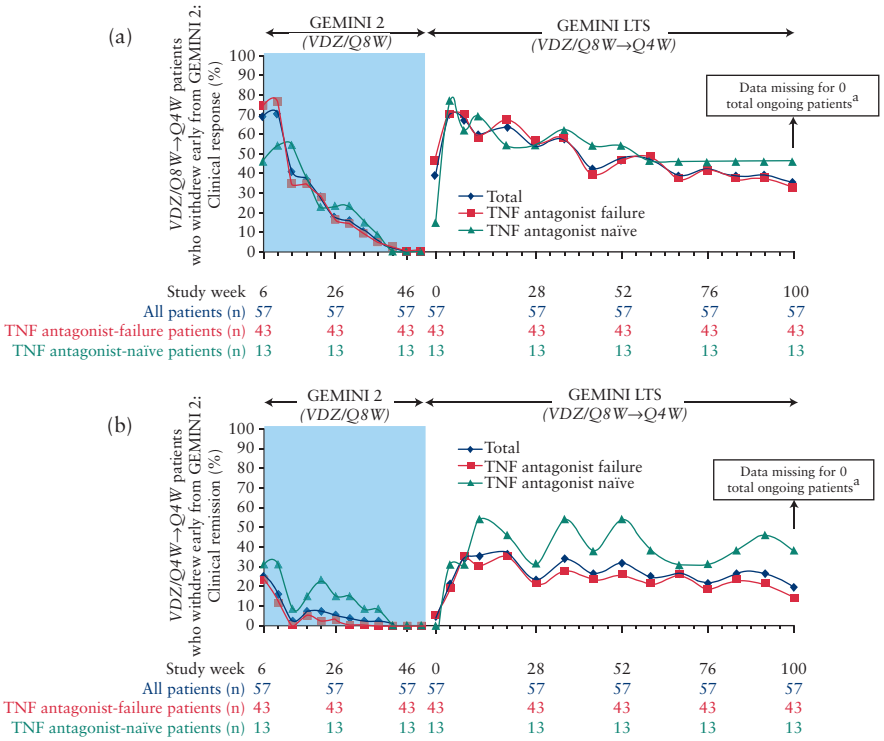

Figure 7. Clinical response and remission following increased dosing frequency. Patients in the *VDZ/Q8W→Q4W* population who had response to vedolizumab at week 6 of GEMINI 2 and were randomized to vedolizumab Q8W maintenance before their dose was intensified to vedolizumab Q4W in GEMINI LTS were evaluated. In the population who withdrew early from GEMINI 2, percentages of [a] clinical response and [b] clinical remission were assessed by changes in HBI score[b] with missing data counted as failure and are plotted over time. The response and remission rates were higher at week 0 of GEMINI LTS than they were at week 46 of GEMINI 2 because some of these patients received rescue medication after withdrawal from GEMINI 2. The number of patients evaluated at each time point is listed below each graph [i.e. the number of patients enrolled in the study]. [a]Ongoing patients in the total population with missing data who, in large part, have yet to reach 100 weeks of vedolizumab treatment during GEMINI LTS. [b]Mean change from baseline HBI score and 95% CI are reported in Supplementary Tables 5–7. CI, confidence interval; HBI, Harvey-Bradshaw Index; LTS, long-term safety; Q4W, every 4 weeks; Q8W, every 8 weeks; TNF, tumour necrosis factor; VDZ, vedolizumab.

particular, some patients who responded to vedolizumab and then lost response after stopping treatment were effectively 'rescued' by retreatment in a well-tolerated and efficacious manner.

Of the GEMINI LTS population, 57 patients had terminated GEMINI 2 early because of sustained non-response, disease worsening or need for rescue medication despite a response to vedolizumab induction and maintenance dosing every 8 weeks. Compared with patients who completed GEMINI 2 [*n*=69], patients who withdrew early may hypothetically represent a population with more refractory disease. In general, these patients experienced improved clinical outcomes following an increase to every-4-week dosing, which were maintained with continued treatment. This observation suggests that the increase to an every-4-week dosing regimen may be useful as a 'rescue' treatment for some patients who lose response while on 8-weekly dosing. Notably, pharmacokinetic data collected during GEMINI 2 previously showed that, within the every-8-week dosing group, patients who terminated early from GEMINI 2 had numerically lower predicted vedolizumab serum concentrations, based on population pharmacokinetic modelling, at week 52 [32.7 µg/l, range: 10.6–120.4] than those who completed GEMINI 2 [39.5 µg/l, range: 20.7–120.7]; the difference was not statistically significant.[22] Although administration of vedolizumab every 4 weeks is not a currently approved regimen in some countries,[23] these results suggest that a subset of patients may benefit from an increase in dosing frequency. This possibility requires evaluation in future adequately controlled trials.

Details of the interim safety data for GEMINI LTS have been published in a separate safety summary.[19] Overall, the safety profile of vedolizumab was consistent with what has been previously reported in the GEMINI 2 maintenance study.[13] In both GEMINI 2 and GEMINI LTS, the most common adverse event was exacerbation of disease.[13] Serious adverse events were reported in 31% of patients, and serious infections, in particular, occurred in 8% of patients. Malignancy occurred infrequently with <1% of patients experiencing any cancer. Importantly, no cases of PML have been reported to date.[19] Although post-marketing risk assessments are in progress to monitor the occurrence of enteric adverse events and PML, as well as long-term adverse events, the low risk of systemic infections in the present study and the absence of any PML cases to date are reassuring and help to support the gut-selective mechanism of action of vedolizumab.

In conclusion, this preliminary analysis of GEMINI LTS data shows that long-term vedolizumab treatment is efficacious for patients with moderately to severely active CD. This report represents the largest clinical data set for long-term exposure of vedolizumab and highlights the use of vedolizumab in common real-world situations such as retreatment after an interruption of therapy, treatment for patients with prior TNF antagonist failure and treatment for those who are biologic-naïve. Finally, patients who lose response during vedolizumab maintenance may benefit from an increase in dosing frequency; however, future, prospective studies are warranted to confirm the efficacy of such a strategy and to identify which patients might benefit.

Funding

The clinical study was funded by Millennium Pharmaceuticals, Inc. [d/b/a Takeda Pharmaceuticals International Co.].

Conflict of Interest

Severine Vermeire has received financial support for research from Merck, AbbVie, UCB; and has served as a consultant for Pfizer, AbbVie, Merck, Takeda, UCB, Shire, Ferring Pharmaceuticals, Genentech/Roche. Edward V. Loftus Jr has received financial support for research from AbbVie, Janssen, UCB, Takeda, Pfizer, GlaxoSmithKline, Amgen, Bristol-Myers Squibb, Genentech, Robarts Clinical Trials, Gilead, Receptos; and has served as a consultant for AbbVie, Janssen, UCB, Takeda, Immune Pharmaceuticals, Celgene, MedImmune, Theradiag, Genentech, Seres Health, Sun Pharmaceuticals, Bristol-Myers Squibb. Jean-Frédéric Colombel has served as a consultant, an advisory board member, or a speaker for AbbVie, AB Science, Amgen, Bristol-Myers Squibb, Celltrion, Danone, Ferring Pharmaceuticals, Genentech, Giuliani S.p.A., Given Imaging, Janssen, Immune Pharmaceuticals, MedImmune, Merck & Co., Millennium Pharmaceuticals, Inc., Neovacs, Nutrition Science Partners Ltd, Pfizer, Prometheus Laboratories, Protagonist, Receptos, Sanofi, Schering-Plough Corporation, Second Genome, Shire, Takeda, Teva Pharmaceuticals, TiGenix, UCB, Vertex Pharmaceuticals, Dr August Wolff GmbH & Co. Brian G. Feagan has received financial support for research from Abbott/AbbVie, Amgen, AstraZeneca, Bristol-Myers Squibb [BMS], Janssen Biotech [Centocor], JnJ/Janssen, Roche/Genentech, Millennium, Pfizer, Receptos, Santarus, Sanofi, Tillotts Pharma AG, UCB; has received lecture fees from Abbott/AbbVie, JnJ/Janssen, Takeda, Warner Chilcott, UCB; served as a consultant for Abbott/AbbVie, ActoGeniX, Albireo Pharma, Amgen, AstraZeneca, Avaxia Biologics, Avir Pharma, Axcan, Baxter Healthcare Corp., Biogen Idec, Boehringer Ingelheim, Bristol-Myers Squibb, Calypso Biotech, Celgene, Elan/Biogen, enGene, Ferring Pharmaceuticals, Roche/Genentech, GiCare Pharma, Gilead, Given Imaging, GSK, Ironwood Pharmaceuticals, Janssen Biotech [Centocor], JnJ/Janssen, Kyowa Hakko Kirin Co., Ltd, Lexicon, Lilly, Merck, Millennium, Nektar, Novo Nordisk, Pfizer, Prometheus Therapeutics and Diagnostics, Protagonist, Receptos, Salix Pharmaceuticals, Serono, Shire, Sigmoid Pharma, Synergy Pharma Inc., Takeda, Teva Pharmaceuticals, TiGenix, Tillotts Pharma AG, UCB, Vertex Pharmaceuticals, Warner Chilcott, Wyeth, Zealand, Zyngenia; and has served on advisory boards for Abbott/AbbVie, Amgen, AstraZeneca, Avaxia Biologics, Bristol-Myers Squibb, Celgene, Centocor, Elan/Biogen, Ferring Pharmaceuticals, JnJ/Janssen, Merck, Novartis, Novo Nordisk, Pfizer, Prometheus Laboratories, Protagonist, Salix Pharmaceuticals, Takeda, Teva Pharmaceuticals, TiGenix, Tillotts Pharma AG, UCB; and holds a directorship as CEO and Senior Scientific Director, Robarts Clinical Trials, Inc., Western University, London, Ontario. William J. Sandborn has received financial support for research from Janssen, AbbVie, Pfizer, Amgen, Genentech; has received lecture fees from AbbVie, Takeda; and has served as a consultant to Janssen, AbbVie, Pfizer, Amgen, Genentech, Takeda. Bruce E. Sands has served as a consultant for Abbott Immunology, AbbVie, Amgen, Astellas Pharma Global Development, AstraZeneca, Avaxia Biologics, Baxter Healthcare, Bracco Diagnostics Inc., Bristol-Myers Squibb, Creative Educational Concepts, Curatio CME Institute/Axis Healthcare Communications, Sumitomo Dainippon Pharma, Dyax Corporation, Elan Pharmaceuticals, Emmi Solutions LLC, GlaxoSmithKline Inc., Glaxo Wellcome, IMEDEX, Immune Pharmaceuticals, Janssen Biotech, Kyowa Hakko Kirin Pharma, Inc., Luitpold Pharmaceuticals, Mechanisms in Medicine, Pfizer, Prometheus Laboratories, PureTech Ventures, LLC, Sigmoid Pharma, Takeda Pharmaceuticals International Company, Teva Pharmaceutical Industries; has received financial support for research from Prometheus Laboratories, Pfizer, Janssen Biotech, Bristol-Myers Squibb, AbbVie, MedImmune; has served as a speaker for Creative Educational Concepts; and is a shareholder of Avaxia Biologics. Silvio Danese has served as a consultant, an advisory board member, or a review panel member for MSD, Schering-Plough Corporation, Abbott Laboratories, UCB, Ferring Pharmaceuticals, Cellerix, Takeda Pharmaceutical Company Ltd, Nycomed, Actelion, AstraZeneca, Danone Research, Chiesi, Novo Nordisk, Cosmo Technologies Ltd., Celltrion, Pharmacosmos, Alfa Wassermann, Genentech, Grünenthal, Pfizer, TiGenix, Vifor, Johnson & Johnson. Geert R. D'Haens has served as a consultant advisor for AbbVie, Ablynx, Amakem, AM-Pharma, Avaxia Biologics, Biogen, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Celltrion, Cosmo, Covidien, Dr Falk Pharma, enGene, Ferring Pharmaceuticals, Galapagos, Gilead, GlaxoSmithKline, Hospira, Immunic, Johnson & Johnson, Lycera, Medimetrics, Millennium/Takeda, Mitsubishi Pharma, Merck Sharp & Dohme, Mundipharma, Novo Nordisk, Pfizer, Prometheus Laboratories/Nestle, Protagonist, Receptos, Robarts Clinical Trials, Salix Pharmaceuticals, Sandoz, Setpoint, Shire, Teva, TiGenix, Tillotts Pharma AG, TopiVert, Versant, Vifor; and received speaker fees from AbbVie, Ferring Pharmaceuticals, Johnson & Johnson, Merck Sharp & Dohme, Mundipharma, Norgine, Pfizer, Shire, Millennium/Takeda, Tillotts Pharma AG, Vifor. Arthur Kaser has served as a consultant or advisory board member for GlaxoSmithKline, Genentech, Boehringer Ingleheim, Ferring Pharmaceuticals, Janseen Johnson & Johnson, Hospira. Remo Panaccione has served as a consultant, an advisory board member, or speaker for Abbott, Biogen/IDEC, Axcan Pharma Inc., Bristol-Myers Squibb, Centocor, ChemoCentryx, Ferring Pharmaceuticals, Genentech, Lippincott Williams & Wilkins, Medscape, Osiris Therapeutics, Inc., Novartis Pharmaceuticals, Genentech, Elan Pharmaceuticals, UCB; and received research support from Abbott, UCB. David T. Rubin has served as a consultant for Prometheus Pharmaceuticals, AbbVie, UCB, Janssen, Takeda, Ironwood Pharmaceuticals, Emmi, Telsar Pharmaceuticals, Vertex Pharmaceuticals, Santarus/Salix Pharmaceuticals, Genentech; has received grant support from Warner Chilcott, Prometheus Pharmaceuticals, AbbVie, Shire, Elan Pharmaceuticals; and is the co-founder of Cornerstones Health Inc. Ira Shafran has received financial support for research and lecture fees from Takeda. Megan McAuliffe was an employee of Takeda Pharmaceuticals International Inc., Deerfield, IL, USA. Arpeat Kaviya is an employee of Takeda Development Centre Europe Ltd, London, UK. Serap Sankoh is an employee of Takeda Pharmaceuticals International Co., Cambridge, Massachusetts, USA. Reema Mody was an employee of Takeda Pharmaceuticals International Inc., Deerfield, IL, USA. Brihad Abhyankar is an employee of Takeda Development Centre Europe Ltd, London, UK. Michael Smyth is an employee of Takeda Development Centre Europe Ltd, London, UK.

Acknowledgments

Medical writing assistance was provided by inVentiv Medical Communications and supported by Takeda Pharmaceuticals International, Inc. We thank Alexandra James and Alessandro Previtali, MSc, of Takeda Pharmaceuticals International for statistical support; Stephen B. Hanauer, MD, for his participation and critical reviews of earlier manuscript versions; Caterina Hatzifoti, PhD, of Takeda Pharmaceuticals International for publication management support.

Author Contributions

All authors contributed to the study design and interpretation of data. SV is the primary author of the manuscript. All authors provided critical review and approved the final manuscript for submission.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

References

1. Baumgart DC, Sandborn WJ. Crohn's disease. *Lancet* 2012;**380**:1590–605.
2. McLean LP, Shea-Donohue T, Cross RK. Vedolizumab for the treatment of ulcerative colitis and Crohn's disease. *Immunotherapy* 2012;**4**:883–98.
3. Patel V, Wang Y, MacDonald JK, McDonald JW, Chande N. Methotrexate for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2014;**8**:CD006884
4. Pearson DC, May GR, Fick G, Sutherland LR. Azathioprine for maintaining remission of Crohn's disease. *Cochrane Database Syst Rev* 2000:CD000067.

5. Carter MJ, Lobo AJ, Travis SP; Inflammatory Bowel Disease Section, British Society of Gastroenterology. Guidelines for the management of inflammatory bowel disease in adults. *Gut* 2004;**53**[Suppl 5]:v1–v16.
6. Garnock-Jones KP. Vedolizumab: a review of its use in adult patients with moderately to severely active ulcerative colitis or Crohn's disease. *BioDrugs* 2015;**29**:57–67.
7. Fedyk ER, Wyant T, Yang LL, *et al*. Exclusive antagonism of the α4β7 integrin by vedolizumab confirms the gut-selectivity of this pathway in primates. *Inflamm Bowel Dis* 2012;**18**:2107–19.
8. Soler D, Chapman T, Yang LL, Wyant T, Egan R, Fedyk ER. The binding specificity and selective antagonism of vedolizumab, an anti-α4β7 integrin therapeutic antibody in development for inflammatory bowel diseases. *J Pharmacol Exp Ther* 2009;**330**:864–75.
9. Hesterberg PE, Winsor-Hines D, Briskin MJ, *et al*. Rapid resolution of chronic colitis in the cotton-top tamarin with an antibody to a gut-homing integrin α4β7. *Gastroenterology* 1996;**111**:1373–80.
10. Briskin M, Winsor-Hines D, Shyjan A, *et al*. Human mucosal addressin cell adhesion molecule-1 is preferentially expressed in intestinal tract and associated lymphoid tissue. *Am J Pathol* 1997;**151**:97–110.
11. World Medical Association. *The World Medical Association Declaration of Helsinki - Ethical principles for medical research involving human subjects*. Updated October 2013. http://www.wma.net/en/30publications/10policies/b3/. Accessed December 22, 2014.
12. Parikh A, Fox I, Leach T, *et al*. Long-term clinical experience with vedolizumab in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2013;**19**:1691–9.
13. Sandborn WJ, Feagan BG, Rutgeerts P, *et al*.; for the GEMINI 2 Study Group. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2013;**369**:711–21.
14. Sands BE, Feagan BG, Rutgeerts P, *et al*. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. *Gastroenterology* 2014;**147**:618–27.e3.
15. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. *Lancet* 1980;**1**:514.
16. Loftus EV, Feagan BG, Colombel JF, *et al*. Effects of adalimumab maintenance therapy on health-related quality of life of patients with Crohn's disease: patient-reported outcomes of the CHARM trial. *Am J Gastroenterol* 2008;**103**:3132–41.
17. Coteur G, Feagan B, Keininger DL, Kosinski M. Evaluation of the meaningfulness of health-related quality of life improvements as assessed by the SF-36 and the EQ-5D VAS in patients with active Crohn's disease. *Aliment Pharmacol Ther* 2009;**29**:1032–41.
18. Rosario M, Dirks NL, Gastonguay MR, *et al*. Population pharmacokinetics-pharmacodynamics of vedolizumab in patients with ulcerative colitis and Crohn's disease. *Aliment Pharmacol Ther* 2015;**42**:188–202.
19. Colombel JF, Sands BE, Rutgeerts P, *et al*. The safety of vedolizumab for ulcerative colitis and Crohn's disease. *Gut* 2016. [Epub ahead of print].
20. Ben-Horin S, Mazor Y, Yanai H, *et al*. The decline of anti-drug antibody titres after discontinuation of anti-TNFs: implications for predicting re-induction outcome in IBD. *Aliment Pharmacol Ther* 2012;**35**:714–22.
21. Vande Casteele N, Gils A, Singh S, *et al*. Antibody response to infliximab and its impact on pharmacokinetics can be transient. *Am J Gastroenterol* 2013;**108**:962–71.
22. Sands BE, Dubinsky M, Vermeire S, Sankoh S, Rosario M, Milch C. Effects of increased vedolizumab dosing frequency on disease activity in ulcerative colitis and Crohn's disease. *Am J Gastroenterol* 2014;**109**[Suppl 2]:S478–S479.
23. *Takeda. Entyvio (vedolizumab)* [package insert]. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; 2014.