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Long-term Efficacy of Vedolizumab for Ulcerative Colitis

Edward V. Loftus Jr,[a] Jean-Frédéric Colombel,[b] Brian G. Feagan,[c] Severine Vermeire,[d] William J. Sandborn,[e] Bruce E. Sands,[b] 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]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota, USA [b]Icahn School of Medicine at Mount Sinai, Mount Sinai Hospital, New York, New York, USA [c]Robarts Clinical Trials, Robarts Research Institute, University of Western Ontario, London, Ontario, Canada [d]University Hospitals, Leuven, Belgium [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: Edward V. Loftus Jr, MD, Mayo Clinic, 200 First St. SW, Rochester, MN 55905, USA. Tel.: +1 507 266 0873; fax: +1 507 284 0538; email: loftus.edward@mayo.edu.

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Abstract

Background and Aims: The GEMINI long-term safety [LTS] study is a continuing phase 3 trial investigating the safety and efficacy of vedolizumab, an $\alpha_4\beta_7$ integrin antagonist for ulcerative colitis [UC] and Crohn's disease. We provide an interim analysis of efficacy in patients with UC.
Methods: Patients from the C13004 and GEMINI 1 studies and a cohort of vedolizumab-naïve patients received open-label vedolizumab every 4 weeks. Interim data were collected from May 22, 2009 to June 27, 2013. Clinical response and remission, evaluated using partial Mayo scores, and health-related quality of life [HRQL] were assessed for up to 152 weeks of cumulative treatment in the efficacy population.
Results: As of June 27, 2013, 63% of the efficacy population [$n = 532/845$] were continuing treatment. Among patients who responded to vedolizumab induction and had data available, 88% [$n = 120/136$] were in remission after 104 weeks of exposure (96% [$n = 70/73$] after 152 weeks). Among patients who withdrew from every-8-week vedolizumab maintenance in GEMINI 1 [$n = 32$] before week 52, increased dosing to every 4 weeks in GEMINI LTS resulted in response and remission rates of 41% and 28%, respectively, after 52 weeks, an increase from 19% and 6%, respectively, from before

the dose increase. Similar benefits were demonstrated regardless of prior tumour necrosis factor-antagonist exposure. Durable benefits on HRQL were also observed.
Conclusions: Patients with UC experienced clinical and HRQL improvements with continued vedolizumab treatment. Increased dosing frequency to every 4 weeks was beneficial in patients who had loss of response to 8-weekly dosing.

Key Words: Vedolizumab; ulcerative colitis; long-term efficacy

1. Introduction

Ulcerative colitis [UC] is an idiopathic inflammatory disease of the large bowel that is characterized by symptoms of bloody diarrhoea, faecal urgency and abdominal cramps.[1] Since no cure exists, patients with UC usually require long-term maintenance therapy. Conventional non-biologic therapies, such as corticosteroids, thiopurines and methotrexate, have limited long-term efficacy and may cause serious adverse effects.[1–5] While the introduction of tumour necrosis factor [TNF] antagonists has greatly improved the management of UC, some patients do not respond or lose response to these agents.[4] Furthermore, TNF antagonists are systemic immunosuppressive drugs that place patients at risk of serious infections.[6,7]

Vedolizumab, a monoclonal antibody specifically targeting the $\alpha_4\beta_7$ integrin heterodimer, is a new treatment for moderately to severely active UC.[8] Distinct from TNF antagonists and thiopurines, vedolizumab selectively inhibits binding of the $\alpha_4\beta_7$ integrin to mucosal addressin cell adhesion molecule-1 [MAdCAM-1], which is preferentially expressed in the intestinal endothelium.[9] Blockade of the $\alpha_4\beta_7$ integrin–MAdCAM-1 interaction interferes with migration of inflammatory cells into the gastrointestinal tract.[10–12] Systemic immune responses are preserved after treatment with vedolizumab.[13]

Treatment of UC with vedolizumab was demonstrated to be well-tolerated and efficacious in the phase 3, placebo-controlled GEMINI 1 study [ClinicalTrials.gov ID NCT00783718].[14] Herein we present an interim analysis of data from the continuing GEMINI long-term safety [LTS] extension study [ClinicalTrials.gov ID NCT00790933], with emphasis on the durability of treatment response over time and the potential value of increasing dose frequency from every 8 weeks to every 4 weeks in patients with a loss of response. We also report efficacy outcomes in the overall population and by previous TNF antagonist exposure. In addition, safety data are provided.

2. Methods

2.1. Study design and patient enrolment

The GEMINI LTS study, a single-arm, open-label phase 3 study in patients with moderately to severely active UC or Crohn's disease, was underway at 292 centres internationally at the time of these analyses. The primary objective of this study is to evaluate the safety of long-term vedolizumab treatment. Patient-reported health-related quality of life [HRQL] assessments and efficacy endpoints of clinical response and remission were pre-specified exploratory objectives. This report presents interim efficacy and safety data for participants from May 22, 2009 to June 27, 2013.

This study was designed and implemented by the GEMINI Steering Committee [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.[15] All patients gave written informed consent.

The study enrolled patients from qualifying lead-in studies, which included the long-term phase 2 C13004 study [ClinicalTrials.gov ID NCT00619489][16] and the phase 3 GEMINI 1 study [ClinicalTrials.gov ID NCT00783718].[14] The remainder of the enrolled UC population consisted of a new cohort of vedolizumab-naïve patients [Supplementary Figure 1]. As of June 27, 2013, the maximum duration of exposure for patients from the vedolizumab-naïve cohort was 399 days [57 weeks]. In contrast, patients who entered the study from GEMINI 1 had a maximum duration of exposure of up to 1622 days [232 weeks]. 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 1 study.

Patients were withdrawn from the study and considered a treatment failure if they required rescue medication or major surgical intervention for the treatment of UC; if they had a study drug-related adverse event that led to discontinuation; if, in the opinion of the investigator or patient, they were not benefiting from therapy; or if they became pregnant. Investigators were strongly advised to withdraw patients who required multiple courses of corticosteroids or those who were corticosteroid-dependent.

2.1.1. GEMINI 1 patients

GEMINI 1 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 UC [Supplementary Figure 1]. Study details of GEMINI 1 have been published elsewhere.[14] Briefly, patients received either vedolizumab or placebo at weeks 0 and 2 during the induction phase, and those who responded to vedolizumab at week 6 were randomized to receive placebo or vedolizumab every 4 weeks or every 8 weeks (the maintenance intent-to-treat [ITT] population) during the maintenance phase. Clinical response in GEMINI 1 was defined as a decrease in total Mayo Clinic score of ≥3 points and a ≥30% decrease from the baseline score along with a decrease in the rectal bleeding subscore of ≥1 point or an absolute rectal bleeding subscore of ≤1. Patients who did not respond at week 6 could continue to receive vedolizumab every-4-week maintenance treatment in the non-ITT arm [Supplementary Figure 1].[14] Patients originally assigned to placebo induction continued to receive placebo during maintenance or withdrew from the study. Patients who either completed the maintenance phase 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. Vedolizumab-naïve patients

Eligibility criteria for the vedolizumab-naïve cohort of patients were similar to those for GEMINI 1[14] except that a partial Mayo score was used to measure disease activity instead of the complete score. A complete Mayo Clinic score consists of four items [stool frequency, rectal bleeding, endoscopic findings and the physician's global assessment], which are individually scored from 0 to 3, with higher scores indicating more active disease. Scores range from 0, indicating no disease activity, to 12, indicating severe disease. A partial Mayo score excludes the endoscopic item, resulting in a maximum score of 9. Vedolizumab-naïve patients with a partial Mayo score of 3–9 [moderately to severely active UC] within 7 days before the first dose of vedolizumab were eligible for GEMINI LTS. Vedolizumab-naïve patients were ineligible if they had prior exposure to natalizumab, efalizumab or rituximab, or had received adalimumab or any investigational non-biologic therapy for inflammatory bowel disease [IBD] in the past 30 days, or had received infliximab, certolizumab pegol or any investigational or approved biologic agent within the past 60 days.

2.2. Treatment regimen and follow-up

As per study protocol, participants received intravenous infusions of 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 GEMINI 1 and C13004 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, had demonstrated sufficient improvement in clinical signs and symptoms were tapered off corticosteroids using a defined regimen [Supplementary Material] as required by the U.S. Food and Drug Administration [FDA] for these investigational studies. Outside of the United States, corticosteroid tapering was recommended, but not required. Immunosuppressives such as azathioprine, mercaptopurine and methotrexate were permitted at stable doses at sites outside of the United States only. Topical corticosteroids were permitted during the study at all sites.

2.3. Evaluation of safety

Patients were evaluated in the outpatient clinic at least every 4 weeks. At each visit, including unscheduled visits, 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 [MedDRA] 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 partial Mayo 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[17] was administered before dosing.

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

GEMINI LTS was not specifically designed or powered to evaluate efficacy-related hypotheses. Accordingly, the efficacy data are presented using descriptive statistics. All available data for enrolled patients in the efficacy population are included. For all change from baseline assessments, the baseline score was defined at week 0 of the study in which the patient first participated, before any study drug was received.

Evaluation of clinical efficacy included: [1] clinical response defined by a reduction of ≥2 points and ≥25% from the baseline partial Mayo score, with an accompanying decrease in rectal bleeding subscore of ≥1 point or an absolute rectal bleeding subscore of ≤1 point; and [2] clinical remission defined by a partial Mayo score of ≤2 with no individual subscore of >1. 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 nonresponder 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 assessed 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 1 and at week 28, every 24 weeks for the first 4 years, and yearly from year 5 onward during GEMINI LTS. Improvement in HRQL measures was reported as the mean change from the baseline score; a higher, more positive change indicated improvement. Increases from baseline scores of ≥16 points for IBDQ,[18] ≥3 points for SF-36 MCS and PCS,[18] and ≥9 points for EQ-5D VAS are considered the minimums for clinically meaningful improvement.[19]

2.4.1. Populations studied in the efficacy analyses

For the purpose of this efficacy report, we focused on patients with moderately to severely active UC. Patients from study C13004 were excluded from the analyses because some patients in study C13004 had mild UC [median partial Mayo score at baseline: 3.0; range: 0–8]. This efficacy population comprised vedolizumab-naïve patients and GEMINI 1 patients who received any 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 1 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] prior to 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 1 and those who withdrew early formed pre-specified subgroups of the efficacy population.

Long-term efficacy was evaluated for patients who completed GEMINI 1 on the *VDZ/Q8W→Q4W* and *VDZ/Q4W→Q4W* treatment regimens. These patients received vedolizumab continuously after having 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 1[14] 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

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

Subpopulation	Treatment		
	GEMINI 1 induction [6 weeks][a]	GEMINI 1 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.

experienced an interruption in therapy for up to 1 year when receiving placebo during GEMINI 1 maintenance after initially responding to vedolizumab induction. The effect of increasing vedolizumab dosing frequency was analyzed in the *VDZ/Q8W→Q4W* population who had a response to vedolizumab induction, but withdrew early from maintenance dosing every 8 weeks in GEMINI 1—for example, because of a loss of response [Supplementary Table 1], before receiving vedolizumab every 4 weeks in GEMINI LTS.

Patients who had prior TNF antagonist failure and 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. Because 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 the safety population among patients in the *VDZ/PBO→VDZ Q4W* dosing group by measuring serum anti-vedolizumab antibody [AVA] concentrations during time off vedolizumab in GEMINI 1 maintenance. The last dose of vedolizumab during GEMINI 1 for these patients was week 2. Samples for AVA measurement were collected 30 min before dosing during GEMINI 1 at weeks 0, 6, 14, 26, 38 and 52. AVAs were measured using an enzyme-linked immunosorbent assay with a drug tolerance of 1 µg/ml.[20] Patients with at least one positive AVA sample were considered AVA positive.[20] The proportions of AVA-positive and AVA-negative patients who had clinical response and who were in clinical remission after 1 year of retreatment were reported.

3. Results

3.1. Patient disposition and vedolizumab exposure

A total of 894 UC patients who were enrolled in the GEMINI LTS study constituted the safety population [Figure 1a]. The subset of patients with moderately to severely active UC on enrolment constituted the efficacy population [*n*=845]; this population excluded patients from the C13004 study [*n*=29] and patients without a post-baseline disease activity measurement [*n*=20]. Of the GEMINI 1 patients included in the efficacy population, 344 completed the 52-week study, while 313 withdrew before GEMINI 1 completion [Figure 1].

As of June 27, 2013, the median duration of vedolizumab exposure was 759 days [range: 113–2146] in the safety population and 793 days [range: 134–2146] in the efficacy population. In the total safety population, 343 patients had discontinued the trial; 20% had discontinued because of lack of efficacy. Among the efficacy population, 532 patients [63%] were continuing treatment at the time of this analysis. At week 100, 270 patients [32%] were ongoing, yet had not reached that time point in GEMINI LTS or had data missing for that visit [Figure 1b].

Patient demographics and baseline disease characteristics of the total enrolled UC population, except for patients from C13004, at the time of entry into GEMINI LTS are given in Table 2. Additional baseline demographics and disease characteristics are shown in Supplementary Table 2. Nearly half of patients had prior TNF antagonist therapy. Baseline characteristics for the subpopulation of patients with prior TNF antagonist failure [44%] or who were TNF antagonist-naïve [52%] were similar to the total population [Table 2]. At enrolment in GEMINI LTS, the mean partial Mayo score was 6.0 ± 1.4 for vedolizumab-naïve patients. Patients who completed GEMINI 1 had a lower mean partial Mayo score [1.7 ± 2.0] when enrolling in GEMINI LTS than those who withdrew early from GEMINI 1 [6.2 ± 1.9].

3.2. Safety

At the time of this interim data analysis on June 27, 2013, the incidence of any adverse event or serious adverse event in GEMINI LTS was 88% and 20%, respectively [Table 3]. The most common MedDRA terms reported as adverse events were exacerbation of UC and nasopharyngitis [Table 3]. Serious infections and infusion-related reactions were infrequent with 5% and 3% of patients, respectively, experiencing such events [Table 3]. Approximately 10% of patients experienced adverse events that led to study discontinuation [Table 3] with gastrointestinal disorders reported as the most common cause. No patient discontinued the study because of nasopharyngitis. Postoperative wound infection occurred in two [<1%] patients; no other postoperative adverse event was reported. Six patients [<1%] developed a malignancy [two with malignant melanoma and on each with breast cancer *in situ*, metastases to peritoneum/colon cancer, renal cancer, and malignant lung neoplasm]. No cases of PML were reported.

3.3. Long-term efficacy

Clinical efficacy was evaluated using the partial Mayo score. For the vedolizumab-naïve population, treatment with vedolizumab for 28 weeks resulted in 67% [*n*=102/153] of patients with a partial Mayo score of ≤2 [Figure 2a]. Few vedolizumab-naïve patients [*n*=13] had reached 52 weeks of exposure at the time of the interim analysis [Figures 1b and 2a]. Consistent with efficacy outcomes, HRQL improvements were observed in vedolizumab-naïve patients as measured by changes in IBDQ, EQ-5D VAS, SF-36 PCS and SF-36 MCS from baseline [Supplementary Table 3]. When vedolizumab-naïve patients were evaluated by prior TNF antagonist exposure, 63% [*n*=55/87] of those with TNF antagonist failure and 69% [*n* = 41/59] of those who were TNF antagonist-naïve had a partial

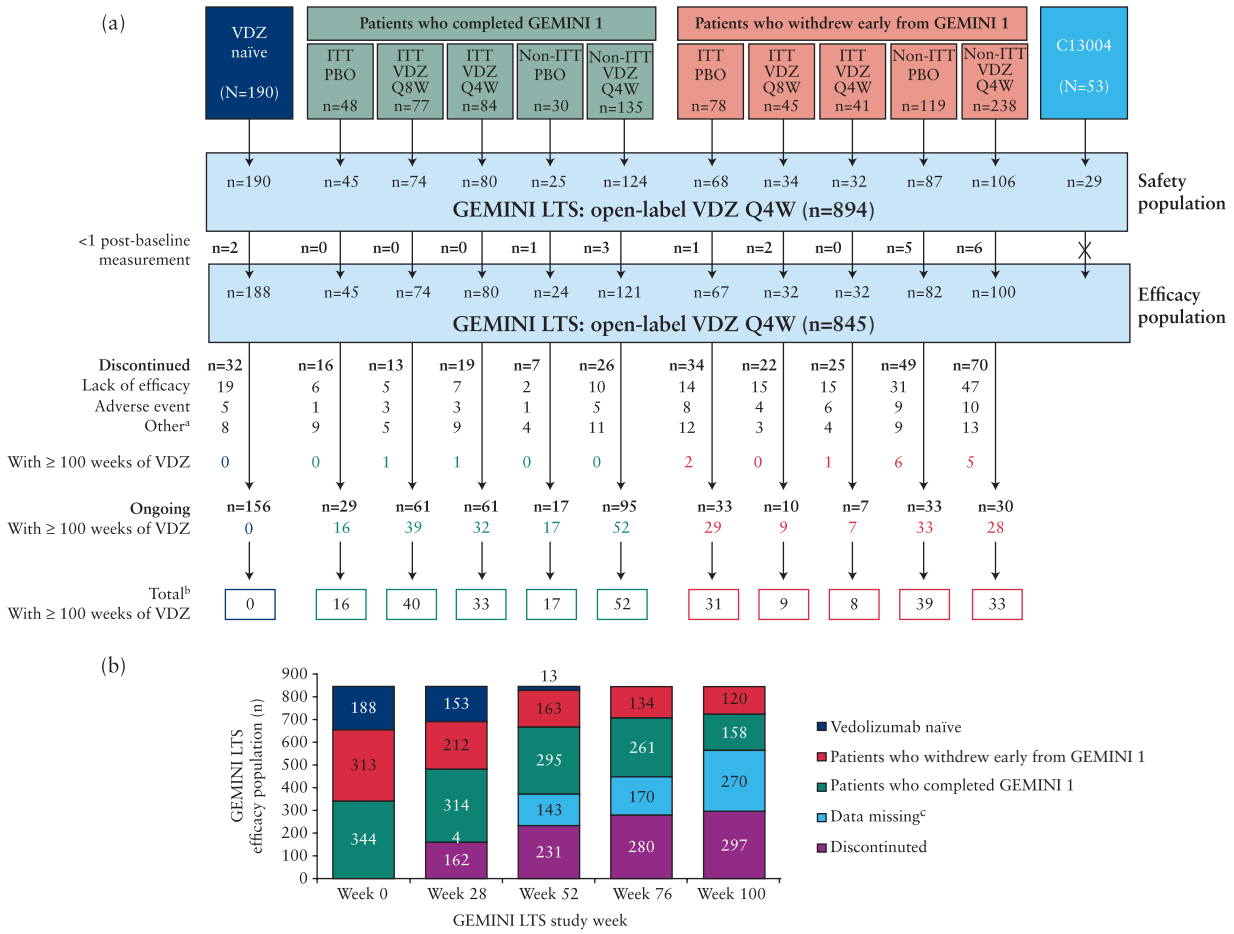

Figure 1. Distribution of the UC patient population in the GEMINI LTS study. [a] Patient disposition. In total, 894 patients with UC enrolled in GEMINI LTS. Patients who completed GEMINI 1 and those who withdrew early are shown according to treatment received during the maintenance phase. The efficacy population [*n* = 845] is a subset of the safety population in which the patient must have had moderately to severely active UC 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. ITT, intent-to-treat; LTS, long-term safety; PBO, placebo; Q4W, every 4 weeks; Q8W, every 8 weeks; UC, ulcerative colitis; VDZ, vedolizumab.

Mayo score of ≤2 after 28 weeks of treatment in GEMINI LTS [Supplementary Table 4].

After completing the 52-week GEMINI 1 study, 71% [*n* = 243/342] of that population had a partial Mayo score of ≤2 [Figure 2b]. At week 100 of GEMINI LTS, 79 patients had withdrawn from the study and 109 patients were missing data, largely because they had not yet reached that time point [Figure 2b]. Among those with data available at week 100, the proportion of ongoing patients with partial Mayo score of ≤2 was 90% [*n* = 141/156] [Figure 2b]. Among the TNF antagonist-failure and TNF antagonist-naïve subpopulations with data available, 88% [*n* = 42/48] and 92% [*n* = 97/106], respectively, had a partial Mayo score of ≤2 at week 100 of GEMINI LTS [Supplementary Table 4]. The mean change from baseline partial Mayo score and 95% confidence intervals for GEMINI 1 patients who continued vedolizumab treatment in GEMINI LTS are shown in Supplementary Tables 5–7. For these analyses, partial Mayo scores were not available for 143 and four ongoing vedolizumab-naïve and GEMINI 1 patients, respectively, at week 52 of GEMINI LTS, and for 109 ongoing GEMINI 1 patients at week 100 [Figure 2].

The percentages of patients with partial Mayo score of ≤2 reported here differ from those in clinical remission, because the pre-specified definition of remission had the added qualifier that no individual subscore was >1. The long-term effects of vedolizumab treatment on clinical response, clinical remission and HRQL are described for the population of patients who received vedolizumab continuously through GEMINI 1 and GEMINI LTS [*VDZ/Q8W→Q4W* and *VDZ/Q4W→Q4W* populations combined]. Clinical response was reported in 91% [*n* = 124/136] of those with available data after 104 weeks of cumulative exposure and 97% [*n* = 71/73] after 152 weeks [Figure 3a]. Similarly, 88% [*n* = 120/136] and 96% [*n* = 70/73] of patients with available data were in clinical remission after 104 and 152 weeks of cumulative treatment, respectively [Figure 3b]. When taking into account the number of patients without data at the study visit, which includes those who had withdrawn from the study, 81% [*n* = 124/154] and 46% [*n* = 71/154] of enrolled patients in the efficacy population had clinical response at weeks 104 and 152, respectively, and 78% [*n* = 120/154] and 46% [*n* = 70/154] were in clinical remission [Figure 3c and 3d]. Importantly, 51 patients who were missing data, largely because they were still ongoing in GEMINI LTS and had not yet reached 152 weeks of vedolizumab exposure, were counted as treatment failures in this analysis [Figure 3c and 3d]. No statistically significant differences in clinical response and remission rates were reported between patients who completed GEMINI 1 regardless of whether they were dosed every 8 weeks or every 4 weeks during maintenance before enrolling in GEMINI LTS [Supplementary

Table 2. UC patient demographics and baseline disease characteristics.

Characteristic	By study			By TNF antagonist exposure[a]		All studies[a]
	GEMINI 1		Vedolizumab-naïve	TNF antagonist-failure	TNF antagonist-naïve	Total
	Patients who completed	Patients who withdrew early				
	[*n* = 348]	[*n* = 327]	[*n* = 190]	[*n* = 380]	[*n* = 453]	[*n* = 865]
Age [years], mean ± SD[b]	40.9 ± 13.0	41.5 ± 13.5	40.9 ± 14.6	41.5 ± 13.7	41.1 ± 13.5	41.1 ± 13.6
Sex [male], *n* [%]	184 [53]	211 [65]	112 [59]	221 [58]	263 [58]	507 [59]
BMI [kg/m^2], mean ± SD	25.6 ± 5.3	25.2 ± 5.5	N/A[c]	25.7 ± 5.3	25.1 ± 5.5	25.4 ± 5.4
Current smoker, *n* [%][d]	20 [6]	18 [6]	5 [3]	16 [4]	26 [6]	43 [5]
Duration of disease [years], mean ± SD[e]	8.2 ± 6.5	7.6 ± 6.7	8.7 ± 8.2	8.5 ± 7.1	7.8 ± 7.0	8.1 ± 7.0
Partial Mayo score, mean ± SD	1.7 ± 2.0	6.2 ± 1.9	6.0 ± 1.4	4.9 ± 2.7	3.9 ± 2.9	4.4 ± 2.9
Mayo Endoscopic subscore[f]						
0, *n* [%]	116 [33]	3 [1]	N/A	40 [11]	73 [16]	119 [14]
1, *n* [%]	125 [36]	28 [9]	N/A	48 [13]	104 [23]	153 [18]
2, *n* [%]	66 [19]	133 [41]	N/A	79 [21]	114 [25]	199 [23]
3, *n* [%]	41 [12]	163 [50]	N/A	97 [26]	96 [21]	204 [24]
Missing, *n* [%]	0	0	190 [100]	116 [31]	66 [15]	190 [22]
Disease location, *n* [%][d]						
Proctosigmoiditis	43 [12]	42 [13]	18 [9]	36 [9]	63 [14]	103 [12]
Left-sided colitis	144 [41]	122 [37]	84 [44]	133 [35]	205 [45]	350 [40]
Extensive colitis [pancolitis]	161 [46]	163 [50]	88 [46]	211 [56]	185 [41]	412 [48]
Faecal calprotectin [µg/g], mean ± SD[d]	1776 ± 2602	2037 ± 2977	1305 ± 2027	1832 ± 2852	1767 ± 2556	1777 ± 2657
History of EIMs [yes], *n* [%][d]	107 [31]	111 [34]	81 [43]	159 [42]	134 [30]	299 [35]
Concomitant medications [yes], *n* [%]						
CS only	41 [12]	179 [55]	104 [55]	153 [40]	156 [34]	324 [37]
IS only	100 [29]	59 [18]	47 [25]	60 [16]	133 [29]	206 [24]
CS and IS	7 [2]	31 [9]	25 [13]	16 [4]	41 [9]	63 [7]
Neither CS nor IS	214 [61]	120 [37]	64 [34]	183 [48]	205 [45]	398 [46]
Prior TNF antagonist therapy, *n* [%][d]	125 [36]	163 [50]	124 [65]	380 [100]	0	412 [48]
Prior TNF antagonist failure, *n* [%][d]	114 [33]	150 [46]	116 [61]	380 [100]	0	380 [44]
Prior IS and TNF antagonist failure, *n* [%][d]	92 [26]	123 [38]	62 [33]	277 [73]	0	277 [32]

BMI, body mass index; CS, corticosteroid; EIM, extraintestinal manifestation; IS, immunosuppressive; N/A, not available; SD, standard deviation; TNF, tumour necrosis factor; UC, ulcerative colitis.

[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 the baseline of GEMINI 1 for rollover patients or at the baseline of GEMINI LTS for vedolizumab-naïve patients.

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

[f]The last available post-baseline endoscopy score from GEMINI 1. Note, endoscopy was only pre-specified at weeks 6 and 52.

Figure 2]. Clinical response and remission rates observed in the subpopulation of patients with prior TNF antagonist failure and those who were TNF antagonist-naïve were similar to the overall population [Figure 3].

HRQL improvements, assessed by IBDQ, EQ-5D VAS, SF-36 PCS and SF-36 MCS mean change from baseline scores, were observed among patients who had received 152 weeks of cumulative vedolizumab treatment in the total population as well as the TNF antagonist-failure and TNF antagonist-naïve subpopulations [Figure 4]. After 80 weeks of exposure, the mean change from baseline scores of ≥60 for IBDQ, >20 for EQ-5D VAS, >8 for SF-36 PCS and >11 for SF-36 MCS was similar for patients who completed GEMINI 1 regardless of prior TNF antagonist treatment and was generally maintained through 152 weeks of exposure for most scores [Figure 4].

3.4. Efficacy following retreatment

The GEMINI 1 study design and enrolment of patients in GEMINI LTS allowed for the evaluation of an inherent vedolizumab retreatment population. During GEMINI 1, patients in the *VDZ/PBO→VDZ Q4W* population [45 completed GEMINI 1; 68 withdrew early; Figure 1a] received two induction doses of vedolizumab before experiencing up to 1 year of interrupted therapy while on placebo maintenance. Vedolizumab was re-initiated upon enrolment in GEMINI LTS. The median duration of time off drug was 229 days. After an initial response to vedolizumab during GEMINI 1 induction, some patients in the *VDZ/PBO→VDZ Q4W* population who completed GEMINI 1 [*n* = 45] experienced a loss of clinical response while receiving placebo between week 6 and week 52 of GEMINI 1 [Figure 5a]. At the end of placebo maintenance in GEMINI 1 [week 52], 69% [*n* = 31/45] of patients had clinical response [vs 91% at week 6] and 56% [*n* = 25/45] were in remission [vs 69% at week 6]. After re-initiation of vedolizumab treatment in GEMINI LTS, response and remission rates improved with 84% [*n* = 38/45] of patients having clinical response and 73% [*n* = 33/45] in remission following 8 weeks of retreatment [Figure 5]. This change is similar to what was observed when these same patients were initially treated with vedolizumab during GEMINI 1 induction; 91% [*n* = 41/45] had clinical response and

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

Category	Safety population [*n* = 894]
	Patients, *n* [%]
Any adverse event	789 [88]
Drug-related adverse event[a]	317 [35]
Adverse event resulting in study discontinuation[b]	87 [10]
Serious adverse event	183 [20]
Serious infection adverse event	42 [5]
Drug-related serious adverse event[a]	24 [3]
Serious adverse event resulting in study discontinuation[b]	38 [4]
Death	3 [<1]
Malignancy	6 [<1]
Progressive multifocal leucoencephalopathy	0
Infusion-related reactions[c]	28 [3]
Common adverse events reported by ≥5% of patients	
Colitis ulcerative	218 [24]
Nasopharyngitis	207 [23]
Headache	142 [16]
Upper respiratory tract infection	136 [15]
Arthralgia	127 [14]
Cough	99 [11]
Nausea	81 [9]
Abdominal pain	78 [9]
Anaemia	76 [9]
Fatigue	72 [8]
Influenza	66 [7]
Pyrexia	66 [7]
Gastroenteritis	63 [7]
Back pain	60 [7]
Sinusitis	59 [7]
Bronchitis	56 [6]
Diarrhoea	55 [6]
Oropharyngeal pain	55 [6]
Urinary tract infection	48 [5]
Rash	47 [5]
Dizziness	42 [5]
Abdominal pain upper	41 [5]

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

69% [*n* = 31/45] were in remission at week 6 of GEMINI 1. With continued treatment in GEMINI LTS, 78% [*n* = 35/45] and 76% [*n* = 34/45] of patients had clinical response and remission at week 28, respectively [Figure 5]. Corresponding values at week 100 of GEMINI LTS were 33% [*n* = 15/45] and 33% [*n* = 15/45]. Efficacy with retreatment was observed regardless of TNF antagonist treatment history; however, lower response and remission rates were generally observed among patients with TNF antagonist failure during the first 52 weeks of retreatment [Figure 5].

In addition, among patients who withdrew early from GEMINI 1 while on placebo maintenance [*n* = 67 in the efficacy population], clinical response and remission rates improved within 28 weeks of retreatment (58% and 45%, respectively, up from 21% and 6% before retreatment [week 0] in GEMINI LTS). No trend was observed between the incidence of AVAs and duration of treatment interruption in the combined *VDZ/PBO→VDZ Q4W* population who completed GEMINI 1 or withdrew early; however, the highest proportion of AVA-positive patients was reported in the group with the longest duration of therapy interruption [Supplementary Table 8]. Although sample sizes were small, no apparent trends were observed between AVA-positivity during interrupted therapy and clinical response or clinical remission after 1 year of retreatment [Supplementary Table 8].

3.5. Effects of increased dosing frequency

The effect of vedolizumab dose intensification was evaluated in patients who had been receiving vedolizumab every 8 weeks during GEMINI 1 maintenance and then had an increase in dosing frequency to every 4 weeks during GEMINI LTS [*VDZ/Q8W→Q4W*]. Specifically, 32 patients [30%] receiving vedolizumab every 8 weeks during GEMINI 1 withdrew from the study early because of sustained non-response, disease worsening or the need for rescue medication before enrolling in GEMINI LTS [Figure 1 and Supplementary Table 1]. Of these patients, 19% [*n* = 6/32] had clinical response and 6% [*n* = 2/32] were in remission at enrolment into GEMINI LTS before their dosing frequency was increased to every 4 weeks. After 28 weeks of the increased vedolizumab dosing frequency, clinical response and remission were reported in 53% [*n* = 17/32] and 25% [*n* = 8/32] of patients, respectively [Figure 6]. Corresponding values for response and remission at week 100 were 28% [*n* = 9/32] and 22% [*n* = 7/32], respectively. The magnitude of improvement noted following an increase in dosing frequency in this population of patients was similar in TNF antagonist-naïve and TNF antagonist-failure subgroups, although the absolute rates of response were higher in the former group [Figure 6].

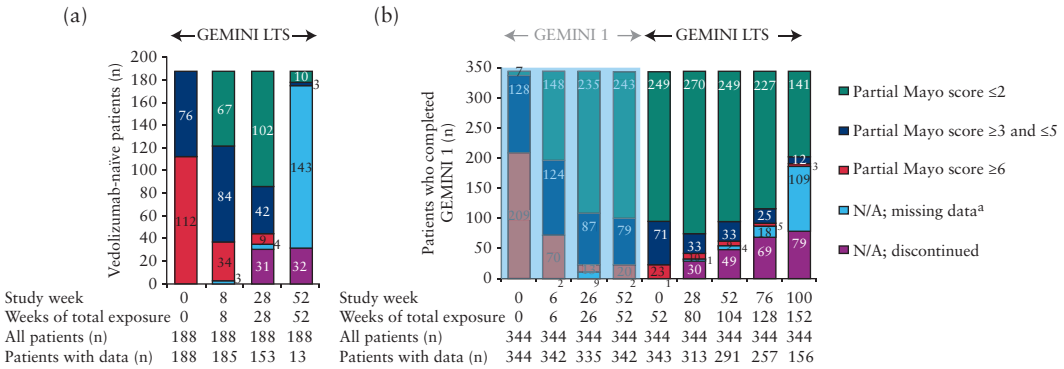

Figure 2. Distribution of disease activity. Numbers of patients with a partial Mayo score of ≤2, a partial Mayo score of ≥3 and ≤5, or a partial Mayo score of ≥6 during GEMINI 1 and GEMINI LTS are depicted. Disease activity is shown in the population of [a] vedolizumab-naïve patients and [b] patients who completed GEMINI 1 and enrolled in GEMINI LTS. [a]Includes patients who are still ongoing, but have yet to reach 100 weeks of vedolizumab treatment during GEMINI LTS. LTS, long-term safety; N/A, not available.

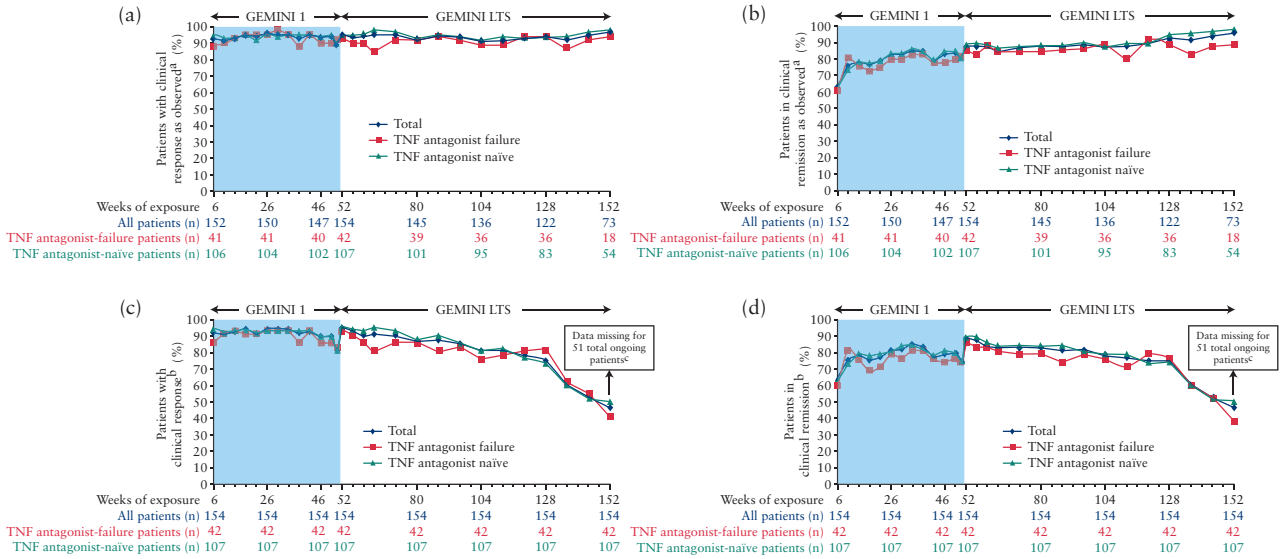

Figure 3. Clinical response and remission among patients who completed double-blind vedolizumab maintenance in GEMINI 1. Percentages of patients with [a] clinical response[a] and in [b] clinical remission[a] as observed overall and by prior TNF antagonist exposure were assessed by changes in partial Mayo score[d] and are plotted over time without imputation for missing data. Percentages of patients with [c] clinical response[b] and in [d] clinical remission[b] are plotted over time with missing data counted as failure. 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 with data available 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 partial Mayo score and 95% CI are reported in Supplementary Tables 5–7. CI, confidence interval; LTS, long-term safety; TNF, tumour necrosis factor.

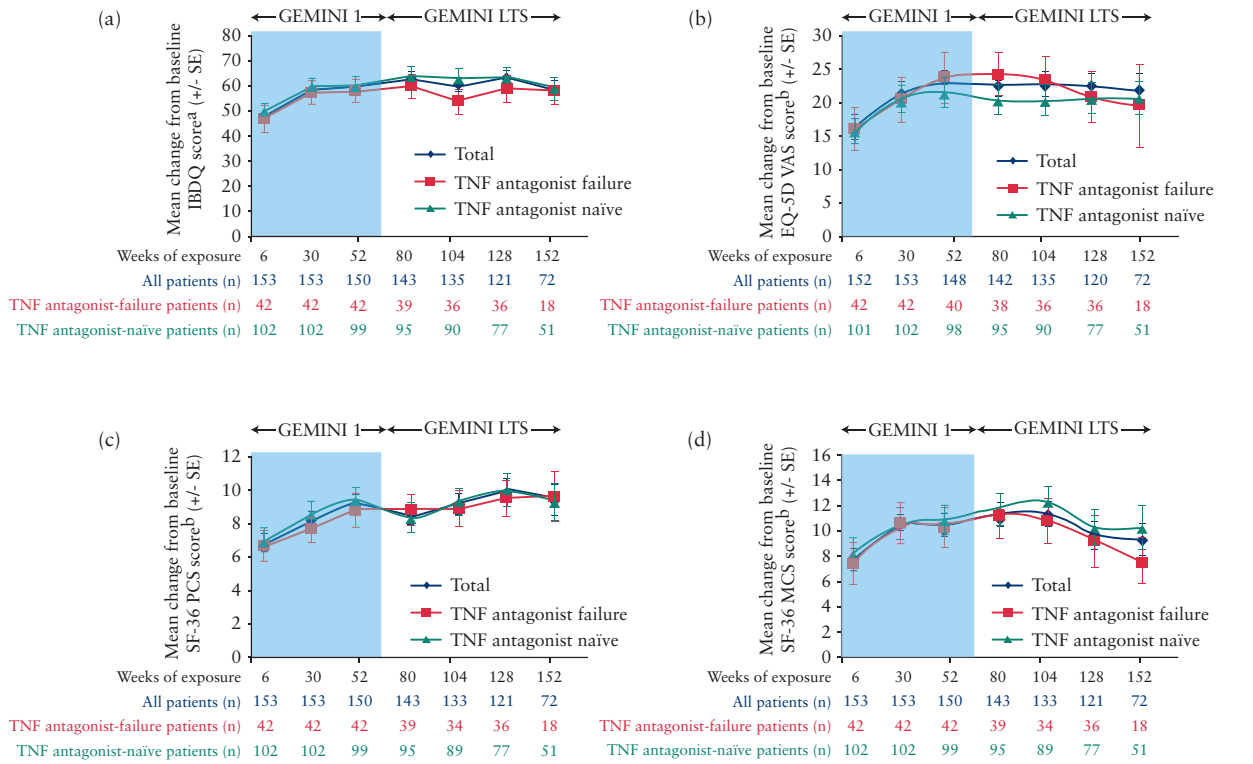

Figure 4. Health-related quality of life among patients who completed double-blind vedolizumab treatment in GEMINI 1. Mean change from baseline scores were plotted for [a] IBDQ, [b] EQ-5D VAS, [c] SF-36 PCS and [d] SF-36 MCS according to weeks of exposure to vedolizumab during GEMINI 1 and GEMINI LTS 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.

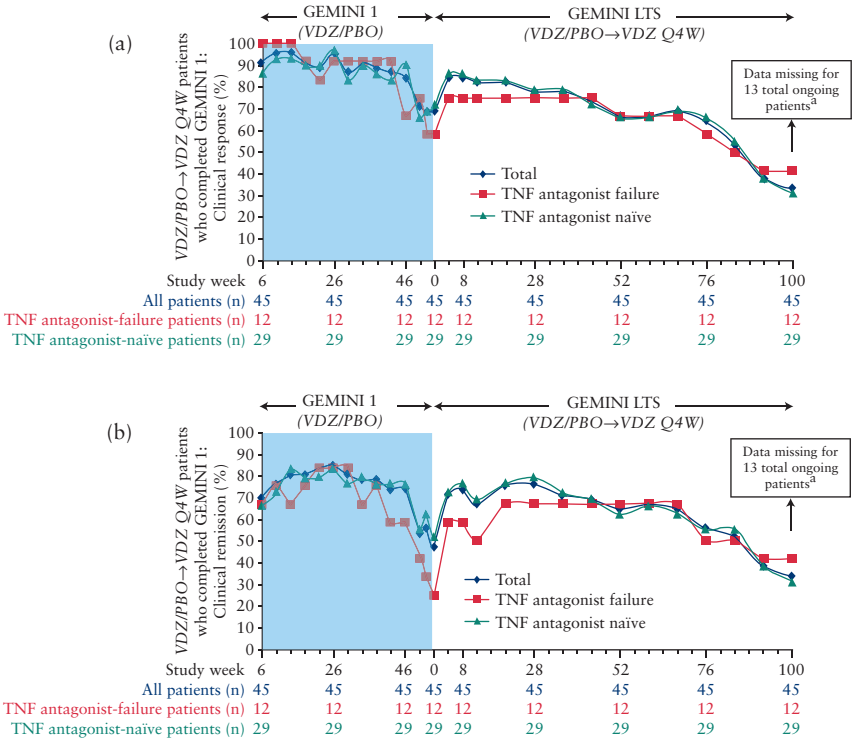

Figure 5. Clinical response and remission following retreatment. Patients in the *VDZ/PBO→VDZ Q4W* population who had response to vedolizumab at week 6 of GEMINI 1 and were randomized to placebo maintenance before retreatment with vedolizumab in GEMINI LTS were evaluated. In the population who completed GEMINI 1, percentages of [a] clinical response and [b] clinical remission were assessed by changes in partial Mayo score[b] 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 reported 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]Mean change from baseline partial Mayo score and 95% CI are reported in Supplementary Tables 5–7. CI, confidence interval; LTS, long-term safety; PBO, placebo; Q4W, every 4 weeks; TNF, tumour necrosis factor; VDZ, vedolizumab.

4. Discussion

The GEMINI LTS study was designed to investigate the safety of vedolizumab with long-term exposure in patients with UC and Crohn's disease. In addition, while exploratory in nature, the study also allowed for the evaluation of long-term efficacy, both in the largest vedolizumab-treated cohort of patients with UC and with the longest duration of exposure to vedolizumab in a clinical trial to date. The results of this interim report provide valuable new information to clinicians regarding the efficacy of vedolizumab with continuous exposure for up to 152 weeks [approximately 3 years], after increased dosing frequency and after an interruption of treatment for up to 1 year.

In the vedolizumab-naïve, TNF antagonist-naïve and TNF antagonist-experienced populations, improvement in clinical outcomes and HRQL was observed with long-term treatment in GEMINI LTS. Among patients with clinical response at week 6 who continued vedolizumab exposure throughout both studies, 81% [n = 114/140] were in remission after 52 weeks, 88% [n = 120/136] after 104 weeks and 96% [n = 70/73] after 152 weeks. To account for patients who may have discontinued the study because of lack of efficacy, patients with missing data at each study visit were conservatively considered treatment failures. Corresponding remission rates using this latter approach [n = 154] were 74%, 78% and 46% after 52 weeks, 104 weeks and 152 weeks, respectively. Although it may appear that the remission rates decline at this 3-year mark, a large number of 'treatment failures' in this calculation are misrepresented by the fact that patients who had not yet reached this time point in the study were considered failures. The collection of concomitant medication use was not part of the GEMINI LTS study protocol, precluding any conclusions on the steroid-sparing effects of vedolizumab. However, post-hoc analyses of GEMINI 1 data have shown that vedolizumab maintenance therapy resulted in numerically greater reductions in corticosteroid use than placebo and higher percentages of patients who were corticosteroid-free.[21] The range of validated assessment tools[22–24] that showed improved HRQL in this study is further evidence of the consistent positive effects in both disease-specific and global measures of well-being experienced by patients treated with vedolizumab long-term.

Because of the chronic nature of UC, the majority of patients require life-long treatment, but may need to interrupt therapy for medical or non-medical reasons. However, reinitiating biologic treatment after interrupted therapy may be associated with immunogenicity and reduced efficacy. We did not prospectively evaluate vedolizumab efficacy and immunogenicity with retreatment. However, we did observe that retreatment with vedolizumab in GEMINI LTS after up to 1 year of interrupted therapy was as efficacious in inducing clinical response and remission as initial vedolizumab induction treatment in the same population (84% [38/45] and 73% [33/45], respectively, at week 8 of retreatment in GEMINI LTS versus 91% [41/45] and 69% [31/45], respectively, at week 6 of GEMINI 1). Furthermore, development of AVAs during interrupted therapy did not appear to affect retreatment efficacy; however, these data are limited by the small number of patients who were AVA-positive.

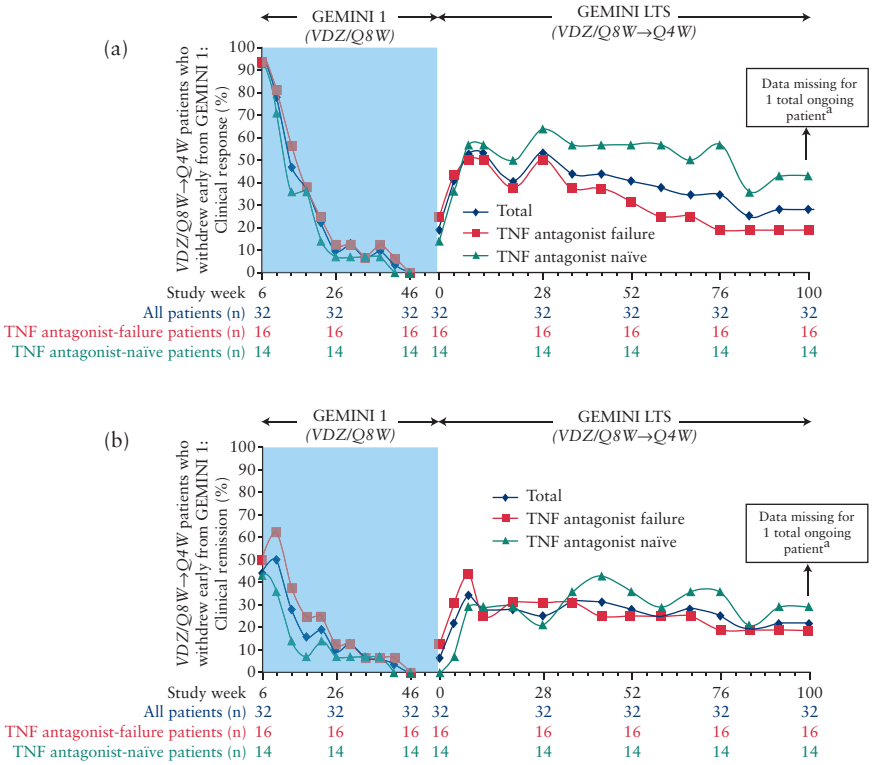

Figure 6. Clinical response and remission following increased dosing frequency. Patients in the *VDZ/Q8W→Q4W* population who had response to vedolizumab at week 6 of GEMINI 1 and were randomized to vedolizumab Q8W maintenance before their dose was intensified to vedolizumab Q4W in GEMINI LTS were evaluated. In the population who withdrew early from GEMINI 1, percentages of [a] clinical response and [b] clinical remission were assessed by changes in partial Mayo 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 1 because some of these patients received rescue medication after withdrawal from GEMINI 1. 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]Mean change from baseline partial Mayo score and 95% CI are reported in Supplementary Tables 5–7. CI, confidence interval; LTS, long-term safety; Q4W, every 4 weeks; Q8W, every 8 weeks; TNF, tumour necrosis factor; VDZ, vedolizumab.

At the time of this interim report, 178 UC patients had discontinued participation citing a lack of vedolizumab efficacy. One possible strategy in patients who lose response to a TNF antagonist is to increase the dose and/or dosing frequency.[25] Long-term experience with vedolizumab has thus far been limited because of its relatively recent approval. However, because of the different dosing protocols in GEMINI 1 and GEMINI LTS, the effect of dose intensification from every 8 weeks to every 4 weeks in patients who withdrew early from the GEMINI 1 study could be evaluated. Although dosing of vedolizumab every 4 weeks is not approved by some countries, including the United States[26] and Canada, our data suggest that a subset of patients may benefit from an increased dosing regimen. These patients may have discontinued GEMINI 1 because of the need for rescue medication or disease worsening as outlined in the GEMINI LTS enrolment criteria and may hypothetically represent a population of patients with more refractory disease than those in the same dosing group who completed the study. Within 28 weeks of treatment in GEMINI LTS, an increase in vedolizumab dosing frequency offered improvements in clinical outcomes of response [53%] and remission [25%] and HRQL, suggesting a benefit of an increase to 4-weekly dosing for some patients who lose response to 8-weekly dosing. Notably, population pharmacokinetics modelling[20] using data collected during GEMINI 1 showed that among patients who were receiving vedolizumab every 8 weeks during maintenance, those who withdrew early had numerically lower predicted vedolizumab serum concentrations at week 52 [30.5 μg/ml; range, 15.7–98.9] than those who completed the study [36.9 μg/ml; range, 18.1–138.2] despite the same dosing frequency.[27] A greater inflammatory burden may hypothetically lead to increased drug clearance and reduced serum drug concentration, as has been observed for TNF antagonists.[28] Future studies that prospectively examine the dose–response relationship of vedolizumab are required to investigate the clinical impact of tailoring dosing frequency in select patient populations.

While TNF antagonists are commonly used for treatment of UC, long-term treatment is limited by the loss or lack of response in up to 40% of patients.[4] Furthermore, after failure with one TNF antagonist, patients may be less likely to respond to another.[29] A prospective trial comparing vedolizumab to a second TNF antagonist in this patient population should clarify whether a switch to vedolizumab offers an advantage. The data presented here show that the subpopulation of patients with prior failure to TNF antagonist therapy experienced clinical benefits with vedolizumab similar to those experienced by the overall population, and that these benefits continued with long-term treatment. Similarly, patients who were TNF antagonist-naïve responded well to vedolizumab treatment and continued to demonstrate improvements for up to 152 weeks of treatment. Considering the efficacy in the anti-TNF-naïve subpopulation, vedolizumab may serve as an attractive first-line alternative in UC patients who have failed conventional therapies such as immunosuppressives, 5-aminosalicylates and corticosteroids. Furthermore, these

data suggest that once a patient has initially responded with vedolizumab, the likelihood that the patient will maintain response is high, regardless of past treatment history.

The adverse event profile with long-term vedolizumab treatment during GEMINI LTS was similar to what has been previously reported.[14,30] In particular, the incidence of serious adverse events was relatively low, with 5% of patients experiencing serious infections during GEMINI LTS. The low risk of systemic infections supports the gut-selective mechanism of action of vedolizumab; however, ongoing risk assessments are in progress to monitor the occurrence of enteric adverse events and long-term adverse events such as malignancy, and the risk of PML. Importantly, no cases of PML have been reported to date.[30] More detailed analyses of the interim safety data from GEMINI LTS are included in a separate comprehensive safety summary of vedolizumab.[30]

Taken together, preliminary data from GEMINI LTS demonstrate the long-term efficacy of vedolizumab treatment for the maintenance of remission in patients with UC. Despite the limitations of these analyses, including the potential bias associated with a non-blinded, non-randomized, uncontrolled study, the fact that 63% of patients within the efficacy population were still enrolled in the study at the time of this interim report is notable. The efficacy of vedolizumab for this chronic disease is further illustrated by different clinical scenarios, such as retreatment after an interruption in therapy, treatment in patients who have previously failed TNF antagonist therapy and treatment in biologic-naïve patients. Although this study – which began years before regulatory approval of vedolizumab every 8 weeks – administered vedolizumab every 4 weeks, the results still provide valuable insight for clinical practice. Increase in vedolizumab dosing frequency, for example, may be a viable treatment approach for a subset of patients; however, prospective studies are needed to identify which patients might benefit.

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Conflict of Interest

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. 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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. 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Author Contributions

All authors contributed to the study design and interpretation of data. EVL Jr 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.

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