

Vedolizumab treatment persistence and safety in a 2-year data analysis of an extended access programme

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Summary

Background: Vedolizumab was shown to be effective and safe for patients with ulcerative colitis (UC) or Crohn's disease (CD) in the GEMINI phase 3 and long-term safety (LTS) studies.

Aim: To report treatment persistence and safety results up to 2 years after enrolment in the vedolizumab extended access programme (XAP)

Methods: Vedolizumab XAP is a phase 3b/4, prospective, open-label, multinational, interventional study. At rollover from GEMINI LTS, patients who were experiencing continued clinical benefit with vedolizumab received reduced dosing frequency from every 4 weeks (Q4W) to every 8 weeks (Q8W). Patient persistence on Q8W dosing, incidence of relapse, and safety 2 years after enrolment were investigated.

Results: We enrolled 311 patients (142 UC and 169 CD). At baseline, 93.7% (UC) and 89.3% (CD) of patients were in clinical remission; 93.0% (UC) and 84.6% (CD) reduced dosing frequency to Q8W at enrolment. Of those who reduced dosing frequency to Q8W at enrolment, 93.9% (UC) and 91.6% (CD) remained on Q8W dosing; 6.1% (UC) and 8.4% (CD) re-escalated to Q4W dosing. Relapse was reported in 9.1% (UC) and 14.0% (CD) of patients who reduced dosing to Q8W. Adverse events related to vedolizumab were infrequent; no new events were reported.

Conclusion: We observed high patient persistence on vedolizumab Q8W in the first 2 years after the reduction of dosing frequency in the XAP along with low rates of Q4W dose re-escalation and relapse. The safety profile was consistent with previous reports.

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1 | INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory bowel diseases, characterised by bloody diarrhoea, abdominal pain, and faecal urgency and incontinence. The primary goal of management is to treat patient symptoms and improve quality of life by preventing disease complications and surgery.^{1,2} Treatment is generally tailored to the patient's disease activity (mild, moderate, or severe) and treatment stage (remission induction vs maintenance).

Conventional treatments for the induction of remission in moderately to severely active UC and CD include 5-aminosalicylate, corticosteroids, and immunomodulators (eg, azathioprine, methotrexate).^{1,2} Anti-tumour necrosis factor (TNF) therapies (eg, infliximab or adalimumab for UC or CD, golimumab for UC, certolizumab pegol for CD) are effective for the treatment of patients who respond inadequately to corticosteroids and immunomodulators.² However, corticosteroids and immunomodulators are associated with serious adverse events (AEs); concomitant immunosuppression with corticosteroids during anti-TNF therapy appears to be an important risk factor for serious infections, and treatment with azathioprine and 6-mercaptopurine may place patients at increased risk of lymphoma.³⁻⁵

Vedolizumab and ustekinumab are approved biologic treatments for patients who failed previous treatment with corticosteroids, immunomodulators, or anti-TNF agents.^{1,2} Vedolizumab is a gut-selective, humanised monoclonal antibody that binds specifically to the leukocyte integrin $\alpha_4\beta_7$ and blocks leukocyte trafficking into the intestinal mucosa.^{6,7} The clinical efficacy and safety of vedolizumab as both induction and maintenance therapy was established with every-8-week (Q8W) and every-4-week (Q4W) dosing for patients with moderately to severely active UC or CD in the GEMINI phase 3 and long-term safety (LTS) studies.⁸⁻¹² Vedolizumab was also shown to induce endoscopic, radiologic, and histologic healing and to improve quality of life in patients with CD for up to 52 weeks in the VERSIFY trial.¹³

The vedolizumab extended access programme (XAP) was initiated to monitor ongoing safety and to provide continued access to vedolizumab for patients who participated in the GEMINI LTS and VERSIFY studies and who were benefiting from vedolizumab maintenance therapy but did not have access to commercial vedolizumab. Vedolizumab was administered Q8W in the XAP, representing reduced frequency from Q4W to Q8W dosing for patients enrolling from GEMINI LTS and continuation of Q8W dosing for patients enrolling from VERSIFY. Recently, the results of a pharmacokinetics (PK) substudy conducted with 167 patients (UC, 79; CD, 88) in the XAP were published.¹⁴ The data showed vedolizumab serum trough concentrations dropped after the reduction of dosing frequency, as expected. Even at lower serum vedolizumab concentrations, both the clinical remission rate and C-reactive protein concentrations remained stable, thereby suggesting no loss of efficacy for patients who undergo a reduction in dosing frequency.¹⁴ This 2-year data analysis now reports treatment persistence of patients with UC or

CD on Q8W dosing following the reduction of dosing frequency, the incidence of relapse, and safety results up to 2 years after enrolment in the XAP from GEMINI LTS.

2 | METHODS

2.1 | Study design

Vedolizumab XAP (NCT02743806), a phase 3b/4, prospective, open-label, multinational, interventional study, was established to provide patients with access to vedolizumab and monitor ongoing safety. The study protocol was approved by an Institutional Review Board or Ethics Committee at each study site and all patients provided informed consent prior to enrolment in the study. Eligible patients were those who received vedolizumab in the two qualifying studies GEMINI LTS (NCT00790933, EudraCT 2008-002784-14) and VERSIFY (NCT02425111, EudraCT 2014-003509-13), experienced continued clinical benefit, and did not have access to commercially available vedolizumab. Vedolizumab 300 mg was given intravenously Q4W during GEMINI LTS; vedolizumab 300 mg was given intravenously Q8W after three induction doses for up to 52 weeks in VERSIFY. Results from these two studies have been previously reported.¹¹⁻¹³

The sample size for this study was not based on statistical assumptions. The number of patients enrolled was determined by the number of eligible patients who received vedolizumab during the qualifying studies. This 2-year interim analysis focused on results after the reduction of vedolizumab dosing frequency from Q4W to Q8W; hence, only patients who rolled over from GEMINI LTS were included. Patients from VERSIFY were not eligible for this analysis because they had received vedolizumab Q8W during the study.

2.2 | Treatment and follow-up

Enrolment occurred at the final dosing visit of GEMINI LTS (the last dose in GEMINI LTS was considered the first of the XAP dose regimen). In general, patients received vedolizumab 300 mg intravenously Q8W in this study. Patients could remain on Q4W dosing if medically indicated based on the treating physician's clinical judgement and acknowledged by the study medical monitor. Re-escalation to Q4W dosing due to loss of response was also allowed.

Patients were required to leave the study if vedolizumab became commercially available to them. However, if patients had not been stable on Q8W dosing for the previous 6 months and only Q8W dosing was available but not Q4W dosing, they were encouraged to remain in the study until they become stable for 6 months before moving to commercially available vedolizumab. Patients should have also received their last vedolizumab dose in this study within 60 days of having access to the commercial product. Patients were considered to have completed the study once they transitioned to a commercially available product.

2.3 | Study outcomes

This 2-year data analysis assessed persistence on Q8W dosing, rates of re-escalation to Q4W dosing, incidence of relapse, and safety events up to 2 years after rollover from GEMINI LTS to the XAP. Relapse was defined as the occurrence of any of the following events occurring after study enrolment: vedolizumab re-escalation from Q8W to Q4W dosing, study withdrawal due to AE indicating the worsening of UC or CD, loss of adequate benefit from vedolizumab, commencement or increased dose of corticosteroid or immunomodulator therapy due to the worsening of UC or CD, or serious AE indicating the worsening of UC or CD. Patients re-escalated to Q4W dosing if they experienced a reduction in efficacy on Q8W dosing based on the physician's assessment of their clinical status. Safety outcomes were assessed throughout the treatment period and included AEs, serious AEs, AEs leading to the discontinuation of vedolizumab, or worsening of UC or CD.

2.4 | Statistical analyses

Analyses were based on patients who were enrolled in the study and who had their last vedolizumab dose in GEMINI LTS at least 2 years prior to the cut-off date (31 July 2019). This included patients who prematurely discontinued or completed the study due to access to commercially available vedolizumab within the first 2 years after enrolment.

For the consistent presentation of results, only the data from the last vedolizumab dose during GEMINI LTS up to 2 years were considered in this analysis, even if the patient participated in the XAP for more than 2 years. Kaplan-Meier curves were generated separately for the time from study enrolment to re-escalation to Q4W dosing and for the time from study enrolment to relapse for patients with UC and CD who started the study on Q8W dosing.

As the study aimed to provide continued access to vedolizumab and to monitor ongoing safety, there was no active comparator group, and patients with UC or CD were analysed separately. No comparisons were made between the two populations; hence, no formal statistical testing was performed. All study outcomes were summarised descriptively.

3 | RESULTS

3.1 | Patient baseline characteristics and study disposition

A total of 657 patients with UC from GEMINI 1 and 1072 patients with CD from GEMINI 2 and 3 enrolled in GEMINI LTS;^{11,12} then 311 patients (142 with UC and 169 with CD) from GEMINI LTS enrolled in the XAP and were eligible for analysis (Table 1). The mean time since diagnosis was 13.9 years and 13.4 years for patients with UC and CD, respectively. Patients had been treated with vedolizumab for a

mean of 6.8 years (UC) and 6.3 years (CD) inclusive of vedolizumab therapy in prior studies.

At baseline, 133 of 142 (93.7%) patients with UC and 151 of 169 (89.3%) patients with CD were in clinical remission (Table 1). Most patients were anti-TNF therapy naïve (UC, 114 of 142 [80.3%]; CD, 107 of 169 [63.3%]) and not taking concomitant corticosteroids or immunosuppressive drugs (UC, 109 of 142 [76.8%]; CD, 128 of 169 [75.7%]) at the time of enrolment. Only 6 of 142 (4.2%) and 7 of 169 (4.1%) patients with UC or CD, respectively, had acute disease exacerbations within the past 12 months, while only 4 of 169 (2.4%) patients with CD had been hospitalised within the past 12 months.

Overall, 132 of 142 (93.0%) patients with UC and 143 of 169 (84.6%) patients with CD started the study on Q8W dosing (Table 2). Most patients who remained on Q8W dosing at enrolment were in clinical remission (UC, 127 of 132 [96.2%]; CD, 132 of 143 [92.3%]) at baseline (Tables S1 and S2). Of those who remained on Q4W dosing at enrolment, 5 of 8 (62.5%) patients with UC and 19 of 26 (73.1%) patients with CD were in clinical remission (Tables S1 and S2).

At 2 years, 119 of 142 (83.8%) patients with UC and 133 of 169 (78.7%) patients with CD remained in the study and continued to benefit from vedolizumab treatment (Table 2). A total of 18 of 142 (12.7%) and 26 of 169 (15.4%) patients with UC and CD, respectively, discontinued the study prematurely. The most common reason for study discontinuation was voluntary withdrawal (UC, 7 patients; CD, 12 patients) followed by loss of adequate benefit (UC, 5 patients; CD 9 patients) and AE (UC, 4 patients; CD, 2 patients). Only 5 of 142 (3.5%) patients with UC and 10 of 169 (5.9%) patients with CD completed the study due to access to commercial vedolizumab. In this 2-year analysis, the cumulative median duration of vedolizumab treatment, including exposure in prior studies, was 8.0 years (range, 5.2-10.0 years) for patients with UC and 7.5 years (range, 5.4-9.9 years) for patients with CD.

3.2 | Dosing persistence, dosing re-escalation, and disease relapse

Over the 2 years in the study, 124 of 132 (93.9%) patients with UC and 131 of 143 (91.6%) patients with CD who started with a dose reduction to Q8W remained on Q8W dosing (Table 3). Eight of 132 (6.1%) patients with UC and 12 of 143 (8.4%) patients with CD re-escalated from Q8W to Q4W dosing. The median time to dose re-escalation was 445 days and 410 days for patients with UC and CD, respectively (Table 3, Figure 1A). Of patients who re-escalated to Q4W dosing, 4 of 8 (50%) with UC and 7 of 12 (58.3%) with CD had prior anti-TNF exposure at baseline (Tables S1 and S2), and 4 of 8 (50.0%) with UC and 4 of 12 (33.3%) with CD discontinued the study early, mostly due to loss of adequate benefit (Tables S3 and S4). At 2 years, 4 of 8 (50.0%) patients with UC and 8 of 12 (66.7%) patients with CD who required re-escalation to Q4W dosing remained on and continued to benefit from vedolizumab treatment.

TABLE 1 Baseline patient characteristics

| | UC n = 142 | CD n = 169 | Total N = 311 |
|--|---------------|---------------|------------------|
| Age, mean (SD), years | 47.7 (11.8) | 42.5 (11.8) | 44.9 (12.0) |
| Male, n (%) | 79 (55.6) | 95 (56.2) | 174 (55.9) |
| UC/CD clinical remission, ^a n (%) | 133 (93.7) | 151 (89.3) | 284 (91.3) |
| Corticosteroid-free clinical remission, n (%) | 132 (93.0) | 149 (88.2) | 281 (90.4) |
| Time since UC/CD diagnosis, mean (SD), years | 13.9 (6.8) | 13.4 (6.7) | 13.6 (6.7) |
| Time since start of vedolizumab therapy, mean (SD), years | 6.8 (1.33) | 6.3 (0.97) | 6.6 (1.17) |
| Prior anti-TNF therapy, n (%) | | | |
| Prior anti-TNF therapy experience | 28 (19.7) | 62 (36.7) | 90 (28.9) |
| Anti-TNF therapy naïve | 114 (80.3) | 107 (63.3) | 221 (71.1) |
| Prior anti-TNF therapy failure | 18 (12.7) | 40 (23.7) | 58 (18.6) |
| No prior anti-TNF therapy failure | 124 (87.3) | 129 (76.3) | 253 (81.4) |
| Concomitant medications, n (%) | | | |
| Corticosteroid only | 5 (3.5) | 7 (4.1) | 12 (3.9) |
| Immunomodulator only | 26 (18.3) | 32 (18.9) | 58 (18.6) |
| Corticosteroid + immunomodulator | 2 (1.4) | 2 (1.2) | 4 (1.3) |
| No corticosteroid or immunomodulator | 109 (76.8) | 128 (75.7) | 237 (76.2) |
| Partial Mayo score, mean (SD) | 0.5 (1.0) | – | – |
| Harvey-Bradshaw Index score, mean (SD) | – | 1.7 (2.3) | – |
| Acute exacerbations within the past 12 months, n (%) | 6 (4.2) | 7 (4.1) | 13 (4.2) |
| Hospitalisation within the past 12 months, n (%) | 0 | 4 (2.4) | 4 (1.3) |
| Corticosteroid use over the last 12 months, mean (SD), weeks | 3.4 (12.3) | 4.8 (14.5) | 4.1 (13.5) |

Abbreviations: CD, Crohn's disease; SD, standard deviation; TNF, tumour necrosis factor; UC, ulcerative colitis.

^aClinical remission was defined as partial Mayo score ≤ 2 with no subscore > 1 for UC and as Harvey-Bradshaw Index score ≤ 4 for CD.

Among patients who entered the study and reduced dosing frequency to Q8W, disease relapse was reported for 12 of 132 (9.1%) and 20 of 143 (14.0%) patients with UC and CD, respectively (Table 3). The median time to relapse (due to dose re-escalation, study withdrawal due to an AE indicating a worsening of UC or CD, loss of adequate benefit from vedolizumab, commencement or increased dose of corticosteroids or immunomodulators, or serious AE indicating the worsening of UC or CD) was 441 days for patients with UC and 284 days for patients with CD (Table 3, Figure 1B).

3.3 | Safety

Three of 142 (2.1%) and 7 of 169 (4.1%) patients with UC and CD, respectively, reported AEs related to vedolizumab (Table 4). The most frequently reported AEs were gastrointestinal disorders and infections in patients with UC or CD. One patient with UC and one with CD experienced serious AEs related to vedolizumab; six patients (four UC, two CD) discontinued the study due to AEs; one patient with CD died due to the exacerbation of chronic obstructive pulmonary disease that was not related to vedolizumab.

4 | DISCUSSION

The XAP was designed to provide continued access for patients with UC or CD who benefited from vedolizumab in GEMINI LTS but did not have access to commercial vedolizumab, and to assess the long-term safety of vedolizumab. Because both UC and CD require long-term maintenance treatment, there is a need to evaluate therapeutic options that are efficacious and well tolerated over the long term. Results presented in this XAP 2-year data analysis demonstrate high patient persistence (UC, 93.9%; CD, 91.6%) with vedolizumab 300 mg intravenous Q8W dosing in the first 2 years after the reduction of dosing frequency from Q4W to Q8W, with a similar safety profile to that reported for patients with UC or CD in GEMINI LTS.^{11,12}

Almost all patients who enrolled in the study underwent a reduction in vedolizumab dosing frequency from Q4W to Q8W (UC, 93.0%; CD, 84.6%). These patients were typically in clinical remission at baseline (UC, 96.2%; CD, 92.3%) and not taking concomitant corticosteroid or immunomodulator therapies (UC, 77.3%; CD, 74.1%), indicating that the patients were a stable cohort with long-term benefit from vedolizumab. Patients entering the study who remained on Q4W dosing were less likely to be in clinical remission, and more patients with CD who stayed on Q4W dosing had a recent

TABLE 2 Patient disposition

| | UC n = 142 | CD n = 169 | Total N = 311 |
|----------------------------------|---------------|---------------|------------------|
| Received study drug, n (%) | 142 (100) | 169 (100) | 311 (100) |
| Started on Q8W | 132 (93.0) | 143 (84.6) | 275 (88.4) |
| Started on Q4W | 8 (5.6) | 26 (15.4) | 34 (10.9) |
| Other/multiple dosing changes | 2 (1.4) | 0 | 2 (0.6) |
| Ongoing at 2-year cut-off, n (%) | 119 (83.8) | 133 (78.7) | 252 (81.0) |
| Completed study, n (%) | 5 (3.5) | 10 (5.9) | 15 (4.8) |
| Discontinued prematurely, n (%) | 18 (12.7) | 26 (15.4) | 44 (14.1) |
| Voluntary withdrawal | 7 (4.9) | 12 (7.1) | 19 (6.1) |
| Loss of adequate benefit | 5 (3.5) | 9 (5.3) | 14 (4.5) |
| AE | 4 (2.8) | 2 (1.2) | 6 (1.9) |
| Pregnancy | 1 (0.7) | 2 (1.2) | 3 (1.0) |
| Lost to follow-up | 1 (0.7) | 0 | 1 (0.3) |
| Other | 0 | 1 (0.6) | 1 (0.3) |

Abbreviations: AE, adverse event; CD, Crohn's disease; Q4W, every 4 weeks; Q8W, every 8 weeks; UC, ulcerative colitis.

acute exacerbation than did patients with CD who enrolled on Q8W dosing (5 of 26 [19.2%] vs 2 of 131 [1.5%]).

At 2 years, the majority of patients (UC, 83.8%; CD, 78.7%) remained on study and were continuing vedolizumab treatment, with most patients still on Q8W dosing and only a few patients (UC, 12.7%; CD, 15.4%) discontinuing early. Patients who escalated to Q4W dosing discontinued the study early at a higher rate than those who remained on Q8W dosing (UC, 4 of 8 [50.0%] vs 11 of 124

[8.9%]; CD, 4 of 12 [33.3%] vs 15 of 131 [11.5%]), mostly due to loss of adequate benefit.

Patient persistence on Q8W dosing in this 2-year analysis (UC, 93.9%; CD, 91.6%) and rates of re-escalation to Q4W dosing (UC, 6.1%; CD, 8.4%) were similar to previous findings in the XAP-PK substudy, which included a smaller number of patients (n = 167) and a shorter duration of follow-up (56 weeks).¹⁴ In the XAP-PK substudy cohort, 89.9% and 86.4% of patients with UC and CD, respectively, persisted on Q8W dosing through Week 56, whereas only 2.5% and 4.5% re-escalated to Q4W dosing. Reduction of dosing frequency to Q8W was not associated with a loss of efficacy. Most patients who remained on Q8W dosing were in clinical remission, defined as a partial Mayo score ≤ 2 with no subscore >1 for UC and a Harvey-Bradshaw Index score ≤ 4 for CD (UC, 94.7%; CD, 80.8%), and corticosteroid-free remission (UC, 92.0%; CD, 73.1%) through Week 56. C-reactive protein concentrations were also stable over time. Median C-reactive protein concentrations were 1.7 mg/L at baseline and 1.2 mg/L at Week 56 for patients with UC, and 2.2 mg/L at baseline and Week 56 for patients with CD. In patients with UC or CD who remained on Q8W dosing for 56 weeks, baseline median vedolizumab trough concentrations decreased from 42.4 $\mu\text{g/mL}$ and 43.6 $\mu\text{g/mL}$, respectively, to 13.3 $\mu\text{g/mL}$ and 10.4 $\mu\text{g/mL}$ at Week 56.

Overall, 11.6% of patients enrolled on Q8W dosing (UC, 12 of 132 [9.1%]; CD, 20 of 143 [14.0%]) experienced disease relapse up to 2 years after rollover from GEMINI LTS. Although efficacy outcomes (partial Mayo score for UC and Harvey-Bradshaw Index for CD) were not investigated in this study, the high treatment persistence on Q8W dosing, together with the low rates of relapse, suggests there is minimal loss of efficacy with a reduction of dosing frequency to Q8W. However, it should be noted that only including patients who were experiencing clinical benefit with vedolizumab in GEMINI LTS and were expected to derive continued clinical benefit might have contributed to the high treatment persistence observed in this study. Endoscopy and measurement of C-reactive protein or faecal calprotectin concentrations may also provide insight into disease

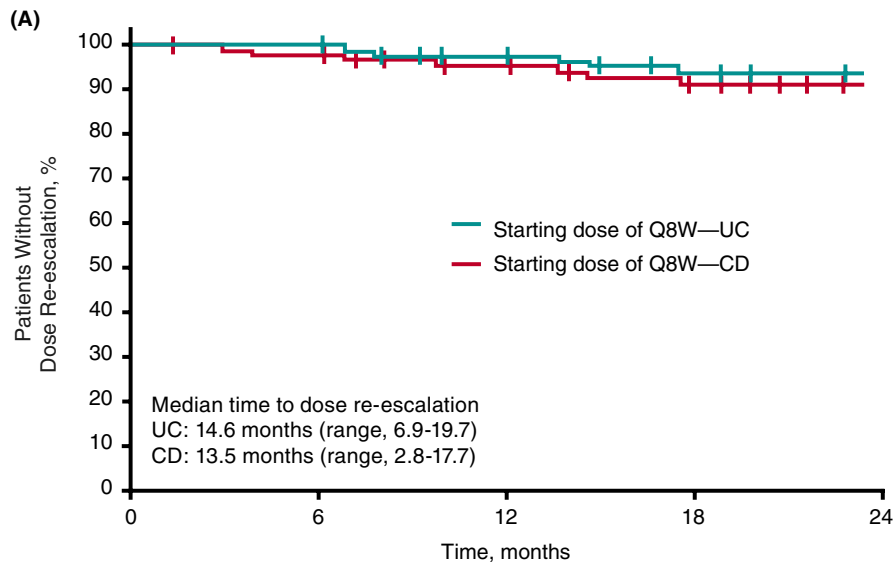
TABLE 3 Dosing persistence and re-escalation of dosing in patients on Q8W at enrolment

| | UC n = 132 | CD n = 143 | Total N = 275 |
|--|----------------|---------------|------------------|
| Remained on Q8W after dose reduction, n (%) | 124 (93.9) | 131 (91.6) | 255 (92.7) |
| Re-escalated to Q4W, n (%) | 8 (6.1) | 12 (8.4) | 20 (7.3) |
| Time to re-escalation to Q4W dosing, median (min, max), days | 445 (211, 598) | 410 (85, 538) | 423.5 (85, 598) |
| Disease relapse, ^a n (%) | 12 (9.1) | 20 (14.0) | 32 (11.6) |
| Time to relapse, median (min, max), days | 441 (2, 571) | 284 (1, 536) | 300 (1, 571) |

Note: Only patients starting the study on Q8W dosing are included.

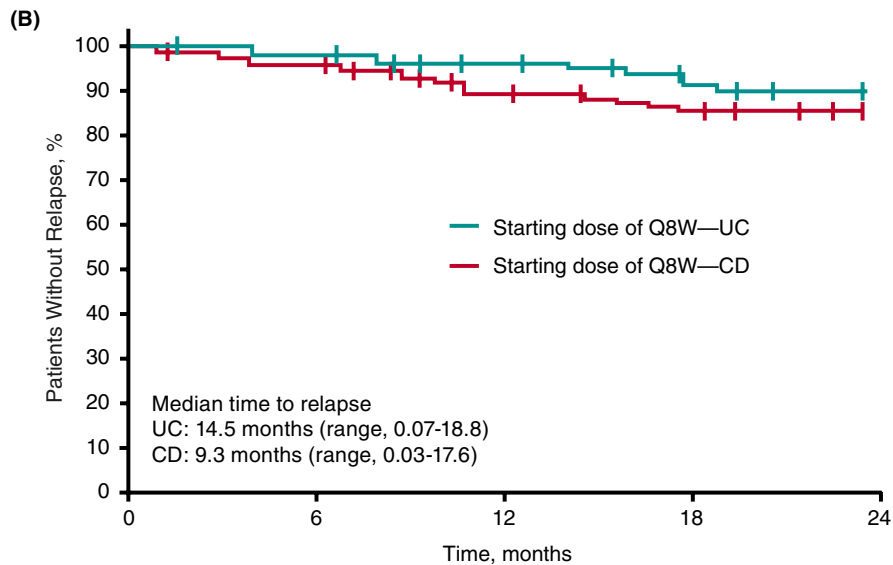
Abbreviations: AE, adverse event; CD, Crohn's disease; Q4W, every 4 weeks; Q8W, every 8 weeks; UC, ulcerative colitis.

^aRelapse was defined as re-escalation from Q8W to Q4W dosing, study withdrawal due to AE indicating the worsening of UC or CD, loss of adequate benefit from vedolizumab, commencement or increased dose of corticosteroid or immunomodulator therapy due to the worsening of UC or CD, or serious AE indicating the worsening of UC or CD.



Patients at risk:

| | | | | |
|----|-----|-----|-----|-----|
| UC | 132 | 131 | 121 | 112 |
| CD | 143 | 137 | 127 | 118 |



Patients at risk:

| | | | | |
|----|-----|-----|-----|-----|
| UC | 132 | 128 | 120 | 110 |
| CD | 143 | 134 | 120 | 113 |

FIGURE 1 Time to re-escalation to Q4W dosing and relapse. (A) Time to dosing re-escalation was defined as the time from the last vedolizumab dose during GEMINI LTS to the date of the first dose on the Q4W regimen. (B) Time to relapse is defined as the time from the last vedolizumab dose during GEMINI LTS to the date of relapse. Relapse was considered any of the following events: vedolizumab re-escalation from Q8W to Q4W dosing, study withdrawal due to AE indicating the worsening of UC or CD, loss of adequate benefit from vedolizumab, commencement or increased dose of corticosteroid or immunomodulator therapy due to the worsening of UC or CD, or serious AE indicating the worsening of UC or CD. Only patients starting the study on Q8W dosing were included. AE, adverse event; CD, Crohn's disease; LTS, long-term safety; Q4W, every 4 weeks; Q8W, every 8 weeks; UC, ulcerative colitis

activity and vedolizumab Q8W dosing efficacy, helping physicians assess the need for re-escalation to Q4W dosing.

The safety profile of vedolizumab was similar to that previously reported in patients with UC and CD. In GEMINI LTS, AEs leading to the discontinuation of vedolizumab and serious infections were particularly low at 10%-12% and 5%-8%, respectively. The most commonly reported AEs were the exacerbation of UC or CD and nasopharyngitis.^{11,12} Long-term exposure to vedolizumab also did not increase AE frequency (eg, gastrointestinal AEs and serious infections).¹⁵

The data from this 2-year analysis support continued safety and minimal loss of efficacy with Q8W vedolizumab maintenance dosing frequency. However, due to the few incidences of relapse in this

study, no additional conclusions can be made regarding patient or disease characteristics that may predict loss of adequate response to Q8W dosing. Additional patient follow-up and assessment of disease activity may be needed to further identify any predictive factors for loss of response. Additionally, patients enrolled in the preceding clinical trials and the XAP only partially represent the inflammatory bowel disease population; hence, real-world studies are recommended to confirm the effectiveness and safety of the reduction of vedolizumab dosing frequency to Q8W in routine clinical practice.

In conclusion, high patient persistence with vedolizumab 300 mg intravenously Q8W was observed in the first 2 years after the reduction of dosing frequency in the XAP. There were low rates of Q4W dose re-escalation and UC or CD disease relapse,

TABLE 4 Adverse events

| | UC N = 142 | | CD N = 169 | |
|--|---------------|-----------------|----------------|-----------------|
| | Events, n | Patients, n (%) | Events, n | Patients, n (%) |
| Any AEs | 185 | 63 (44.4) | 212 | 83 (49.1) |
| Related | 7 | 3 (2.1) | 7 | 7 (4.1) |
| Not related | 178 | 60 (42.3) | 205 | 76 (45.0) |
| Mild | 97 | 23 (16.2) | 106 | 32 (18.9) |
| Moderate | 80 | 34 (23.9) | 97 | 43 (25.4) |
| Severe | 8 | 6 (4.2) | 9 | 8 (4.7) |
| Serious AEs | 13 | 12 (8.5) | 19 | 18 (10.7) |
| Related | 2 | 1 (0.7) | 1 | 1 (0.6) |
| Not related | 11 | 11 (7.7) | 18 | 17 (10.1) |
| Mild | 1 | 1 (0.7) | 1 | 1 (0.6) |
| Moderate | 5 | 5 (3.5) | 11 | 11 (6.5) |
| Severe | 7 | 6 (4.2) | 7 | 6 (3.6) |
| AEs leading to vedolizumab discontinuation | 4 | 4 (2.8) | 2 | 2 (1.2) |
| Deaths | 0 | 0 | 1 ^a | 1 (0.6) |
| Common AEs reported by ≥3% of patients | | | | |
| Colitis (excluding infective) | | 15 (10.6) | | 26 (15.4) |
| Nasopharyngitis | | 7 (4.9) | | 5 (3.0) |
| Necrotising enterocolitis | | 5 (3.5) | | 5 (3.0) |
| Influenza | | — | | 8 (4.7) |
| Lower respiratory tract and lung infection | | — | | 6 (3.6) |
| Arthralgia | | — | | 6 (3.6) |
| Herpes | | 5 (3.5) | | — |

Note: Patients with more than one AE were counted only once at their closest relationship level (related vs not related) and only once at their maximum intensity level (severe vs moderate vs mild). Abbreviations: AE, adverse event; CD, Crohn's disease; UC, ulcerative colitis.

^aOne patient died due to chronic obstructive pulmonary disease exacerbation.

and the safety of vedolizumab was consistent with the established safety profile with no new signals observed. Overall, this 2-year data analysis suggests the reduction of vedolizumab dosing frequency to Q8W is a safe and clinically relevant long-term treatment strategy in patients with well-controlled UC or CD. High treatment persistence together with low rates of relapse in patients on Q8W dosing may help inform physician decisions on necessary dose adjustments in patients with UC or CD treated with vedolizumab.

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AUTHORSHIP

Guarantor of the article: Silvio Danese, MD, PhD.

Author contributions: All authors contributed to the study concept and design and were involved in interpreting the data. DL was involved in the statistical analysis. All authors contributed to the drafting or revising of the manuscript and gave their final approval of the version to be published.

PRIOR PRESENTATION

An abstract for this study was presented as a digital oral presentation (DOP60) at the 2020 European Crohn's and Colitis Organisation Congress held February 12 to 15, 2020 in Vienna, Austria, and as a poster (Tu1865) at the 2020 Digestive Disease Week Virtual Congress.

DATA AVAILABILITY STATEMENT

The datasets, including the redacted study protocol, redacted statistical analysis plan, and individual participants data supporting the results reported in this article, will be made available within three months from initial request to researchers who provide a methodologically sound proposal. The data will be provided after its de-identification, in compliance with applicable privacy laws, data protection and requirements for consent and anonymisation.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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