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The safety of vedolizumab for ulcerative colitis and Crohn's disease

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ABSTRACT

Objective Vedolizumab is a gut-selective antibody to $\alpha_4\beta_7$ integrin for the treatment of ulcerative colitis (UC) and Crohn's disease (CD). We report an integrated summary of the safety of vedolizumab.

Design Safety data (May 2009–June 2013) from six trials of vedolizumab were integrated. Adverse events were evaluated in patients who received ≥ 1 dose of vedolizumab or placebo and were reported as exposure-adjusted incidence rates as the number of patients experiencing the event per 100 person-years (PYs) of exposure. Predictors of serious infection were assessed using a Cox proportional hazards model.

Results In total, 2830 patients had 4811 PYs of vedolizumab exposure (median exposure range, 1–1977 days). No increased risk of any infection or serious infection was associated with vedolizumab exposure. Serious clostridial infections, sepsis and tuberculosis were reported infrequently ($\leq 0.6\%$ of patients). No cases of progressive multifocal leucoencephalopathy were observed. Independent risk factors for serious infection in UC were prior failure of a tumour necrosis factor α antagonist (HR, 1.99; 95% CIs 1.16 to 3.42; $p=0.0122$) and narcotic analgesic use (HR, 2.68; 95% CI 1.57 to 4.58; $p=0.0003$), and in CD were younger age (HR, 0.97; 95% CI 0.95 to 0.98; $p<0.0001$), corticosteroid (HR, 1.88; 95% CI 1.35 to 2.63; $p=0.0002$) or narcotic analgesic use (HR, 2.72; 95% CI 1.90 to 3.89; $p<0.0001$). Investigator-defined infusion-related reactions were reported for $\leq 5\%$ of patients in each study. Eighteen vedolizumab-exposed patients ($<1\%$) were diagnosed with a malignancy.

Conclusions Vedolizumab has a favourable safety profile with low incidence rates of serious infections, infusion-related reactions and malignancies over an extended treatment period.

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INTRODUCTION

Leucocyte migration into inflamed intestinal tissue is regulated by specific molecular mechanisms. The $\alpha_4\beta_7$ integrin, a cell surface glycoprotein variably expressed on circulating B lymphocytes and T lymphocytes, interacts with mucosal addressin cell adhesion molecule-1 on intestinal vasculature.¹ Vedolizumab is a gut-selective, humanised

Significance of this study

What is already known on this subject?

- Vedolizumab is a monoclonal antibody that targets the $\alpha_4\beta_7$ integrin and selectively prevents the infiltration of leucocytes into the gastrointestinal submucosa.
- The efficacy and safety of vedolizumab in adults with IBD have been demonstrated in several clinical trials with follow-up to 1 year.
- Safety issues such as progressive multifocal leucoencephalopathy, infection and malignancy have been associated with other therapeutic monoclonal antibodies that are used to treat UC and CD, such as tumour necrosis factor α antagonists and the integrin antagonist, natalizumab.

What are the new findings?

- Treatment with vedolizumab for up to 5 years in a population of over 2800 patients demonstrated a favourable safety profile.
- No cases of progressive multifocal leucoencephalopathy have been reported with vedolizumab to date.
- Vedolizumab is not associated with an increased risk of serious or opportunistic infections, and the rate of malignancy (0.1/100 person-years) is consistent with that observed in patients with IBD normally.
- Infusion-related reactions, enteric infections and autoimmune events occur infrequently with vedolizumab treatment.

How might it impact on clinical practice in the foreseeable future?

- A favourable benefit-risk profile makes vedolizumab a useful option for the long-term treatment of IBD.



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monoclonal antibody targeting $\alpha_4\beta_7$ integrin.^{2–3} Clinical studies have demonstrated a positive benefit-risk profile of vedolizumab in adult patients with moderately to severely active ulcerative colitis (UC) or Crohn's disease (CD).^{4–6} No major differences in safety profiles were observed between placebo-treated and vedolizumab-treated patients.

Nevertheless, important questions remain about the long-term safety (LTS) of vedolizumab in patients with inflammatory bowel disease (IBD). To address this issue, the cumulative LTS of vedolizumab was assessed in an integrated summary of data from six double-blind or open-label trials of patients with UC or CD.⁴⁻¹⁰

METHODS

Patients

Safety data were analysed from six clinical studies of vedolizumab (two phase 2 and four phase 3 studies) in patients with UC or CD that were conducted from 2 May 2007 through 27 June 2013 (figure 1 and online supplementary table S1).⁴⁻¹⁰ These trials have been described previously.⁴⁻¹⁰ The data reported here represent all phase 2 and phase 3 clinical studies in patients with IBD conducted to date with a bioequivalent formulation of the approved drug.

The overall safety population was defined as all patients (N=2932) who received one or more doses of study drug (vedolizumab or placebo) in at least one of the six studies (figure 1). The phase 3 safety population included patients from the phase 3 studies only (N=2884). Patients who received only placebo during GEMINI 1, GEMINI 2 or GEMINI 3 (n=504) represented the placebo-exposed group; however, these patients may have received vedolizumab during GEMINI LTS. Integrated analyses were performed separately for each indication (UC or CD). For patients who participated in multiple studies, all safety data during vedolizumab exposure were combined. For GEMINI LTS, which is still ongoing, an interim data cut through 27 June 2013 was used.

Safety and tolerability end points and analyses

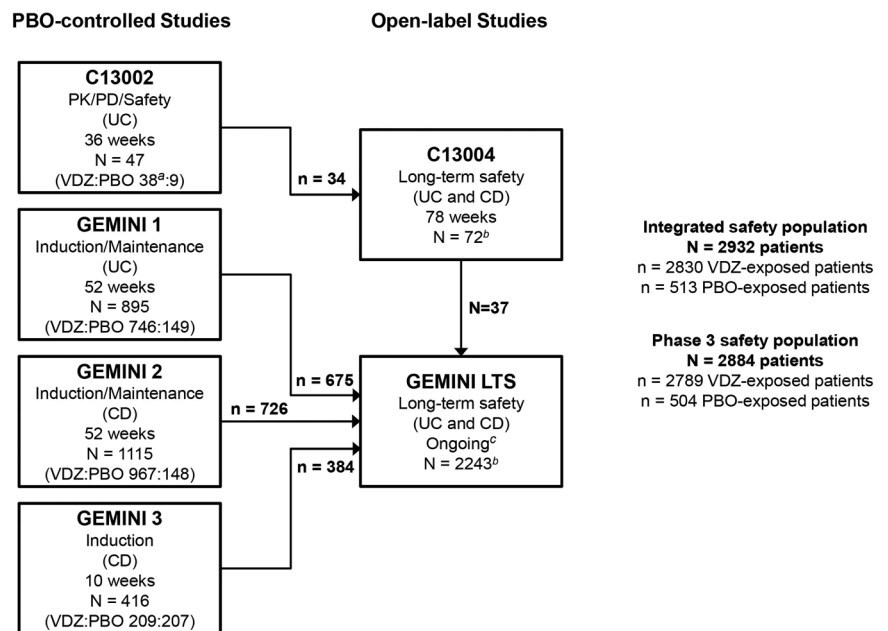
Safety and tolerability were evaluated in all patients in the safety population according to their exposure to study drug. Exposure was calculated using the number of days the patient received study drug, based on first and last dose dates. For patients not enrolled in the ongoing GEMINI LTS study at the data cut-off date, 16 weeks were added to the date of the last dose to account for the known duration of detectable vedolizumab

serum concentrations.¹¹ In phase 2 studies, a dose was defined as any amount of infusion, and in phase 3 studies, as $\geq 75\%$ of the infusion by volume. Total vedolizumab exposure for a patient was calculated as the sum of exposures in all applicable studies. For patients who received only placebo, exposure to vedolizumab was calculated as 0 days.

Adverse events (AEs) were defined as any untoward medical occurrence in a patient administered a pharmaceutical product, which did not necessarily have a causal relationship with the treatment, and serious AEs (SAEs) were defined as any diagnosis of progressive multifocal leucoencephalopathy (PML) or any AE that was considered an important medical event, a congenital anomaly or life-threatening, or resulted in significant disability, hospitalisation or death. AEs and SAEs were classified by intensity (see online supplementary materials) and according to the *Medical Dictionary for Regulatory Activities* (MedDRA)¹² V14.0. Verbatim terms defined by MedDRA were used. Exposure-adjusted incidence rates, defined as the number of patients experiencing the event per 100 person-years (PYs) of exposure, were reported for AEs. Days of exposure were calculated from the AE onset date minus the date of first dose plus 1. PYs of exposure were calculated for the first occurrence of each AE, and truncated after a patient experienced the AE, although the patient continued to contribute PYs for different AEs experienced, if applicable. Thus, the total PYs of exposure could differ by AE. Patients randomised to placebo in a placebo-controlled study and then enrolled in an open-label study could contribute to events in either the placebo or vedolizumab group depending on when they experienced the AE. PYs were calculated accordingly for placebo or vedolizumab for each AE. Recognising the disproportionate PYs of follow-up for placebo compared with vedolizumab, statistical comparisons were not performed between the two groups. Calculation of 95% CIs when the number of events was 0 followed the rule of 3 (ie, $(0, (3/\text{total PYs}) \times 100)$).

Infusion-related reactions (IRRs) were defined as AEs occurring on the day of or one calendar day after the infusion that were assessed by the investigator as infusion-related. In addition, blood samples for antivedolizumab antibody (AVA) assessment

Figure 1 Patient distribution within the overall safety population. The overall safety population includes all patients who received ≥ 1 dose of study drug in the six studies. The phase 3 safety population includes patients from the phase 3 GEMINI studies only. Patients randomised to PBO in GEMINI 1, GEMINI 2 or GEMINI 3 and who enrolled into GEMINI LTS received open-label VDZ in that study. Thus, VDZ-exposed patients may also have been exposed to PBO. CD, Crohn's disease; LTS, long-term safety; PBO, placebo; PD, pharmacodynamics; PK, pharmacokinetics; UC, ulcerative colitis; VDZ, vedolizumab. ^aOne enrolled patient randomised to VDZ was not dosed. ^bIncludes 38 and 421 VDZ-naïve patients who enrolled directly into C13004 or GEMINI LTS, respectively. ^cIncludes data collected from 22 May 2009 to 27 June 2013.



were collected within 30 min before dosing in the phase 3 studies and within 2 h in the phase 2 studies. Immunogenicity was determined as described elsewhere.¹³

Predictors of serious infections

A Cox proportional hazards model with time-dependent covariates was used to determine the relative contribution (HRs and 95% CIs) of different factors to the occurrence of serious infections in the phase 3 safety population, which included patients in both treatment arms. Predictors were analysed in the UC and CD populations alone and combined. Factors assessed were age, sex, disease duration, baseline disease activity, prior history of tumour necrosis factor α antagonist (anti-TNF) failure, baseline use of immunosuppressives, on-study use of narcotic analgesics (all opioids) or on-study use of corticosteroids. Patients were considered corticosteroid users in this model if they received corticosteroids within 30 days before the infection date. When patients with UC and CD were combined, a common disease activity index was created to measure the contribution of baseline disease activity (see online supplementary table S2). Vedolizumab treatment was not included as a covariate because nearly all patients analysed were exposed to vedolizumab at one point (97%), invariably resulting in significantly lower HRs for serious infection.

Progressive multifocal leucoencephalopathy screening and hypothetical estimation of risk

Patients were screened for symptoms of PML with an algorithm for PML risk minimisation as described elsewhere.¹⁴ Briefly, when new neurological symptoms were reported, patients were referred to a dedicated study neurologist co-investigator for further evaluation, and when indicated, the case was reviewed by an independent adjudication committee (IAC) composed of academic neurologists, neuroradiologists and a virologist (see online supplementary materials).

The likelihood of observing any PML cases with vedolizumab was calculated assuming that the PML incidence rate was similar to that of natalizumab and that the number of expected cases

would follow a Poisson distribution (see online supplementary materials).

RESULTS

Patient baseline characteristics and treatment exposure

The overall safety population included 2932 patients who enrolled in the six studies (figure 1). Of these, 2830 patients were exposed to one or more doses of vedolizumab, contributing a total of 4811 PYs of vedolizumab exposure (see online supplementary figure S1). The phase 3 safety population was composed of 2884 patients, of whom 504 patients received placebo (figure 1), contributing a total of 214 PYs of placebo exposure (see online supplementary figure S1). Placebo-treated patients from GEMINI 1, GEMINI 2 and GEMINI 3 who enrolled in GEMINI LTS received open-label vedolizumab and therefore also contributed to PYs of vedolizumab exposure. Thus, most patients (97%) in the phase 3 safety population received one or more doses of vedolizumab (table 1). The median vedolizumab exposure in the phase 3 safety population was 378 days (range, 1–1977) and 338 days (range, 1–1927) for patients with UC and CD, respectively (table 2). In the overall safety population, the number of PYs of vedolizumab exposure was >22 times that for placebo.

Baseline characteristics are reported for the phase 3 safety population by disease and separately for the 504 patients who received placebo (table 1). Placebo-exposed patients were similar to the overall population with respect to age, sex, disease duration, concomitant medication use, narcotic analgesic use, smoking status and prior anti-TNF failure history.

Adverse events and serious adverse events

Exposure-adjusted incidence rates for all AEs and all SAEs were lower with vedolizumab exposure than with placebo. In the overall safety population, 247.8 (95% CI 229.8 to 265.8) and 20.0 (95% CI 18.5 to 21.5) vedolizumab-exposed patients experienced an AE or SAE, respectively, per 100 PYs of follow-up compared with 419.4 (95% CI 359.3 to 479.5) and 28.3 (95% CI 20.6 to 35.9) patients receiving placebo (table 3). The majority of SAEs in UC and CD populations and with

Table 1 Baseline characteristics of the phase 3 safety population

| Characteristic | UC (n=1114) | CD (n=1770) | UC and CD* (N=2884) | UC and CD Placebo† (n=504) |
|--|-----------------|-----------------|---------------------|----------------------------|
| Received ≥ 1 dose of vedolizumab, n (%) | 1077 (97) | 1712 (97) | 2789 (97) | 409 (81) |
| Age, mean years \pm SD | 40.4 \pm 13.4 | 36.8 \pm 12.5 | 38.2 \pm 13.0 | 38.8 \pm 13.1 |
| Sex, female, n (%) | 462 (42) | 974 (55) | 1436 (50) | 254 (50) |
| Disease duration, n (%)‡ | | | | |
| <7 years | 679 (61) | 833 (47) | 1512 (52) | 269 (53) |
| ≥ 7 years | 404 (36) | 929 (53) | 1333 (46) | 235 (47) |
| Mean years \pm SD | 7.2 \pm 6.8 | 9.5 \pm 8.1 | 8.7 \pm 7.7 | 8.6 \pm 7.8 |
| Disease activity, mean score \pm SD | | | | |
| Partial Mayo score | 5.9 \pm 1.8 | N/A | 5.9 \pm 1.8 | 6.1 \pm 1.5 |
| HBI score | N/A | 11.0 \pm 3.6 | 11.0 \pm 3.6 | 10.7 \pm 3.4 |
| Prior anti-TNF therapy failure, n (%) | 483 (45) | 1127 (64) | 1610 (57) | 289 (57) |
| Concomitant medications, n (%) | | | | |
| Corticosteroid | 591 (53) | 925 (52) | 1516 (53) | 263 (52) |
| Immunosuppressive | 359 (32) | 558 (32) | 917 (32) | 164 (33) |
| Narcotic analgesic use, n (%) | 102 (9) | 310 (18) | 412 (14) | 70 (14) |
| Current smoker, n (%) | 60 (5) | 469 (27) | 529 (18) | 103 (20) |

*Phase 3 safety population includes patients from studies GEMINI 1, GEMINI 2, GEMINI 3 and GEMINI LTS. Patients in study C13004 who rolled over to GEMINI LTS are included.

†Includes patients who were randomised to placebo in studies GEMINI 1, GEMINI 2 and GEMINI 3.

‡Does not include patients who began treatment in study C13002 or C13004.

anti-TNF, tumour necrosis factor α antagonist; CD, Crohn's disease; HBI, Harvey-Bradshaw index; LTS, long-term safety; N/A, not applicable; SD, standard deviation; UC, ulcerative colitis.

Table 2 Exposure to study drug in the phase 3 safety population

| | UC (n=1114) | CD (n=1770) | UC and CD* (N=2884) |
|--|---------------------------|---------------------------|---------------------|
| Patients exposed to vedolizumab, n (%) | | | |
| ≥1 dose | 1077 (97) | 1712 (97) | 2789 (97) |
| ≥6 months | 837 (75) | 1163 (66) | 2000 (69) |
| ≥12 months | 574 (52) | 827 (47) | 1401 (49) |
| ≥18 months | 473 (42) | 677 (38) | 1150 (40) |
| ≥24 months | 428 (38) | 478 (27) | 906 (31) |
| ≥36 months | 198 (18) | 209 (12) | 407 (14) |
| ≥48 months | 30 (3) | 10 (1) | 40 (1) |
| Extent of vedolizumab exposure, days | | | |
| Median (Min, Max) | 378 (1, 1977) | 338 (1, 1927) | 365 (1, 1977) |
| Extent of placebo exposure, days | | | |
| | UC GEMINI 1 (n=149) | CD GEMINI 2 (n=148) | GEMINI 3 (n=207) |
| Median (Min, Max) | 99 (1, 362) | 106 (1, 372) | 42 (1, 72) |

*Patients participated in studies GEMINI 1, GEMINI 2, GEMINI 3 and GEMINI LTS. Patients in study C13004 who rolled over to GEMINI LTS are included. CD, Crohn's disease; LTS, long-term safety; UC, ulcerative colitis.

either treatment were gastrointestinal (GI) events and infections. Prolonged exposure to vedolizumab did not increase the frequency of AEs or SAEs, including GI SAEs or serious infections (see online supplementary table S3 and figure S2).

Uncommon but important non-infectious events associated with anti-TNFs, such as congestive heart failure exacerbation or demyelination, were not seen with vedolizumab. A single case of demyelination occurred in a placebo-treated patient. Overall, 15 patients exposed to vedolizumab developed psoriatic conditions, with a rate of 0.3/100 PYs (95% CI 0.2 to 0.5), and no placebo-exposed patients.

Infections and serious infections

In the overall safety population, the exposure-adjusted incidence rates of any infection were lower among patients receiving vedolizumab (63.5/100 PYs; 95% CI 59.6 to 67.3) than placebo (82.9/100 PYs; 95% CI 68.3 to 97.5) (table 4). Most infections were mild to moderate in severity and responded to standard treatment while patients had continued exposure to vedolizumab. The exposure-adjusted incidence rates of serious infections were similar for vedolizumab and placebo (table 5). Few patients (<1%) discontinued treatment because of infection.

Upper respiratory tract infections accounted for approximately half or more of the total infections reported (table 4). The incidence rates of upper respiratory tract infections were 28.6/100 PYs with vedolizumab and 34.7/100 PYs with placebo. Abdominal and GI infections and lower respiratory tract and lung infections occurred with similar incidence rates for vedolizumab and placebo. All other infections with vedolizumab occurred with an incidence rate of <5/100 PYs (table 4).

Serious infections of interest, including clostridial infections, sepsis, tuberculosis (TB) and *Listeria* meningitis were reported for between 1 and 15 patients (≤0.6%) (table 5). All clostridial infections occurred in vedolizumab-exposed patients (tables 4 and 5). Of the four reports of TB, three were diagnoses of pulmonary TB in patients (one UC and two CD) enrolled in GEMINI LTS who had negative screenings for TB at enrolment and were taking concomitant immunosuppressives. All cases were considered to be primary infections with no extrapulmonary manifestations. In addition, latent TB was diagnosed in one

patient with CD who was previously treated with immunosuppressives. All cases of active TB occurred in hyperendemic jurisdictions. One vedolizumab-treated patient taking concomitant methylprednisolone and azathioprine developed *Listeria* meningitis; the infection resolved with treatment.

The higher rate of GI infections in vedolizumab patients was largely due to gastroenteritis. Rates of gastroenteritis with vedolizumab and placebo, respectively, were 3.7/100 PYs and 0/100 PYs in patients with UC and 4.2/100 PYs and 2.3/100 PYs in patients with CD. As expected, abscesses were prevalently observed in the CD population. Rates of abscess and serious abscess were 4.8/100 PYs and 2.4/100 PYs, respectively, in vedolizumab-treated patients with CD, the majority being anal, rectal or perirectal (tables 4 and 5). Notably, abscess rates were higher with placebo than vedolizumab (table 4).

Progressive multifocal leucoencephalopathy

Unexplained neurological symptoms were experienced by 10% of patients in the overall safety population. Serial evaluation of these 290 patients revealed that 64 had evidence of neurological abnormalities. None of the 86 cases referred to the IAC were identified as PML after extensive review. No confirmed PML cases have been documented during 2 years of telephone follow-up.

Across all vedolizumab clinical studies, 3326 participants were exposed to vedolizumab for ≤24 months, and 906 participants were exposed to vedolizumab for >24 months. Approximately 80% of patients in both subgroups had prior immunosuppressive exposure. Assuming 50% seropositivity for anti-John Cunningham virus (JCV) antibodies, modelling the expected number of cases as a Poisson distribution using natalizumab risk estimates suggests that an average of six to seven cases would have occurred in the current vedolizumab safety population had the risk of PML been similar to that of natalizumab. The probability of observing 0 PML cases in this context is exceedingly low ($p < 0.0012$) (see online supplementary figure S3).

Risk factors for serious infection

Risk factors for serious infection were assessed with a Cox proportional hazards model (table 6). Independent risk factors for serious infection in patients with UC were prior anti-TNF failure (HR, 1.99; 95% CI 1.16 to 3.42; $p = 0.0122$) and concomitant narcotic analgesic use (HR, 2.68; 95% CI 1.57 to 4.58; $p = 0.0003$). For patients with CD, younger age (HR, 0.97; 95% CI 0.95 to 0.98; $p < 0.0001$), concomitant corticosteroid use (HR, 1.88; 95% CI 1.35 to 2.63; $p = 0.0002$) and concomitant narcotic analgesic use (HR, 2.72; 95% CI 1.90 to 3.89; $p < 0.0001$) were independent risk factors for serious infection. The same risk factors identified for patients with CD alone were observed in the combined UC and CD population (younger age (HR, 0.98; 95% CI 0.97 to 1.00; $p = 0.0003$), concomitant corticosteroid use (HR, 1.72; 95% CI 1.30 to 2.28; $p = 0.0002$) and concomitant narcotic analgesic use (HR, 2.76; 95% CI 2.06 to 3.72; $p < 0.0001$)). Baseline disease activity was not associated with a greater risk of serious infection (table 6).

Immunogenicity

AVAs were detected in 56 of 1434 patients (4%) from GEMINI 1 and GEMINI 2 treated with vedolizumab continuously for up to 52 weeks; of these 56 patients, 9 were persistently positive (defined by AVA-positive samples on two or more consecutive visits), and 33 developed neutralising antibodies. During follow-up, among 320 patients who had data available from a

Table 3 Exposure-adjusted incidence rates of adverse events in the overall safety population

| Adverse event | UC | | | CD | | | UC and CD | | | | | |
|---|----------------------------|--|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|------------------------|------|------------------------|
| | Placebo n=149* | Wedolizumab n=1107† | Placebo n=355‡ | Placebo n=504§ | Wedolizumab n=1723§ | Placebo n=504 | Placebo n=2830** | Placebo n=504 | Wedolizumab n=1723§ | | | |
| | No. of patients with event | No. of patients with event/100 PY (95% CI) | No. of patients with event | No. of patients with event | No. of patients with event | No. of patients with event | No. of patients with event | No. of patients with event | No. of patients with event | | | |
| Any AE | 114 | 351.6 (269.6 to 433.7) | 973 | 198.4 (175.1 to 221.7) | 241 | 461.5 (378.4 to 544.6) | 1576 | 292.8 (266.8 to 318.7) | 355 | 419.4 (359.3 to 479.5) | 2549 | 247.8 (229.8 to 265.8) |
| Any SAE | 17 | 22.6 (11.6 to 33.6) | 258 | 13.7 (11.9 to 15.4) | 39 | 31.8 (21.5 to 42.0) | 584 | 25.1 (22.9 to 27.4) | 56 | 28.3 (20.6 to 35.9) | 842 | 20.0 (18.5 to 21.5) |
| Common AEs (≥10 patients with events/100 PY in any patient group) | | | | | | | | | | | | |
| Nasopharyngitis | 11 | 13.9 (5.5 to 22.4) | 226 | 13.1 (11.3 to 14.9) | 18 | 14.1 (7.5 to 20.8) | 315 | 13.8 (12.2 to 15.4) | 29 | 14.1 (8.8 to 19.3) | 541 | 13.5 (12.3 to 14.7) |
| Abdominal pain† | 10 | 13.2 (4.9 to 21.5) | 138 | 7.3 (6.0 to 8.5) | 31 | 25.3 (16.4 to 34.2) | 367 | 16.0 (14.3 to 17.7) | 41 | 20.7 (14.3 to 27.1) | 505 | 12.1 (11.0 to 13.2) |
| Headache | 13 | 17.1 (7.5 to 26.7) | 172 | 9.6 (8.0 to 11.1) | 34 | 27.9 (18.1 to 37.8) | 299 | 13.0 (11.4 to 14.6) | 47 | 23.7 (16.7 to 30.8) | 471 | 11.5 (10.4 to 12.6) |
| Arthralgia | 10 | 13.0 (4.9 to 21.2) | 151 | 8.2 (6.8 to 9.5) | 29 | 23.1 (14.6 to 31.5) | 314 | 13.7 (12.1 to 15.3) | 39 | 19.3 (13.2 to 25.4) | 465 | 11.2 (10.1 to 12.3) |
| Upper respiratory tract infection | 23 | 30.7 (17.7 to 43.7) | 159 | 8.6 (7.2 to 10.0) | 44 | 37.2 (25.8 to 48.6) | 175 | 7.0 (5.9 to 8.0) | 24 | 11.6 (6.9 to 16.3) | 334 | 7.7 (6.8 to 8.5) |
| Nausea | 11 | 14.3 (5.8 to 22.7) | 95 | 4.8 (3.8 to 5.8) | 16 | 12.6 (6.2 to 19.0) | 230 | 9.5 (8.2 to 10.8) | 27 | 13.2 (8.1 to 18.3) | 325 | 7.4 (6.6 to 8.3) |
| Pyrexia | 5 | 6.3 (0.7 to 11.8) | 78 | 3.9 (3.0 to 4.8) | 30 | 23.8 (15.1 to 32.6) | 232 | 9.4 (8.2 to 10.7) | 35 | 17.0 (11.3 to 22.8) | 310 | 7.0 (6.2 to 7.8) |
| Vomiting | 6 | 7.6 (1.5 to 13.6) | 51 | 2.5 (1.8 to 3.2) | 15 | 11.7 (5.8 to 17.7) | 177 | 7.0 (6.0 to 8.1) | 21 | 10.1 (5.8 to 14.5) | 228 | 5.0 (4.4 to 5.7) |
| Anaemia | 11 | 14.3 (5.7 to 22.9) | 91 | 4.6 (3.7 to 5.6) | 10 | 7.7 (2.9 to 12.5) | 98 | 3.7 (3.0 to 4.5) | 21 | 10.2 (5.8 to 14.6) | 189 | 4.1 (3.5 to 4.7) |
| Exacerbation of CD | N/A | N/A | N/A | N/A | 57 | 47.3 (34.4 to 60.2) | 486 | 20.4 (18.5 to 22.4) | 57 | 47.3 (34.4 to 60.2) | N/A | N/A |
| Exacerbation of UC | 29 | 38.2 (24.2 to 52.1) | 290 | 15.5 (13.6 to 17.4) | N/A | N/A | N/A | N/A | 29 | 38.2 (24.2 to 52.1) | N/A | N/A |

Exposure-adjusted incidence rates for each AE were calculated by dividing the number of patients experiencing the event by the total PYs, multiplied by 100. PYs were calculated as the sum of each patient's contribution, calculated from the days of exposure (ie, AE onset date minus the date of first dose plus 1 day). For each AE, the PYs were truncated after a patient experienced the AE and each AE was counted only once per patient. Patients who were randomised to placebo and then rolled over into an open-label study could contribute to events in either the placebo or vedolizumab group depending on when they experienced the AE. PYs were calculated accordingly for placebo or vedolizumab for each AE. When the number of events=0, the 95% CI was calculated based on rule of 3 (ie, (0, 3/total PYs)×100).

*Includes patients from GEMINI 1.
 †Includes patients from studies C13002, C13004, GEMINI 1 and GEMINI LTS.
 ‡Includes patients from GEMINI 2 and GEMINI 3.
 §Includes patients from studies C13004, GEMINI 2, GEMINI 3 and GEMINI LTS.
 ¶Includes patients from GEMINI 1, GEMINI 2 and GEMINI 3.
 **Includes patients from all six studies.
 ††Includes MedDRA preferred terms: abdominal pain, abdominal rebound tenderness, abdominal rigidity, abdominal tenderness, abdominal pain upper, GI pain, AE, adverse event, CD, Crohn's disease; LTS, long-term safety; MedDRA, Medical Dictionary for Regulatory Activities; N/A, not applicable; PY, person-year; SAE, serious adverse event; UC, ulcerative colitis.

Table 4 Exposure-adjusted incidence rates of infections in the overall safety population

| Adverse event | UC | | | CD | | | UC and CD | | |
|---|--|--|--|--|--|--|--|--|--|
| | Placebo n=149* | Vedolizumab n=1107† | Placebo n=355‡ | Placebo n=504¶ | Vedolizumab n=1723§ | Placebo n=504¶ | Vedolizumab n=2830** | | |
| | No. of patients with event/100 PY (95% CI) | No. of patients with event/100 PY (95% CI) | No. of patients with event/100 PY (95% CI) | No. of patients with event/100 PY (95% CI) | No. of patients with event/100 PY (95% CI) | No. of patients with event/100 PY (95% CI) | No. of patients with event/100 PY (95% CI) | | |
| Any infection†† | 46 | 625 | 93 | 139 | 981 | 139 | 1606 | | |
| Common infections (≥0.5 patient events/100 PY in any patient group) | 71.9 (49.7 to 94.1) | 56.8 (51.2 to 62.3) | 89.7 (70.5 to 108.9) | 82.9 (68.3 to 97.5) | 68.6 (63.4 to 73.9) | 82.9 (68.3 to 97.5) | 63.5 (59.6 to 67.3) | | |
| Upper respiratory tract infections | 23 | 398 | 44 | 67 | 569 | 67 | 967 | | |
| Abdominal and GI infections | 4 | 91 | 10 | 14 | 240 | 14 | 331 | | |
| Gastroenteritis (PT) | 0 | 73 | 3 | 3 | 110 | 3 | 183 | | |
| Abscess††, §§, ¶¶ | 3 | 6 | 7 | 10 | 125 | 10 | 131 | | |
| Anal, rectal and perirectal†† | 2 | 5 | 6 | 8 | 91 | 8 | 96 | | |
| Abdominal and intestinal§§ | 0 | 0 | 0 | 0 | 26 | 0 | 26 | | |
| Abscess, other¶¶ | 1 | 1 | 1 | 2 | 11 | 2 | 12 | | |
| Lower respiratory tract and lung infections | 7 | 105 | 9 | 16 | 165 | 16 | 270 | | |
| Urinary tract infections | 5 | 77 | 5 | 10 | 134 | 10 | 211 | | |
| Influenza viral infections | 3 | 79 | 6 | 9 | 102 | 9 | 181 | | |
| Viral infections NEC | 6 | 61 | 5 | 11 | 93 | 11 | 154 | | |
| Candida, tinea and other fungal infections*** | 2 | 50 | 8 | 10 | 93 | 10 | 143 | | |
| Herpes viral infections | 2 | 40 | 7 | 9 | 78 | 9 | 118 | | |
| Herpes zoster (PT) | 0 | 10 | 2 | 2 | 25 | 2 | 35 | | |
| Infections NEC | 2 | 40 | 1 | 3 | 56 | 3 | 96 | | |
| Dental and oral soft tissue infections | 1 | 29 | 2 | 3 | 56 | 3 | 85 | | |
| Skin structures and soft tissue infections | 0 | 16 | 6 | 6 | 58 | 6 | 74 | | |
| Ear infections | 3 | 25 | 1 | 4 | 41 | 4 | 66 | | |
| Eye and eyelid infections | 0 | 18 | 3 | 3 | 21 | 3 | 39 | | |
| Streptococcal infections | 0 | 15 | 1 | 1 | 21 | 1 | 36 | | |
| Clostridial infections | 0 | 18 | 0 | 0 | 16 | 0 | 34 | | |
| Cellulitis (PT) | 2 | 11 | 2 | 4 | 18 | 4 | 29 | | |
| Folliculitis (PT) | 0 | 6 | 0 | 0 | 23 | 0 | 29 | | |
| Female reproductive tract infections | 1 | 5 | 1 | 2 | 11 | 2 | 16 | | |
| Sepsis and related terms††† | 1 | 4 | 1 | 2 | 8 | 2 | 12 | | |

Adverse events are listed according to the MedDRA high-level term unless otherwise indicated. Exposure-adjusted incidence rates for each adverse event (AE) were calculated by dividing the number of patients experiencing the event by the total PYs, multiplied by 100. PYs were calculated as the sum of each patient's contribution, calculated from days of exposure (ie, AE onset date minus the date of first dose plus 1 day). For each AE, the PYs were truncated after a patient experienced the AE and each AE was counted only once per patient. Patients who were randomised to placebo and then rolled over into an open-label study could contribute to events in either the placebo or vedolizumab group depending on when they experienced the AE. PYs were calculated accordingly for placebo or vedolizumab for each AE. When the number of events=0, the 95% CI was calculated based on rule of 3 (ie, (0, 3/total PYs)×100). Infections occurring in ≥0.5 patients per 100 PYs in any patient group are shown.

*Includes patients from GEMINI 1.
 †Includes patients from studies C13002, C13004, GEMINI 1 and GEMINI LTS.
 ‡Includes patients from GEMINI 2 and GEMINI 3.
 §Includes patients from studies C13004, GEMINI 2, GEMINI 3 and GEMINI LTS.
 ¶Includes patients from GEMINI 1, GEMINI 2 and GEMINI 3.
 **Includes patients from all six studies.
 ††Includes all MedDRA preferred terms listed under the 'infections and infestations' system organ class.
 †††Includes all MedDRA preferred terms: anal abscess, perirectal abscess, rectal abscess, rectovaginal septum abscess.
 §§Includes MedDRA preferred terms: abdominal abscess, abscess intestinal.
 ¶¶Includes MedDRA preferred terms: abscess, perineal abscess, pelvic abscess.
 ***Includes MedDRA high-level terms: Candida infections, fungal infections NEC, tinea infections.
 ††††Includes all MedDRA preferred terms listed under the 'sepsis, bacteraemia, viraemia and fungemia NEC' high-level term.
 CD, Crohn's disease; LTS, long-term safety; MedDRA, Medical Dictionary for Regulatory Activities; NEC, not elsewhere classified; PT, preferred term; PY, person-year; UC, ulcerative colitis.

Table 5 Exposure-adjusted incidence rates of serious infections in the overall safety population

| Adverse event | UC | | | | CD | | | | UC and CD | | | |
|--|----------------------------|--|----------------------------|--|----------------------------|--|----------------------------|--|----------------------------|--|----------------------------|--|
| | Placebo n=149* | | Vedolizumab n=1107† | | Placebo n=355‡ | | Vedolizumab n=1723§ | | Placebo n=504¶ | | Vedolizumab n=2830** | |
| | No. of patients with event | No. of patients with event/100 PY (95% CI) | No. of patients with event | No. of patients with event/100 PY (95% CI) | No. of patients with event | No. of patients with event/100 PY (95% CI) | No. of patients with event | No. of patients with event/100 PY (95% CI) | No. of patients with event | No. of patients with event/100 PY (95% CI) | No. of patients with event | No. of patients with event/100 PY (95% CI) |
| Any serious infection or infestation†† | 4 | 5.0 (0.1 to 10.0) | 54 | 2.7 (1.9 to 3.4) | 4 | 3.0 (0.1 to 6.0) | 145 | 5.6 (4.6 to 6.5) | 8 | 3.8 (1.2 to 6.4) | 199 | 4.3 (3.7 to 4.9) |
| Serious infections of interest | | | | | | | | | | | | |
| Gastroenteritis (PT) | 0 | 0.0 (0.0 to 3.7) | 3 | 0.1 (0.0 to 0.3) | 0 | 0.0 (0.0 to 2.3) | 14 | 0.5 (0.2 to 0.8) | 0 | 0.0 (0.0 to 1.4) | 17 | 0.4 (0.2 to 0.5) |
| Abscess‡‡ | 2 | 2.5 (0.0 to 6.0) | 3 | 0.1 (0.0 to 0.3) | 1 | 0.8 (0.0 to 2.2) | 65 | 2.4 (1.8 to 3.0) | 3 | 1.4 (0.0 to 3.0) | 68 | 1.4 (1.1 to 1.8) |
| Clostridial infections | 0 | 0.0 (0.0 to 3.7) | 7 | 0.3 (0.1 to 0.6) | 0 | 0.0 (0.0 to 2.3) | 8 | 0.3 (0.1 to 0.5) | 0 | 0.0 (0.0 to 1.4) | 15 | 0.3 (0.2 to 0.5) |
| Candida, tinea and other fungal infections§§ | 0 | 0.0 (0.0 to 3.7) | 1 | <0.1 (0.0 to 0.1) | 0 | 0.0 (0.0 to 2.3) | 2 | 0.1 (0.0 to 0.2) | 0 | 0.0 (0.0 to 1.4) | 3 | 0.1 (0.0 to 0.1) |
| Sepsis and related terms¶¶ | 1 | 1.2 (0.0 to 3.7) | 4 | 0.2 (0.0 to 0.4) | 1 | 0.8 (0.0 to 2.2) | 7 | 0.3 (0.1 to 0.4) | 2 | 0.9 (0.0 to 2.2) | 11 | 0.2 (0.1 to 0.4) |
| Tuberculosis | 0 | 0.0 (0.0 to 3.7) | 1 | <0.1 (0.0 to 0.1) | 0 | 0.0 (0.0 to 2.3) | 3 | 0.1 (0.0 to 0.2) | 0 | 0.0 (0.0 to 1.4) | 4 | 0.1 (0.0 to 0.2) |
| Cytomegalovirus infections | 0 | 0.0 (0.0 to 3.7) | 2 | 0.1 (0.0 to 0.2) | 0 | 0.0 (0.0 to 2.3) | 1 | <0.1 (0.0 to 0.1) | 0 | 0.0 (0.0 to 1.4) | 3 | 0.1 (0.0 to 1.4) |
| Meningitis (PT) | 0 | 0 | 0 | 0 | 0 | 0.0 (0.0 to 2.3) | 1 | <0.1 (0.0 to 0.1) | 0 | 0.0 (0.0 to 1.4) | 1 | <0.1 (0.0 to 0.1) |
| Salmonella infections | 0 | 0.0 (0.0 to 3.7) | 1 | <0.1 (0.0 to 0.1) | 0 | 0.0 (0.0 to 2.3) | 1 | <0.1 (0.0 to 0.1) | 0 | 0.0 (0.0 to 1.4) | 2 | <0.1 (0.0 to 0.1) |

Adverse events are listed according to the MedDRA high-level term unless otherwise indicated. Exposure-adjusted incidence rates for each adverse event (AE) were calculated by dividing the number of patients experiencing the event by the total PYs, multiplied by 100. PYs were calculated as the sum of each patient's contribution, calculated from days of exposure (ie, AE onset date minus the date of first dose plus 1 day). For each AE, the PYs were truncated after a patient experienced the AE and each AE was counted only once per patient. Patients who were randomised to placebo and then rolled over into an open-label study could contribute to events in either the placebo or vedolizumab group depending on when they experienced the AE. PYs were calculated accordingly for placebo or vedolizumab for each AE. When the number of events=0, the 95% CI was calculated based on rule of 3 (ie, 0, 3/total PYs)×100. Infections occurring in ≥0.5 patients per 100 PYs in any patient group are shown.

*Includes patients from GEMINI 1.
 †Includes patients from studies C13002, C13004, GEMINI 1 and GEMINI LTS.
 ‡Includes patients from GEMINI 2 and GEMINI 3.
 §Includes patients from studies C13004, GEMINI 2, GEMINI 3 and GEMINI LTS.
 ¶Includes patients from GEMINI 1, GEMINI 2 and GEMINI 3.
 **Includes patients from all six studies.
 ††Includes all MedDRA preferred terms listed under the 'Infections and Infestations' system organ class.
 ‡‡Includes MedDRA preferred terms: anal abscess, perirectal abscess, rectal abscess, rectovaginal septum abscess, abdominal abscess, abscess intestinal, abscess, perineal abscess, pelvic abscess.
 §§Includes MedDRA high-level terms: Candida infections, fungal infections NEC, tinea infections.
 ¶¶Includes all MedDRA preferred terms listed under the 'Sepsis, bacteraemia, viraemia and fungemia NEC' high-level term.
 CD, Crohn's disease; LTS, long-term safety; MedDRA, Medical Dictionary for Regulatory Activities; NEC, not elsewhere classified; PT, preferred term; PY, person-year; UC, ulcerative colitis.

Table 6 Predictors of serious infections in the phase 3 safety population

| Variable* | Patients† | Serious infections | Adjusted results | |
|---|-----------|--------------------|---------------------|---------|
| | | | HR (95% CI) | p Value |
| UC phase 3 population | n=1114 | n=59 | | |
| Age, mean years±SD | 40.4±13.4 | 42.1±15.1 | 1.00 (0.98 to 1.02) | 0.98 |
| Sex, female, n (%) | 462 (42) | 28 (48) | 1.10 (0.65 to 1.85) | 0.72 |
| Disease duration ≥7 years, n (%) | 404 (36) | 22 (37) | 0.94 (0.54 to 1.63) | 0.82 |
| Prior anti-TNF therapy failure, n (%) | 483 (45) | 33 (56) | 1.99 (1.16 to 3.42) | 0.0122 |
| Baseline disease activity, mean Mayo score±SD | 5.9±1.8 | 5.9±1.6 | 0.96 (0.82 to 1.12) | 0.56 |
| On-study narcotic use, n (%) | 323 (29) | 34 (58) | 2.68 (1.57 to 4.58) | 0.0003 |
| On-study corticosteroid use, n (%) | 430 (39) | 22 (37) | 1.58 (0.92 to 2.71) | 0.10 |
| Baseline immunosuppressive use, n (%) | 359 (32) | 24 (41) | 1.68 (0.98 to 2.87) | 0.06 |
| Vedolizumab treatment, n (%)‡ | 1077 (97) | 56 (95) | N/A | N/A |
| CD phase 3 population | n=1770 | n=148 | | |
| Age, mean years±SD | 36.8±12.5 | 34.6±11.8 | 0.97 (0.95 to 0.98) | <0.0001 |
| Sex, female, n (%) | 974 (55) | 88 (60) | 1.30 (0.93 to 1.82) | 0.12 |
| Disease duration ≥7 years, n (%) | 929 (53) | 84 (57) | 1.18 (0.82 to 1.68) | 0.37 |
| Prior anti-TNF therapy failure, n (%) | 1127 (64) | 95 (65) | 0.82 (0.57 to 1.19) | 0.30 |
| Baseline disease activity, mean HBI score±SD | 11.0±3.6 | 10.9±3.4 | 1.01 (0.96 to 1.06) | 0.70 |
| On-study narcotic use, n (%) | 731 (41) | 96 (65) | 2.72 (1.90 to 3.89) | <0.0001 |
| On-study corticosteroid use, n (%) | 708 (40) | 66 (45) | 1.88 (1.35 to 2.63) | 0.0002 |
| Baseline immunosuppressive use, n (%) | 558 (32) | 41 (28) | 0.78 (0.54 to 1.13) | 0.19 |
| Vedolizumab treatment, n (%)‡ | 1712 (97) | 144 (97) | N/A | N/A |
| Combined phase 3 population | N=2884 | n=207 | | |
| Age, mean years±SD | 38.2±13.0 | 36.8±13.2 | 0.98 (0.97 to 1.00) | 0.0003 |
| Sex, female, n (%) | 1436 (50) | 116 (56) | 1.28 (0.97 to 1.69) | 0.09 |
| Disease duration ≥7 years, n (%) | 1333 (46) | 106 (51) | 1.12 (0.84 to 1.50) | 0.44 |
| Prior anti-TNF therapy failure, n (%) | 1610 (57) | 128 (62) | 1.19 (0.88 to 1.62) | 0.26 |
| Baseline disease activity, mean score±SD§ | 5.7±1.8 | 5.6±1.7 | 0.98 (0.91 to 1.07) | 0.68 |
| On-study narcotic use, n (%) | 1054 (37) | 130 (63) | 2.76 (2.06 to 3.72) | <0.0001 |
| On-study corticosteroid use, n (%) | 1138 (40) | 88 (43) | 1.72 (1.30 to 2.28) | 0.0002 |
| Baseline immunosuppressive use, n (%) | 917 (32) | 65 (31) | 0.97 (0.72 to 1.31) | 0.86 |
| Vedolizumab treatment, n (%)‡ | 2789 (97) | 200 (97) | N/A | N/A |

*Baseline values are reported for the combined placebo-treated and vedolizumab-treated population with the exception of corticosteroid use. On-study corticosteroid use was defined by corticosteroid use within 30 days before infection date.

†Includes placebo-exposed and vedolizumab-exposed patients.

‡Vedolizumab was not included as a covariate in the model because nearly all patients in the study population (97%) were exposed to vedolizumab.

§The baseline disease activity common index ranges from 0 to 9 and allows for pooling UC and CD disease activity markers.

anti-TNF, tumour necrosis factor α antagonist; CD, Crohn's disease; HBI, Harvey-Bradshaw index; N/A, not applicable; SD, standard deviation; UC, ulcerative colitis.

final safety visit, 10% had positive test results for AVAs 16 weeks after last dose. The coadministration of immunosuppressives at baseline of the studies decreased the AVA positivity rate by 1%, from 4% to 3%. However, these values were determined when patients had a high level of drug present in the serum, which interferes with detection of AVAs with the assay used.¹³ Among patients who received vedolizumab during the induction phase and placebo during the maintenance phase, a greater percentage of patients were AVA-positive (18%) without concomitant immunosuppressive use at baseline compared with those with baseline immunosuppressive use (3%).¹⁵ Based on data from the ongoing GEMINI LTS study, the immunogenicity rate did not appear to increase over time.

Infusion-related reactions

In each of the six studies included here, ≤5% of patients receiving vedolizumab experienced an IRR as defined by the investigator. In the 52-week phase 3 studies, IRRs with vedolizumab and placebo, respectively, were reported for 28 (5%) and 1 (<1%) patients with UC and 33 (4%) and 8 (5%) patients with CD.^{4 5 16} An additional four (2%) and two (<1%) patients with CD experienced an IRR with vedolizumab and placebo,

respectively, in the 10-week GEMINI 3 study.⁶ In the phase 2 studies, IRRs were reported for two patients (one UC, one CD).

Cumulative data for the 2243 patients enrolled in GEMINI LTS showed that 87 patients (4%) had an IRR. The most frequently reported IRRs were nausea (14 patients) and headache (10 patients). All other events occurred in <10 patients (<1%). Twelve patients (<1%) had the infusion interrupted or received an incomplete dose because of an IRR.

Overall, the majority of IRRs were mild or moderate in intensity, and rarely resulted in discontinuation of study drug. Among the 2830 vedolizumab-exposed patients, three IRRs were considered serious and resolved following standard care (see patient narratives in online supplementary materials). With 52 weeks of vedolizumab exposure in GEMINI 1 and GEMINI 2, three of the 61 patients (5%) who experienced an IRR were AVA-positive and three of the 56 patients (5%) who were AVA-positive experienced an IRR.

Malignancies

During the phase 3 studies, all malignancies occurred in 18 patients receiving vedolizumab—six patients in the placebo-

Table 7 Malignancies reported for the overall safety population

| Indication | Age/ sex | Vedolizumab doses* | Malignancy (PT) | Prior therapy |
|----------------------------|-------------|-----------------------|--|---------------------------------|
| Placebo-controlled studies | | | | |
| UC | 70.7/F | 0 | Basal cell carcinoma Squamous cell carcinoma | AZA, 6MP, CS, GLM |
| UC | 40.5/M | 2 | Transitional cell carcinoma | AZA, 6MP, CS† |
| UC | 73.7/M | 2 | Colon cancer | AZA, 6MP, CS |
| UC | 32.7/M | 7 | Colon cancer | AZA†, 6MP, IFX, CS† |
| CD | 45.2/F | 2 | Breast cancer | AZA, 6MP, CS† |
| CD | 52.1/F | 10 | Squamous cell carcinoma | ADA, IFX, AZA, 6MP, MTX, CS |
| CD | 20.7/F | 13 | Carcinoid tumour of the appendix | ADA, IFX, AZA, 6MP, CS |
| Open-label studies | | | | |
| UC | 47.4/M | 2 | Malignant melanoma | IFX, AZA†, 6MP, MTX, CS |
| UC | 75.3/F | 3 | Lung neoplasm malignant | AZA, 6MP, IFX, CS |
| UC | 63.5/M | 6 | Breast cancer in situ | MTX, IFX, AZA, CS |
| UC | 44.1/M | 8 | Metastases to peritoneum | IFX, CS, AZA |
| UC | 70.2/M | 9 | Malignant melanoma | IFX, AZA, 6MP, CS |
| UC | 50.4/M | 29 | Renal cancer | CS |
| CD | 69/F | 3 | Lung neoplasm malignant (hepatic neoplasm malignant) | MTX, ADA, IFX, AZA, 6MP, CS† |
| CD | 45.5/F | 8 | Colon cancer | IFX, AZA, 6MP, CS† |
| CD | 46.8/M | 12 | Basal cell carcinoma | IFX, ADA, AZA, 6MP, MTX, CS |
| CD | 42.9/M | 21 | B cell lymphoma | AZA†, 6MP, IFX, CS†, rituximab† |
| CD | 49.7/M | 37 | Squamous cell carcinoma | AZA†, 6MP, CS |
| CD | 51.1/F | 41 | Hepatic neoplasm malignant | ADA, AZA, 6MP, CS |

*Infusions before or on the first occurrence of selected adverse events. For patients who participated in multiple clinical studies, all doses of vedolizumab were counted.

†Continued use on study.

6MP, mercaptopurine; ADA, adalimumab; AZA, azathioprine; CD, Crohn's disease; CS, corticosteroids; GLM, golimumab; IFX, infliximab; MTX, methotrexate; PT, preferred term; UC, ulcerative colitis.

controlled trials and 12 patients receiving open-label vedolizumab (table 7)—and one patient receiving placebo. Among vedolizumab-exposed patients, GI malignancies were most frequent. Two of the patients with colon cancer had colonoscopies within 1 month of diagnosis, which ultimately confirmed the disease. Five patients had dermatological malignancies, all of which were reported as resolved. Malignant neoplasms reported following ≥ 20 infusions of vedolizumab included renal cancer, B cell lymphoma, squamous cell carcinoma and hepatocellular carcinoma in one patient each (table 7). Risk factors and treatment outcomes for patients with malignancies are summarised in online supplementary table S4.

GI adverse events

In the overall safety population, the incidence rate of any GI AE with placebo (114.5/100 PYs; 95% CI 95.8 to 133.1) was nearly twice as high as with vedolizumab (59.8/100 PYs; 95%

CI 56.2 to 63.4) (table 8). The rate of stenosis was similar in patients with CD irrespective of treatment. The rate of fistulae in patients with CD was lower with vedolizumab (4.6/100 PYs; 95% CI 3.8 to 5.5) than with placebo (10.0/100 PYs; 95% CI 4.5 to 15.5).

Hepatobiliary events

Across the six studies, 23 hepatobiliary events were reported in 22 vedolizumab-treated patients; no cases were observed among placebo-exposed patients (see online supplementary table S5). Nine patients had hepatic steatosis with an incidence rate of 0.2/100 PYs; all other individual incidence rates were $\leq 0.1/100$ PYs. Patients exposed to vedolizumab or placebo had similar low exposure-adjusted incidence rates of liver enzyme abnormalities (vedolizumab, 2.1/100 PYs vs placebo, 2.8/100 PYs) (see online supplementary table S6). No liver enzyme abnormalities led to study drug discontinuation. Five of the hepatic events were considered serious (see patient narratives in online supplementary materials). One patient was later diagnosed with subacute cutaneous lupus erythematosus. All patients were treated accordingly with resolution or near resolution of the liver abnormality.

Deaths

A total of 13 deaths were reported for the vedolizumab clinical development programme—all in GEMINI 1, GEMINI 2 and GEMINI LTS (see online supplementary table S7). No deaths were reported in the 13 phase 1 and phase 2 studies. Detailed accounts of the deaths during GEMINI 1 and GEMINI 2 have been previously reported.^{4–5} All patients with sepsis-related deaths had worsening of underlying disease, significant comorbidities and complicated hospital courses that included surgeries in two cases, all of which confound the assessment of relationship to study drug. The two deaths due to suicide occurred in patients with long durations of CD who were being treated for depression.

DISCUSSION

Integrated safety data for >4000 PYs of vedolizumab exposure in six clinical trials demonstrate that long-term vedolizumab treatment is well-tolerated with an acceptable safety profile in patients with moderately to severely active UC or CD. The safety profile of vedolizumab in the integrated patient population, which considerably extends the available safety data, was similar to that reported in the individual studies.^{4–8} Notably, in the year-long placebo-controlled GEMINI 1 and GEMINI 2 studies, dosing at every 4 weeks or at every 8 weeks yielded similar AE profiles.^{4–5}

The most frequently reported AEs were GI events and infections in patient populations with UC and CD. In general, when adjusted for exposure, AEs were reported more frequently with placebo (419.4/100 PYs) than with vedolizumab (247.8/100 PYs). These exposure-adjusted incidence rates provide an estimate of the number of patients who would experience the event of interest if 100 patients were treated for 1 year. Based upon this approach, a patient who experienced the same AE multiple times was counted only once. Given the longer average duration of exposure to vedolizumab, it is possible that a single patient may have experienced the same event more times with vedolizumab than with placebo. The disproportionate PYs of follow-up with vedolizumab compared with placebo—a limitation of the present analyses—and the low numbers of observed events warrant the need for further investigation. Although the placebo group does not allow for direct comparisons, especially for

Table 8 Exposure-adjusted incidence rates of GI adverse events in the overall safety population

| Adverse event | UC | | | CD | | | UC and CD | | |
|---|--|--|--|--|--|--|--|--|--|
| | Placebo n=149* | Vedolizumab n=1107† | Placebo n=355‡ | Placebo n=504¶ | Vedolizumab n=1723§ | Placebo n=504¶ | Vedolizumab n=2830** | | |
| | No. of patients with event/100 PY (95% CI) | No. of patients with event/100 PY (95% CI) | No. of patients with event/100 PY (95% CI) | No. of patients with event/100 PY (95% CI) | No. of patients with event/100 PY (95% CI) | No. of patients with event/100 PY (95% CI) | No. of patients with event/100 PY (95% CI) | | |
| Any GI AE | 54 | 592 | 126 | 180 | 1090 | 180 | 1682 | | |
| Fistulal†† | 0 | 0 | 13 | 13 | 121 | 13 | 121 | | |
| Stenosis | 1 | 10 | 5 | 6 | 102 | 6 | 112 | | |
| Duodenal and small intestinal stenosis and obstruction††† | 1 | 5 | 3 | 4 | 33 | 4 | 38 | | |
| Ileal stenosis and obstruction§§ | 0 | 3 | 1 | 1 | 32 | 1 | 35 | | |
| Stenosis and obstruction, other¶¶¶ | 0 | 1 | 1 | 1 | 29 | 1 | 30 | | |
| Colonic and rectal stenosis and obstruction**** | 0 | 1 | 0 | 0 | 14 | 0 | 15 | | |
| Anal stenosis and obstruction†††† | 0 | 0 | 0 | 0 | 2 | 0 | 2 | | |
| Pancreatitis††††† | 1 | 2 | 0 | 1 | 10 | 1 | 12 | | |
| Any serious GI AE | 12 | 149 | 30 | 42 | 389 | 42 | 538 | | |
| Fistulal†† | 0 | 0 | 2 | 2 | 21 | 2 | 21 | | |
| Duodenal and small intestinal stenosis and obstruction††† | 1 | 5 | 1 | 2 | 24 | 2 | 29 | | |
| Ileal stenosis and obstruction§§ | 0 | 3 | 0 | 0 | 23 | 0 | 26 | | |
| Stenosis and obstruction, other¶¶¶ | 0 | 1 | 1 | 1 | 16 | 1 | 17 | | |
| Colonic and rectal stenosis and obstruction**** | 0 | 0 | 0 | 0 | 5 | 0 | 5 | | |

Exposure-adjusted incidence rates for each AE were calculated by dividing the number of patients experiencing the event by the total PYs, multiplied by 100. PYs were calculated as the sum of each patient's contribution, calculated from the days of exposure (ie, AE onset date minus the date of first dose plus 1 day). For each AE, the PYs were truncated after a patient experienced the AE and each AE was counted only once per patient. Patients who were randomised to placebo and then rolled over into an open-label study could contribute to events in either the placebo or vedolizumab group depending on when they experienced the AE. PYs were calculated accordingly for placebo or vedolizumab for each AE. When the number of events=0, the 95% CI was calculated based on rule of 3 (ie, (0, 3/total PYs)×100).

* Includes patients from GEMINI 1.
 † Includes patients from studies C13002, C13004, GEMINI 1 and GEMINI LTS.
 ‡ Includes patients from GEMINI 2 and GEMINI 3.
 § Includes patients from studies C13004, GEMINI 2, GEMINI 3 and GEMINI LTS.
 ¶ Includes patients from GEMINI 1, GEMINI 2 and GEMINI 3.
 ** Includes patients from all six studies.
 †† Includes MedDRA PTs: anal fistula, colonic fistula, enterocolonic fistula, enterovesical fistula, female genital tract fistula, fistula, ileal fistula, perineal fistula, postprocedural fistula, rectourethral fistula, vaginal fistula.
 ††† Includes MedDRA PTs: duodenal stenosis, small intestinal obstruction, small intestinal stenosis.
 §§ Includes MedDRA PTs: ileal stenosis, ileus, subileus.
 ¶¶ Includes MedDRA PTs: intestinal obstruction, intestinal stenosis.
 *** Includes MedDRA PTs: colonic obstruction, colonic stenosis, rectal stenosis.
 †††† Includes MedDRA PTs: anal stenosis.
 ††††† Includes MedDRA PTs: pancreatitis acute, pancreatitis chronic.
 AE, adverse event; CD, Crohn's disease; GI, gastrointestinal; LTS, long-term safety; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; PY, person-years; UC, ulcerative colitis.

events occurring beyond 6 months of exposure, incidence rates for vedolizumab-treated patients can be compared with that observed in the HealthCore Integrated Research Database (HIRD), one of the largest commercially insured populations in the USA. The HIRD provides estimates of background incidence rates of AEs from 14 733 commercially insured US patients with moderately to severely active IBD.¹⁷ However, as real-world disease management often differs from that in clinical trials, comparison of outcomes to the HIRD should be interpreted with caution.

Importantly, we did not observe an overall increase in the risk of infection or serious infection with vedolizumab exposure. The overall incidence rates of infection and serious infection with vedolizumab were 63.5/100 PYs and 4.3/100 PYs, respectively (vs 82.9/100 PYs and 3.8/100 PYs for placebo). For the majority of infections and serious infections, the 95% CIs for placebo events overlapped with the point estimates for vedolizumab events. No indication for serious opportunistic infections, such as disseminated TB, systemic candidiasis, disseminated herpes zoster, extraintestinal cytomegalovirus (CMV) infections or *Pneumocystis* pneumonia, was observed. *Listeria* meningitis was reported in one patient with CD. There were three cases of pulmonary TB with no extrapulmonary manifestations in patients from countries with higher endemic rates of TB relative to the USA and western Europe.¹⁸ In a pooled analysis of GEMINI 1 and GEMINI 2 data, the infection profiles in patients who received vedolizumab were similar with or without concomitant corticosteroids and/or immunosuppressives.¹⁹ It should be noted that patients receiving placebo may have more active disease and a greater propensity for intestinal infections, which could confound the reported incidence rates. However, the low incidence of infections with vedolizumab treatment is promising and consistent with what has been reported in HIRD (eg, for clostridial infections, we report 0.7/100 PYs (95% CI 0.5 to 1.0) while the HIRD reports 3.1/1000 PYs (95% CI 2.1 to 4.5) for *Clostridium difficile* diarrhoea/colitis).¹⁷

These observations, which are consistent with vedolizumab's gut-selective mechanism of action, have important clinical implications. Morbidity and mortality from common infections such as community-acquired pneumonia and opportunistic infection are concerns with existing immunosuppressive IBD therapies.^{20–22} Epidemiological studies to evaluate whether vedolizumab may represent a safer alternative are needed.

Enteric infections were infrequent in vedolizumab-exposed patients. Apart from gastroenteritis and abscess, all other enteric infections (eg, clostridial, CMV, streptococcal, appendicitis, diarrhoea, enterocolitis, diverticulitis) were reported with incidence rates of $\leq 0.8/100$ PYs each. All cases of clostridial or CMV infection occurred in patients exposed to vedolizumab. One patient had a streptococcal infection with placebo exposure versus 36 vedolizumab-exposed patients. An increased risk of some GI infections is plausible based on the gut-selective mechanism of action for vedolizumab. To further investigate this potential risk, a prospective patient registry has been initiated to evaluate the risk of enteric and other infections.

The development of PML, an often fatal complication of JCV infection, is a well-established risk of prolonged treatment with natalizumab, a monoclonal antibody directed to the α_4 integrin.²³ In natalizumab clinical trials representing almost 3000 patients with 18 months of exposure, there were three cases of PML that occurred with a mean latency of 18 months.²⁴ As of June 2015, 566 cases of PML had been confirmed among over 138 800 patients exposed to postmarket natalizumab from which PML risk estimates were identified.²⁵ Applying these risk

estimates to the database of all vedolizumab trials, an average of at least six PML events would have been expected if PML risk with vedolizumab were the same as for natalizumab. In contrast, no cases of PML were observed during vedolizumab clinical development in the context of a rigorous risk monitoring programme. These data suggest that any PML risk with vedolizumab, if present, is likely to be significantly lower than for natalizumab.

Collectively, these data indicate that vedolizumab treatment is not associated with increased risk of serious and opportunistic infections. Using a Cox proportional hazards model, the factors independently associated with serious infection in patients with UC and CD were younger age, on-study narcotic analgesic use and on-study corticosteroid use. When analysed separately, the same risk factors were identified in patients with CD. In contrast, prior failure with anti-TNFs was an independent risk factor for serious infection in patients with UC, while younger age and concomitant corticosteroid use were not identified in the UC population alone. These data are in agreement with a study by Lichtenstein *et al*²⁶ which reported that on-study narcotic analgesic use (HR, 1.98; 95% CI 1.44 to 2.73; $p < 0.001$) and prednisone therapy (HR, 1.57; 95% CI 1.17 to 2.10; $p = 0.002$) were independently associated with serious infection in patients with CD. In contrast to our model, Lichtenstein *et al*²⁶ identified disease activity and infliximab treatment as independent predictors of serious infection. Of note, older age (HR, 1.08; 95% CI 1.07 to 1.09; $p < 0.001$) was associated with increased mortality risk in their study.²⁶

The potential for IRRs is a known risk with biological therapeutics, including monoclonal antibodies such as vedolizumab.²¹ Across the six vedolizumab clinical studies, $\leq 5\%$ of patients experienced an IRR, the majority of which were mild or moderate in intensity. Overall immunogenicity rates with long-term exposure were low, and there was no apparent association between AVAs and IRRs. As with other monoclonal antibodies, treatment with vedolizumab is associated with AVAs. Rate of antibody formation can be reduced by coadministration of immunosuppressives. For individual patients, the balance between safety and protection against immunogenicity for long-term durability of remission should be evaluated.

Some treatments for IBD increase the risk of cancer. Patients treated with purine antimetabolites have a well-established increased risk of skin cancer and lymphoma.²⁷ We observed no noticeable relationship between the development of malignancy and age, sex, type of malignancy or duration of vedolizumab exposure. The occurrence of four cases of colon cancer out of a population of >2800 patients (0.1/100 PYs) is consistent with published data regarding the incidence of this complication in patients with IBD and is less than what was observed in HIRD (2.1/1000 PYs; 95% CI 1.3 to 3.2).^{17, 28} Notably, the incidence of non-melanoma skin cancer in vedolizumab-exposed patients was not greater than in patients who received placebo. Non-melanoma skin cancer is the most common malignancy related to immunosuppression²⁹ and can be a useful bellwether for this risk. Further, risk of non-melanoma skin cancer is increased when patients are treated with thiopurines.²⁷ All vedolizumab-exposed patients diagnosed with skin cancer had a history of azathioprine therapy, and two continued azathioprine use on study. While vedolizumab does not have a known effect on impairment of T cell mediated cancer surveillance in extraintestinal organs, prospective studies are required to fully evaluate the risk of malignancy in patients receiving vedolizumab long-term.

In addition to infection, cancer and IRRs, the suppression of systemic immunity by anti-TNFs has been associated with

autoimmune complications including psoriatic lesions, demyelination and drug-induced lupus.^{21 30–32} In a recent review of the US Food and Drug Administration Adverse Event Reporting System (FAERS) database, anti-TNF exposure was associated with a psoriasis-proportional reporting ratio of 9.24 compared with drugs implicated in the development of psoriasis.³³ Of all neurological AEs with anti-TNFs reported to the FAERS, 153 reports (19.8%) were central nervous system and/or spinal cord demyelination.³⁴ Lupus-like syndrome is estimated to occur in 0.2–0.4% of patients treated with anti-TNFs, although some cases may be attributed to unmasking of latent systemic lupus erythematosus rather than true lupus-like syndrome.²¹ In contrast, no signal for these uncommon anti-TNF-related complications was observed with vedolizumab exposure, although there was one case of cutaneous lupus. Liver dysfunction has been associated with normal IBD progression and immunosuppressive use.^{21 35} Although a low incidence of hepatobiliary events was observed among vedolizumab-treated patients only, further study is necessary to determine whether these complications are drug related. Indeed, in the clinical development programme overall, the rates of autoimmune and hepatobiliary events of any type were exceedingly low.

In conclusion, the integrated clinical trial data set of 2932 patients with moderately to severely active UC or CD presented herein provides evidence that there are no significant safety concerns associated with vedolizumab treatment. Vedolizumab offers a targeted, gut-selective mechanism of action without any clear increase in the risk of serious systemic opportunistic infections or other common complications for a set of diseases that typically require lifelong therapy.

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